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Co-funded by the Erasmus+ Programme of the European Union

EACPT

Nederlandse Vereniging voor KLINISCHE FARMACOLOGIE en Biofarmacie

Contents

A. Pain medication

In disease processes, tissue damage is the cause of pain. Tissue injury releases substances that stimulate nociceptors directly or indirectly: histamine, serotonin and bradykinin stimulate the nociceptors directly; prostaglandins increase the sensitivity of sensory nerve endings for the aforementioned substances.

Analgesics can be divided into different groups. The division proposed here is:

A. Non-opioids:
   - A.1 Paracetamol
   - A.2 NSAIDs

B. Opioids:
   - B.1 Opiates
   - B.2 Tramadol

Table 1: The WHO-pain ladder[1]

Phase	Medication indicated	Supplementary information
Phase 1	Paracetamol (500-1000 mg 4 x daily)	Widely used and generally very safe.
	If the effect of paracetamol is insufficient, a NSAID can be added in addition to paracetamol: • Ibuprofen (maximum of 2.4 g in 4-6 doses per day) • Diclofenac (50 mg 3-4x daily) • Naproxen (250-500 mg 2-3x daily)	
Phase 2	• If the resultant analgesic effect is insufficient, the non-opioid chosen in phase 1 can be replaced by or added to a weak opioid: • Codeine (30-60mg dose, max. 200mg per day) • Tramadol (50-100mg 3-4 x daily)	This step is usually skipped when treating nociceptive pain in cancer. Given that tramadol and codeine have a limited efficacy against cancer pain, and that the side effects of these drugs (mainly nausea and dizziness) frequently lead to these drugs being discontinued, patients often start immediately with a (low dose) stronger opioid.
Phase 3	If the weak opioid has an inadequate therapeutic effect, then a stronger opioid should be considered: • Morphine retard (the maximum dosage is determined by the occurrence of side effects) • Fentanyl patch (in patients with a continuous opioid need or problems with swallowing) If the analgesic effect is insufficient, or the side effects are unacceptable, switch to a different strong opioid: 'opioid rotation'.	A drug from phase 3 is always combined with a drug from phase 1; in this way multiple pain mechanisms can be targeted and hence a better therapeutic outcome for the patient can be achieved. The main disadvantages of the fentanyl patch are that there is a considerable delay before a therapeutic effect is seen (due to the slow absorption of the drug through the skin) and that the drug accumulates in the skin under the patch.
Phase 4	If oral routes provide inadequate analgesia, parenteral administration should be considered.	

[1] National Institute for health and Care Excellence (NICE): Guidelines on pain management

A. NON-OPIOIDS

A.1. PARACETAMOL / ACETAMINOPHEN

Paracetamol (also known as acetaminophen) is an analgesic with antipyretic activity, but has no anti-inflammatory effect. The exact mechanism of action is not clear.

1. Side effects

Objectives: The most important/serious side effect of paracetamol is liver damage. This occurs at a dose of more than 150mg/kg. Risk factors for developing liver damage are pre-existing liver damage, alcoholism and a poor nutritional status. N-acetylcysteine is indicated to counteract acetaminophen poisoning.

The most common paracetamol dose prescribed (1000mg 3-4 x daily) has few side effects. Liver damage occurs when the dose of paracetamol exceeds the metabolic processing capacity of the body (> 150mg/kg). If the patient is at risk of developing liver damage (due to alcoholism, pre-existing liver damage or if the patient has a poor nutritional status (table 2)), the maximum dosage permitted is 2g per day.

Table 2: Risk factors for paracetamol use

Risk factor	Pathophysiological effect
Alcoholism	In these patients, chronic use of alcohol may induce the CYP2E1 enzymes to convert a greater proportion of paracetamol into a dangerous metabolite (NAPQ1=N-acetyl-p-benzoquinonimine); this metabolite causes liver damage. Under normal circumstances, radicals produced by NAPQ1 are rapidly detoxified by glutathione. If the concentration of NAPQ1 exceeds the scavenging capacity of glutathione, damage to the liver cells can occur.
Liver failure	Pre-existing liver disease leads to an increased formation of hepatotoxic metabolites.
Malnutrition	People with poor nutritional status have less glutathione in the liver. This is an antioxidant that detoxifies hazardous metabolites (NAPQ1).

A.2. PROSTAGLANDIN SYNTHASE INHIBITORS

Objectives: The mechanism of action of NSAIDs is based on the inhibition of prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX). This leads to analgesic, antipyretic and anti-inflammatory effects. The side effects are linked to the mechanism of action. Examples of classic NSAIDs include: ibuprofen, naproxen and diclofenac. In addition, there are selective COX-2 inhibitors, such as celecoxib.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) or prostaglandin inhibitors, aside from their painkilling properties, also have antipyretic and anti-inflammatory effects.

1. (Patho)physiology

Cyclooxygenase (COX) is the central enzyme in prostaglandin synthesis (Fig. 1).

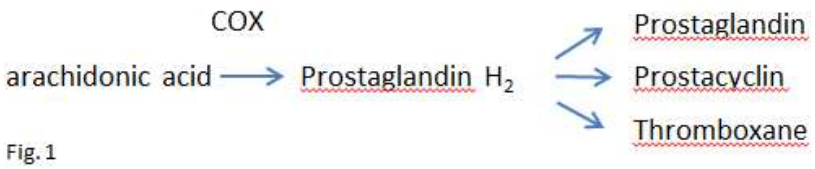


Fig. 1

Multiple isoforms of cyclooxygenase (COX) exist: COX-1 and COX-2 (Table 3).

Table 3: The functions of COX-1 and COX-2 enzymes

COX-1	COX-2
COX-1 produces prostaglandins which play a role in various homeostatic mechanisms, such as: • Maintaining autoregulation of renal perfusion • Gastric protection • Maintaining thrombocyte function	COX-2 has more specific roles, such as: • Maintaining the autoregulation of renal perfusion. • Inflammation • Ovulation • Implantation • Closure of the ductus arteriosus • CNS functions (fever induction, pain perception and cognitive function)

More selective COX-2 inhibitors (e.g. celecoxib) result in fewer gastrointestinal side effects. However, several selective COX-2 inhibitors have been taken off the market, as they have been associated with an increase in incidence of serious cardiovascular events.

2. Side effects

Objectives: The most serious side effects associated with NSAID use are: peptic ulcers, renal failure, thrombocytopathy and worsening of heart failure. Risk factors for the development of a peptic ulcer with the use of NSAIDs are: previous ulcers in medical history, rheumatoid arthritis, heart failure, and diabetes mellitus. Risk factors for the development of renal failure with the use of NSAIDs are: heart failure, dehydration, sepsis and pre-existent kidney failure. For the prevention of peptic ulcers, proton pump inhibitors (PPIs) are prescribed or selective COX-2 inhibitors are used instead.

The most common side effects are gastrointestinal disorders, followed by renal impairment and cardiovascular side effects. The inhibition of platelet aggregation may increase the tendency and duration of bleeding. With the exception of acetylsalicylic acid (aspirin), this effect is reversible, dose-dependent and short-lived.

Gastrointestinal side effects

By inhibiting the production of prostaglandins, the protective function of the gastric mucosa is reduced. There is a higher risk of gastrointestinal (GI) complications (such as bleeding ulcers and gastrointestinal perforation) in patients over 60-70 years of age and in patients who have a previous history of ulcers. Other factors that increase the risk of GI side effects include the use of corticosteroids, SSRIs, oral anti-coagulants or acetylsalicylic acid, the presence of Helicobacter pylori or serious comorbidities such as diabetes or heart failure. For patients with one or more risk factors, a proton pump inhibitor such as omeprazole (1st choice) or misoprostol (a stomach specific prostaglandin agonist) should be additionally prescribed.

Recommendations

When NSAIDS are prescribed, it is important for the physician to consider whether the patient is as at increased risk of injury to the stomach lining:
Preventative measures (against such injury) are indicated in patients:

- With a history of stomach ulcers
- > 70 years old
- With an untreated H. pylori infection in the context of ulcer disease.

Preventative measures should be considered in patients:

- Aged between 60-70 years old.
- Using anti-coagulants or aspirin
- With severe debilitating arthritis
- With heart failure or diabetes
- Using corticosteroids
- Using selective serotonin reuptake inhibitors (SSRIs)

The risk factors listed have a cumulative effect, thus the risk increases with every additional risk factor present.

Renal side effects

Under normal circumstances, the renal blood flow depends only to a small extent on prostaglandins. However, reducing the effective circulating volume results in a decreased perfusion of the kidney, which triggers an increase in prostaglandin production. Prostaglandins cause dilation of the afferent arteriole; this ensures that renal blood flow remains constant even if the circulating volume decreases (Fig. 2). When administering an NSAID, the aforementioned compensation mechanism is inhibited, which can result not only in decreased renal blood flow and fluid retention, but may even lead to acute renal failure.

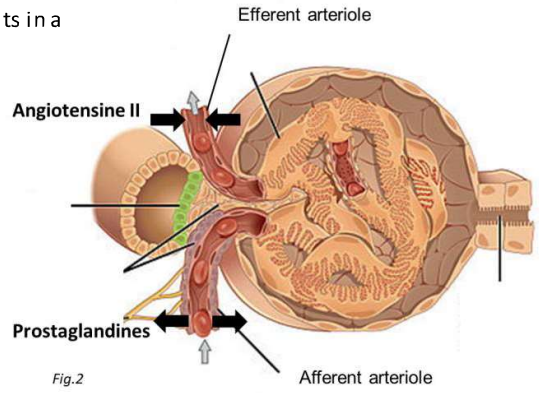


Fig.2

Renal blood flow is prostaglandin-dependent in situations where there is low renal perfusion pressure. The pressure in the kidney is dependent on the pumping force of the heart, the volume status, and the blood pressure. The following conditions will result in a higher risk of developing loss of renal function with the use of NSAIDs:

- Heart failure
- Dehydration as a result of diarrhoea, fever or diuretic use
- Sepsis
- Use of RAAS inhibitors (*Fig. 2*)
- Pre-existent renal failure (MDRD < 30)

NSAIDs may therefore cause a loss of renal function in these patients, which results in electrolyte imbalances (particularly elevated potassium). Furthermore, use of renally-excreted co-medication with a limited therapeutic index (e.g., sotalol, digoxin, lithium, nitrofurantoin), and metformin is more risky given that a reduction in renal clearance results in the accumulation of the drug or its metabolites in toxic concentrations.
N.B. acetylsalicylic acid in the 80 mg antiplatelet dose does **not** reduce renal function.

Cardiovascular side effects

NSAIDs can cause water and salt retention, which in turn can lead to peripheral oedema. In patients with heart failure, the use of NSAIDs should be avoided because of the increased risk of cardiac asthma.

3. Interactions

Objectives: The use of coumarin-related anti-coagulants, antiplatelet medications, steroids, or SSRIs in combination with NSAIDs results in an increased risk of gastrointestinal bleeding. The prescription of NSAIDs in combination with RAAS inhibitors or diuretics carries an increased risk of heart failure (by salt retention) and renal failure. These interactions are to be avoided.

Table 4: Causative drug interactions with NSAIDs	
Drug Interaction	**Side effects**
• Coumarin-related agents • Platelet aggregation inhibitors • SSRIs (due to impaired function of platelets) • Corticosteroids (result in an even worse functioning of the gastric mucosa, so gastric ulcers are more likely to develop)	• Gastrointestinal side effects
• RAAS inhibitors (especially when renal function is impaired or circulating volume is decreased; renal function can decrease even further and there is an increased risk of hyperkalaemia) • Diuretics (these drugs lead to a lower effective circulating volume, meaning that the renal blood flow is more dependent on prostaglandins)	• Renal failure
• Antihypertensives (reduced effect with concomitant NSAID use)	• Hypertension

B. OPIOIDS

B.1. OPIATES (μ-agonists)

Objectives: Opioids bind to opioid receptors. Depending on which receptors are occupied, (μ, κ or δ) the following symptoms can be experienced: analgesia, respiratory depression, miosis, constipation, euphoria, dysphoria, sedation and dependence. The mechanism of action is also responsible for the side effects of this class of medication. Fentanyl, which has a considerably stronger analgesic effect than morphine, can be administered in nasal, transdermal and oral forms. Tramadol has a weak analgesic effect and a considerable number of side effects (dizziness, delirium and nausea). Tramadol also has an inhibitory effect on the reuptake of norepinephrine and serotonin. Codeine is partly dependent on the liver enzyme CYP2D6 for activation; the activity of this enzyme varies markedly amongst individuals and thus the effect of the drug on an individual patient cannot be accurately predicted. Naloxone is a competitive antagonist for all opiate receptors so it can be used as an antidote to counteract side effects experienced by the patient.

Opioids exert their effect by occupying specific receptors in the central nervous system. There are various opioid receptors, of which the most important ones are mu (μ) and kappa (κ) (Table 5).

Table 5: The opioid receptors	
Receptor	**Physiological role**
μ-receptor	• Analgesia • Supraspinal analgesia, respiratory depression, euphoria, and physical dependence
κ-receptor	• Analgesia • Miosis, sedation, dysphoria and psychotomimetic effects

1. Medicinal properties

Most effects of opiate agonists are mediated by activation of the μ-receptor; in other cases κ-receptors and δ-receptors are involved. Differences are seen in the kind of side effects experienced, the time to onset (of the effect), the duration and strength of the effect and the likelihood of developing dependence (Table 6).

Table 6: The properties of different opioids and an opioid antagonist (naloxone)

Drug	Pharmacological properties
Morphine	Morphine is an agonist of all three receptors. The analgesic effect of morphine is mainly attributable to its actions on the μ-receptors in the central nervous system.
Codeine	Codeine has a low affinity for opioid receptors. The analgesic effect of codeine is weak (one tenth that of morphine). About 10% of codeine is converted into morphine by CYP2D6. Approximately 10% of the population is not able to convert codeine into morphine because they lack the enzyme that is required for this conversion. Another disadvantage is its strong constipating effect. It is therefore better not to use this drug.
Fentanyl	Fentanyl has a highly selective affinity for the μ-receptor and has an analgesic effect that is considerably stronger than that of morphine. Due to the high degree of lipophilicity, fentanyl is suitable for transdermal administration. An oromucosal lozenge is also available, of which 25% of the fentanyl is absorbed by the buccal mucosa and hence enters the circulation. Fentanyl is mainly used for unpredictable, acute breakthrough pain. The pharmacokinetics of the drug varies according to the mode of administration; with nasal administration having a T_{max} of 12-20 minutes and a half-life of 3-4 hours. With transdermal administration with controlled release, an effect is seen after 6-12 hours. Fentanyl release continues for 72 hours, with a T½ of approximately 17 hours.
Tramadol	See chapter B.2. Tramadol.
Oxycodone	Oxycodone can be prescribed as a short-acting variant (OxyNorm®) or a long-acting variant (controlled-release tablet) (OxyContin®).
Naloxone	This is a competitive antagonist for the opiate receptors and is used to counteract the side effects of morphine agonists.

Sometimes patients derive greater benefit from one opioid than another; this is often due to differences in affinity of the different receptors. However whilst a greater affinity leads to a greater painkilling effect, it can also lead to an increase in severity of side effects experienced. Thus, if with a particular opiate the painkilling effect is too little or the side effects are too severe, the decision can be made to switch the opioid being taken (this is known as "opioid rotation"). This is beneficial provided that the new opioid binds with different affinities to the different opioid receptors; in this way the patient may respond better to the new drug. Opioid rotation also reduces the likelihood of drug tolerance occurring, whereby the therapeutic effect of the drug decreases.

2. Side effects

Objectives: The main side effects of opioids include constipation, respiratory depression and dependence. COPD is a risk factor for the development of respiratory depression. If this event occurs, naloxone is given as an antidote. Constipation is prevented by prescribing standard laxatives.

Morphine and other opioids have, in addition to a strong analgesic effect, a large number of undesirable effects (Table 7).

Table 7: Common side effects associated with opioid use	
Side effects	**Drug Interactions**
In the central nervous system	• Delirium • Sedation • Inhibition of the respiratory system • Miosis (pupil constriction, pin point)
In the gastrointestinal tract	An increase of the smooth muscle tone and a decrease in gut motility can lead to: • Constipation • Nausea and vomiting • Constriction of the sphincter of Oddi (biliary colic)
In the respiratory system	• Decrease in depth and frequency of breathing • Bronchoconstriction
On the skin	• Itching

After prolonged use, tolerance and dependence can occur; dependence can be both physical and psychological.

Constipation

Risk factors for constipation are being bedridden/immobility, poor intake of water and food (particularly fibre) and the use of certain drugs, such as ondansetron, tricyclic antidepressants, verapamil, oxybutynin and diuretics. Therefore when prescribing opioids, one or more of the following laxatives should be added to the opiate prescription:

1. Movicolon, lactulose (can elicit cramps) or MgO (can result in hypermagnesaemia, renal impairment and may cause drug-drug interaction): soften faeces.
2. Bisacodyl: stimulates the bowel.
3. Enema: the accumulation of hard faeces at the end of the intestine is removed.

Respiratory Depression

Respiratory depression occurs mainly in patients with COPD. Patients with chronic respiratory insufficiency (pO_2 <8 kPa, PCO_2> 6.0 kPa) as a result of COPD have hypercapnia due to alveolar hypoventilation. N.B. In contrast to people who do not have COPD, the ventilatory drive is largely dependent on the pO_2 (instead of pCO_2). Thus if oxygen is administered to a patient with respiratory insufficiency, this may yet further decrease the respiratory drive.

Dependency

All opiates can cause dependence. Patients with a history of substance abuse (e.g. smoking, alcohol, cannabis) are at a greater risk. This risk is also higher with the use of fast-acting opiates (such as fentanyl nasal spray or lollipop). These fast-acting drug forms should NOT be given for pain caused by a benign condition.

If an opiate is given to a patient after surgery, it should only be prescribed for the period for which the patient is expected to have pain. If the patient requests a continuation of opioid therapy after this point, efforts should be made to determine whether this is due to the pain (in this case the cause of this pain should be ascertained), due to the patient becoming dependent on the drug or due to another problem that may lead to prolonged opiate use.

3. Interactions

Table 8: Common drug interactions with opioids	
Drug Interaction	**Side effect**
• Anticholinergics • Antidepressants • Diuretics	• Constipation
• Benzodiazepines (suppression of the respiratory centre)	• Respiratory depression

B.2. TRAMADOL

Tramadol is a relatively weak opioid agonist with some selectivity for the μ-receptor and also has an inhibitory effect on the reuptake of norepinephrine and serotonin. Long-term use can lead to dependence. Therefore, treatment with tramadol should be short and intermittent. Many central side effects can occur, especially in elderly patients. The drug's analgesic effect is also weak, and it can cause comparatively more adverse effects (mainly nausea and dizziness). It is therefore preferable to choose a "low dose opiate" rather than tramadol.

Objectives: The following drugs should be known: paracetamol, diclofenac, naproxen, ibuprofen, morphine, fentanyl, tramadol, oxycodone, codeine, naloxone, omeprazole, furosemide, lisinopril, losartan, warfarin, acetylsalicylic acid, paroxetine.

B. Anticoagulants

For a better understanding of the mechanism of action of the various anti-coagulants, it is essential to first understand the (patho)physiology of blood clotting.

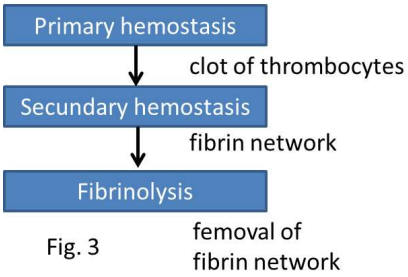


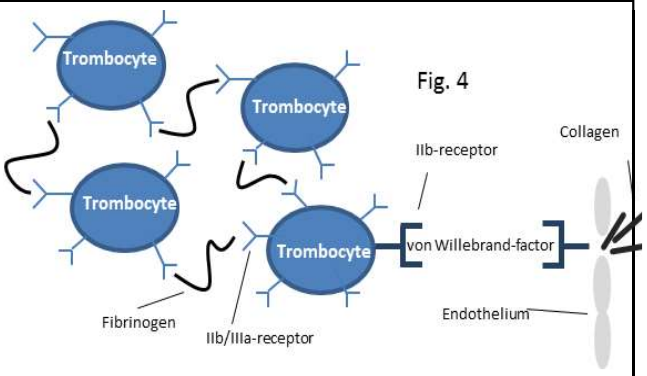
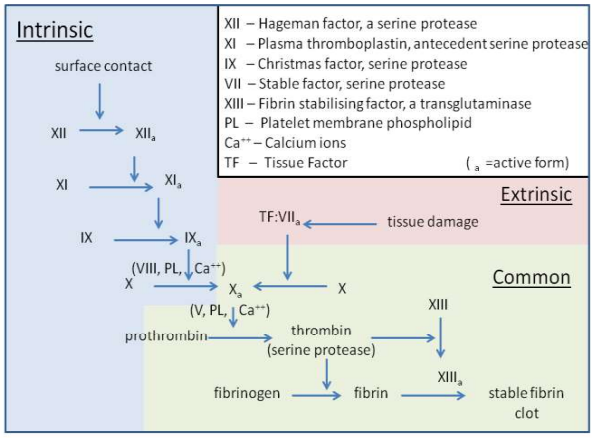
Fig. 3

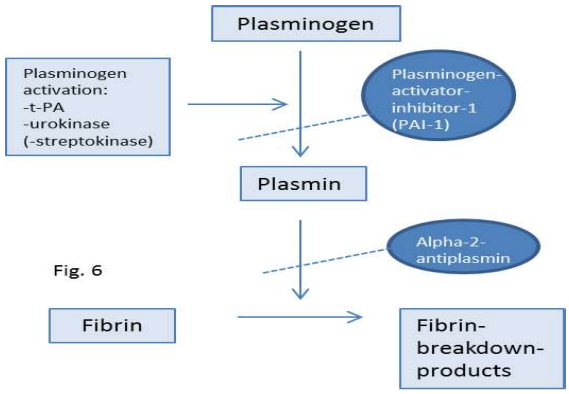
1. (Patho)physiology

Blood coagulation successively consists of (*Fig. 3*):

1. The process of primary haemostasis
2. The formation of a blood clot (secondary haemostasis)
3. The removal of a blood clot, also known as fibrinolysis

Table 9: The three phases of haemostasis

Phase	Biochemical pathway
Phase 1: Primary haemostasis consists of interaction between platelets and the (damaged) vessel wall (adhesion), clumping of platelets to each other (aggregation) and activation of platelets with the consequent production of procoagulant factors (including thromboxane A2). After adhesion of platelets to the vessel wall, the activation of platelets occurs and the glycoprotein IIb / IIIa receptor presents on the platelet membrane: this receptor brings about fibrinogen binding and aggregation of other platelets (*Fig. 4).*	 Fig. 4
Phase 2: The next phase of the blood clotting is the formation of the fibrin clot. Fibrin formation begins when tissue factor (thromboplastin), which is normally below the surface of the endothelium, comes into contact with blood. Through the binding and activation of coagulation factors, fibrinogen is eventually converted to fibrin (Fig. 5). Medications act on factor Xa and/or IIa - these are two essential clotting factors. Almost all clotting factors are produced in the liver and vitamin K is needed in the synthesis of some of these factors (II, VII, IX and X).	Fig 5. 

Phase 3: The fibrinolytic system ensures the removal of blood clots when the normal integrity of the tissue has been restored. Conversion of plasminogen to the active component plasmin is achieved by plasminogen activators (Fig. 6). Plasmin is able to convert the insoluble fibrin into soluble degradable fibrin products.	

Pathological thrombosis

Table 10: Arterial vs Venous thrombosis

Site of thrombotic event	Clinical problem	Relevant medications
Arterial thrombosis Arterial thrombosis is caused by an interruption in the endothelial layer. The resulting white thrombi consist mainly of platelets with little fibrin.	Myocardial infarction, stroke	Antiplatelet agents: • Aspirin • Clopidogrel (Plavix) • Dipyridamole (Persantine)
Venous thrombosis Venous thrombosis is usually caused by circulatory stasis, resulting in a hypercoagulable state. The resulting red thrombi consist primarily of red blood cells and fibrin.	Deep vein thrombosis, pulmonary embolism	Coumarin derivatives & vitamin K antagonists: • Acenocoumarol (Sintrom) • Fenprocoumon (Marcoumar) • Warfarin (Coumadin, Jantoven) Heparins: • Heparin IV • Low dose LMWH • High dose LMWH

Pathological thrombosis occurs as a result of one of the following factors or a combination thereof, as described by the German pathologist Virchow (triad of Virchow):

- Increased coagulability of the blood
- Slowed blood flow velocity
- Damage of the vascular wall

Using the "triad of Virchow", many causes of pathological thrombosis become understandable.

Antithrombotic drugs may be divided into two different groups based on their mechanisms of action: antiplatelet agents and anti-coagulants. Anticoagulants can be divided further into indirectly- (vitamin K antagonists, coumarins) and directly-acting (heparin) agents.
The distinction between arterial and venous thrombosis is important when choosing a pharmacological treatment (Table 10).

A. ANTICOAGULANTIA

Anticoagulants are divided into several groups:

A.1. Antiplatelet agents
A.2. Vitamin K antagonists/Coumarin derivatives
A.3. Heparins

A.1. ANTIPLATELET AGENTS

Objectives: Aspirin inhibits the enzyme cyclooxygenase, which leads to a reduced production of thromboxane A2. This leads to an inhibition of primary hemostasis. Clopidogrel binds to the ADP receptor on thrombocytes. Both drugs irreversibly inhibit platelet function, meaning the effects of these medications continue for approximately one week after the cessation of treatment – this corresponds with the rate at which the platelets are renewed (ca. 10 days).

The platelet aggregation inhibitors may have multiple ways to interfere with platelet aggregation, effectively preventing the formation and growth of thrombi. The adhesion of platelets to subendothelial structures leads to their activation. Upon the activation of platelets, serotonin, ADP and thromboxane A2 among others are released. Thromboxane A2 acts on damaged endothelium, mediates vasoconstriction and promotes platelet aggregation (Fig. 1).

1. Medicinal properties

Table 11: Mechanism of action of antiplatelet agents

Agent	Mechanism of action
Acetylsalicylic acid (ASA)	The antiplatelet effect of acetylsalicylic acid occurs via the inhibition of the formation of the prostaglandin thromboxane A2, through the irreversible inhibition of the membrane-bound cyclooxygenase (Fig. 1). The effect of acetylsalicylic acid on the nucleus-free platelet is equal to the lifetime of the platelet (approximately 10 days).
Clopidogrel	Clopidogrel inhibits platelet aggregation by specific, irreversible blocking of the adenosine diphosphate (ADP) receptor on the platelet. In this way, the ADP-mediated activation of the GPIIb / IIIa complex becomes irreversibly inhibited (Fig. 4). The rate of return to normal platelet function corresponds with the rate at which platelets are renewed (10 days).
Dipyridamole	Dipyridamole has reversible platelet aggregation inhibition activity. The duration of the effect is less than one day ($t_{½}$ 12h).

2. Indications

Objectives: Acetylsalicylic acid is indicated for arterial disease, such as post-infarction, angina pectoris, post TIA or stroke, post CABG and peripheral arterial disease. Clopidogrel is indicated after stent placement, for acute coronary syndrome, and after a TIA or stroke.

Platelet aggregation inhibitors are indicated for the secondary prevention of formation of arterial thrombosis (Table 12).

Table 12: The different types of platelet aggregation inhibitors available

Medication	Indications
Acetylsalicylic acid *(Cardio: 80mg 1dd; Neuro: 30mg 1dd)*	• Secondary prevention after TIA or non-disabling stroke, provided intracerebral haemorrhage has been excluded • Secondary prevention of myocardial infarction • Treatment of acute coronary syndrome • Prevention of cardiovascular morbidity in patients with stable angina pectoris

	• Prevention of graft occlusion after aortic-coronary bypass • Peripheral arterial disease
Clopidogrel *(75mg 1dd)*	• Acute coronary syndrome/myocardial infarction • After implantation of coronary stents in combination with acetylsalicylic acid • After a TIA or stroke
Dipyridamole *(200mg 2dd1)*	• Secondary prevention after TIA or non-disabling stroke in combination with acetylsalicylic acid

3. Side effects

Objectives: The main side effect of platelet aggregation inhibitors is the increased risk of bleeding. This risk is highest in elderly patients. The following drug interactions increase the risk of bleeding: corticosteroids, NSAIDs, and SSRIs. In most surgeries, acetylsalicylic acid can be continued. If a lot of blood loss is expected during an invasive procedure and there is an acute situation, a platelet transfusion may be given.

The main side effect of all medications which intervene in the blood clotting system is, of course, the increased risk of bleeding. The benefit of anti-coagulation therapy must therefore be balanced against the increased risk of this potentially serious side effect. Older people are the main patient group at risk of bleeding.

4. Interactions

Given that acetylsalicylic acid (ASA) is used as an inhibitor of platelet aggregation, the same interactions that are associated with the use of aspirin as a pain reliever and fever-reducing agent are applicable (Table 13).

Table 13: The side effects as a result of drug interactions with acetylsalicylic acid

Drug	Side effect
• Corticosteroids • NSAIDs • SSRIs	• Bleeding

5. Haemorrhage linked to antiplatelet use

For patients taking aspirin, greater blood loss is expected after an invasive procedure. In some cases, it is therefore advisable to discontinue use at least five days prior to surgery (Table 14).

Table 14: Guidelines regarding antiplatelet use and invasive procedures

Situation	Guideline
Stopping treatment in non-acute situations	A few days before the surgery the medication must be stopped: • ASA/clopidogrel: stop five days before surgery. • Dipyridamole: stop one day in advance. The medication can be continued the day after surgery.

Subacute situations	Regarding non-elective surgery, where local haemostasis is an option, it is preferred to wait 3 days before initiating the procedure.
Acute situations	In acute situations, desmopressin (DDAVP) may be administered preoperatively. Most surgical procedures can be carried out with the patient still on aspirin. DDAVP improves the adhesion of platelets to the endothelium and therefore shortens the bleeding time. ASA has to be stopped in procedures where haemostasis cannot be visualised, such as in neurosurgery, head and neck surgery, and liver or kidney biopsies. If surgery cannot be delayed, a platelet transfusion should be given preoperatively. Platelets can be given 40 minutes after administration of ASA and 12 hours after administration of clopidogrel. Regarding dipyridamole, giving a platelet transfusion has no effect, because the platelets will not work properly as long as this drug is present in the blood.

A.2. VITAMIN K-ANTAGONISTS/COUMARINS

Objectives: Coumarin derivatives such as warfarin and phenprocoumon are vitamin K antagonists. Four important clotting factors (factor II, VII, IX and X) are dependent on vitamin K. Because the $T_{½}$ of acenocoumarol (8-11 hours) is much shorter than that of phenprocoumon (160 hours), the effect of acenocoumarol lasts only a few days, while the effect of phenprocoumon may persist for several weeks.

Coumarin derivatives such as warfarin and phenprocoumon are the so-called vitamin K antagonists. Four major coagulation factors (factor II, VII, IX and X, protein C and -S) are dependent on vitamin K. When using coumarin derivatives, the concentration of these factors in the blood decreases, and this leads to a decrease in fibrin formation. Because the coumarin only starts working after 2-3 days, heparin, which works immediately, is co-administered for one week to bridge this interval.

1. Medicinal properties

The available coumarin derivatives differ from each other with regards to time until effect and duration of action (Table 15).

Table 15: Pharmacological differences between coumarin derivatives

Drug	Pharmacological difference
Acenocoumarol *(Sintrom)*	Acenocoumarol has a half-life of 8 hours and a maximum effect after 36-48 hours. The effect lasts several days.
Phenprocoumon *(Marcoumar)*	Phenprocoumon has a half-life of 160 hours and a maximum effect after 48-72 hours. The effect lasts for a few weeks. The advantage of phenprocoumon is that a more stable concentration in the blood can be achieved.

2. Indications

Objectives: Acenocoumarol and phenprocoumon are indicated for atrial fibrillation, pulmonary embolism, deep vein thrombosis and in patients with mechanical valve prostheses. The risk of a TIA or stroke in patients with atrial fibrillation can be calculated using the CHADS2 score (recently adapted to CHA2DS2-Vasc score). With a score of 2 to 6, vitamin K antagonists are indicated. At a score of 0 to 1, the risk of a stroke or TIA is small, so no vitamin K-antagonist is indicated.

Coumarin derivatives are indicated in, among other things, patients with atrial fibrillation (CHADS2 score, Table 18), mechanical valve prosthesis, pulmonary embolism and deep vein thrombosis.

The CHADS2 score/ CHA2DS2-VASc score

In patients with atrial fibrillation, the risk of a TIA or stroke is calculated using the CHADS2 score. This scoring system has recently been updated and is now called CHA2DS2-Vasc score (Table 18). With a score of 0 to 1, no medication or vitamin K antagonist is indicated. With a score of 2 to 6, vitamin K antagonists are recommended.

3. Side effects

Objectives: The main side effect is the risk of bleeding. This risk is greatest in patients who have poor therapy adherence, with irregular alcohol intake and febrile illness. On the basis of the INR value, the correct dosage of medication is calculated. This value should be checked regularly. If bleeding occurs when using vitamin K antagonists, vitamin K may be administered. With phenprocoumon, vitamin K administration should be repeated, given the long $T_{½}$. In the case of severe bleeding, Prothrombin Complex Concentrate (PCC) can be administered, which has an immediate effect.

The main side effect of coumarin derivatives is bleeding. Severe bleeding such as cerebral haemorrhage, haemorrhages that require hospitalisation, or muscle and joint bleeding, occurs in 1-2% of the patients treated with these drugs annually.

4. Interactions

Objectives: The use of NSAIDs and corticosteroids (ulcerogenic) in combination with vitamin K antagonists increases the risk of bleeding and gastrointestinal complications. Concomitant use of the antibiotic cotrimoxazol, a CYP2C9 enzyme inhibitor, provides a rapid, potent increase in the INR and risk of bleeding. This combination should therefore be avoided. Certain anticonvulsants (e.g. phenytoin and carbamazepine) and the antibiotic rifampicin are enzyme inducers, and therefore they decrease the effect of coumarin derivatives - the risk of thrombosis is therefore increased.

Treatment with coumarin derivatives is guided by the INR and frequent dose adjustments are necessary. There are many factors and medications that may interfere with the effects of coumarin derivatives (Table 16).

Table 16: Factors which may influence the efficacy of coumarin derivatives

Factor	Resultant effect
Febrile disease	The enzymes that degrade coumarin derivatives function less well, allowing the INR to rise or peak above the target range.
Low intake of vitamin K	Poor intake of vitamin K can cause the INR to peak. Therefore, the INR is checked more frequently during hospitalisation than when at home (acenocoumarol use every 2-3 days and with phenprocoumon use every 3-4 days).
Irregular alcohol intake	The effects of coumarin derivatives can be enhanced by excessive alcohol use.
NSAIDs, platelet inhibitors, corticosteroids	NSAIDs and salicylates should be very conservatively prescribed to patients using coumarin derivatives, as they increase the risk of bleeding. The clotting time does not increase. Acetylsalicylic acid at analgesic doses (>300mg daily) is contraindicated.
Co-trimoxazole	Co-trimoxazole is a drug that greatly potentiates the effects of coumarin derivatives because it inhibits the metabolism of coumarins by CYP2C9
Anticonvulsants *(carbamazepine, phenytoin)*, rifampicin	Anticonvulsants and rifampicin are drugs that decrease the effects of coumarin derivatives (enzyme inducers). At the initiation of coumarin treatment, a higher dose should be given to the users of these medications to get the INR right.

5. Haemorrhage linked to anti-coagulant use

Most people who use coumarin derivatives as anti-coagulants have a target-INR of between 2.5 and 3.5 (an optimal INR value is between 0-1). The effect of coumarin derivatives can be inhibited by the administration of vitamin K. The required dose of vitamin K depends on the INR value, the indication for inhibiting coumarin derivatives, and the INR target value. During active bleeding the target INR is <1.7 (Table 17).

Table 17: Guidelines for haemorrhage linked to anti-coagulant use

Severity of situation	Guideline
Non-life-threatening situations	5mg of vitamin K orally or IV. Vitamin K after oral administration is effective after 8 hours; when administered intravenously, it has an effect after 6 hours. It is fully effective after 24 hours, and stays active for a further 24 hours. With phenprocoumon, vitamin K administration should be repeated, given the long half-life of phenprocoumon.
In life-threatening situations	Vitamin K should be given in combination with Prothrombin Complex Concentrate (PCC). The effect is immediate and can be controlled by repetition of the INR measurement.

Invasive surgery with anti-coagulant use

Before undergoing an invasive procedure, coumarin derivatives must always be stopped. Bridging treatment, which is given during the period between the stopping of the coumarin derivatives and the procedure, consists of LMWH or, upon exception, unfractionated heparin. In the management of atrial fibrillation, the CHADS2 score (which was recently adapted into the CHA2DS2-Vasc score (Table 18)) is used to assess whether bridging is necessary and if so what form of therapy is appropriate. With a CHADS2-score of zero to two, or a CHA2DS2VASc-score of zero to four, there is insufficient indication for bridging. In Table 19 the absolute indications for bridging are summarised.

Table 18: CHA2DS2-VASc score

		Score
C	Congestive heart failure/ LV dysfunction	1
H	Hypertension	1
A2	Age > 75 years	2
D	Diabetes Mellitus	1
S2	Stroke/TIA/ thrombo-embolism	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex (female = 1/male = 0)	1
	Maximum score	**9**

Table 19: indications for bridging therapy with heparin in cardiovascular risk management

Always stop the vitamin K antagonist!	
Bridging (therapeutic) • LMWH • Heparin i.v. (rarely)	**Bridging therapy indicated in patients with:** • Atrial fibrillation CHA2DS2-VASc score ≥ 8 • Recurrent DVT/LE or recent DVT/LE <3 months • Mechanical or biological artificial valve (CAVE especially mitral valve), rheumatic valve disease • Biological heart valve (surgery < 3 months)

A.3. HEPARINS

Objectives: Heparins (heparin, nadroparin) are direct inhibitors of activated clotting factors (especially thrombin and factor Xa) and can only be administered parenterally.

Heparin and low molecular weight heparins both belong to the heparin group (Table 20).

Table 20: The mechanisms of action of drugs in the heparin group

Drug	Mechanism of action
Heparin	Heparin activates antithrombin III, which results in secondary neutralisation of activated clotting factors. This affects in particular factor IIa (thrombin) and activated factor X (Fig. 5). As a result, the conversion of fibrinogen to fibrin is inhibited. One drawback is that it must be administered intravenously or subcutaneously, and that the potency of the anti-coagulant effect is highly variable. The anti-coagulant effect must therefore be frequently checked (by means of the aPTT).
Low molecular weight heparin (LMWH): • Nadroparin (Fraxiparine) • Enoxaparin (Clexane)	Low molecular weight heparins contain fragments of heparin which have a low molecular weight. LMWH has a 2-3 times higher anti-factor Xa activity and a weaker anti-factor IIa effect than that of unfractionated heparin. The anti-coagulant effect can therefore not be reliably measured by the aPTT, but by an anti-factor Xa activity test. LMWH has two major advantages: (1) the $T_{½}$ is much longer, so that a proper anti-coagulation state can be achieved by subcutaneous administration once or twice/day and (2), the anti-coagulant activity can be predicted in a far more reliable way, such that frequent coagulation checks are not necessary. LMWH is predominantly eliminated by the kidney, as opposed to unfractionated heparin. Therefore, one should be aware of the risk of LMWH accumulation in patients with renal failure. Because of the risk of bleeding, the dose of LMWH must be adapted depending on the renal function.

1. Indications

Objectives: Heparins are used as thromboprophylaxis and to bridge the time until the start of the effect of coumarin derivatives (or during interruption of these drugs).

The heparin group is used as prophylaxis and for therapy of venous and arterial thromboembolic disorders, mainly as an introduction to therapy with coumarin derivatives. Prophylactic anti-coagulant therapy is started six to eight hours after a surgical procedure (Table 21).

Table 21: Thromboprophylaxis Guidelines[2]

Clinical scenario	Guideline
Surgical patients not on anti-coagulants prior to procedure	*No prophylaxis is indicated when:* • Active mobilisation can be achieved immediately after surgery • The intervention is short (< 30 min) • Risk factors for venous thrombosis are absent

[2] For Healthcare CBO. Central guidance body for peer review. Directive diagnosis, prevention and treatment of venous thromboembolism and secondary prevention of arterial thrombosis.
Utrecht: 2009.9

	Standard prophylaxis (= nadroparin 1dd 2850 unit) indicated where: • Interventions > 30 minutes • Duration of prophylaxis in this case is at least 5 days or until the patient is mobilised.
	Intensive prophylaxis (= nadroparin 1dd 5700 units) indicated when: • Patient had thrombosis < 6 months ago.
Surgical patients taking an anti-coagulant	Stop current anti-coagulant therapy and bridge using LMWHs (Table 19).
Non-surgical patients	Prophylaxis indicated in: • Obstetric/gynaecological intervention • Immobility lasting >4 days in the presence of at least 1 risk factor, see Padua Prediction Score at https://www.mdcalc.com/padua-prediction-score-risk-vte

2. Side effects

Objectives: The main side effect of heparins is the risk of bleeding. This risk is particularly high if the patient is also taking corticosteroids and NSAIDs. LMWH is predominantly eliminated by the kidney, in contrast to unfractionated heparin. This means that one must be aware of the risk of accumulation of LMWH in patients with renal failure. If this is the case, blood levels should be regularly checked to determine the required dose of nadroparin. If necessary, anti-factor Xa levels can be measured. Because of the risk of bleeding, the dose of LMWH should be adapted to the renal function. Bleeding in a patient using heparin is treated with protamine.

The main side effect of heparin is bleeding. With the use of LMWHs, there is an increased risk of haemorrhage in patients with renal insufficiency. The anti-factor Xa levels are often increased in patients with poor kidney function. To prevent the occurrence of bleeding in this situation, a dose adjustment is required based on the anti-factor Xa levels. A relatively uncommon complication of heparin treatment is heparin-induced thrombocytopenia (HIT). Although HIT occurs in less than 1% of patients treated with heparin, it is nevertheless necessary to check of the platelet count of these patient weekly in order exclude this complication.

3. Interactions

The anti-coagulant effect of heparin or LMWH can be enhanced by drugs that affect the activity of the platelets or the coagulation system, such as NSAIDs, salicylates, vitamin K-antagonists and substances which have ulcerogenic effects, such as corticosteroids (prednisone).

Table 22: Management of haemorrhage associated with heparin use

Heparin responsible	Guideline	
Unfractionated heparin: The $T_{1/2}$ is about 1.5-2 hrs and increases with increase of the dose	Non- acute situations: stop heparin	Beware of anaphylaxis!
	Acute situations: life-threatening or intracranial haemorrhage. Rapidly inhibit heparin with 1mg protamine (administered intravenously very slowly)	

LMWH: The $T_{1/2}$ is about 3-4 hrs	Acute situations: Protamine can be administered intravenously (slowly). However, this is only partially effective because, even at high doses, the anti-factor Xa activity of LMWH is only neutralised by a maximum of 50%.	

A.4. DIRECT ORAL ANTICOAGULANTS (DOACs)

Objectives: The group of direct oral anti-coagulant drugs, also known as new or non-vitamin K oral anti-coagulants (NOACs) include dabigatran (inhibitor of factor II), apixaban, edoxaban, and rivaroxaban (inhibitors of factor Xa).

DOACs have a direct interaction with activated proteins in the coagulation cascade. Dabigatran binds directly and reversibly to factor II (thrombin) to prevent its action. Apixaban, edoxaban, and rivaroxaban are direct selective inhibitors of factor Xa. These medicines are relatively new.

1. Medicinal properties

Table 23: Pharmacological properties of DOACs

DOAC	Pharmacological properties
Dabigatran	Dabigatran has a half-life of 12-14 hours. The half-life is prolonged with impaired renal function (27-34 hours at eGFR <30 ml / min) because dabigatran is cleared by the kidney to a significant extent (80%).
Rivaroxaban	The half-life is 5-9 hours (11-13 hours in elderly patients). Rivaroxaban is 33% cleared by the kidney. Given that rivaroxaban is only excreted by the kidney to a small extent, the T ½ is hardly prolonged with renal function loss.
Apixaban	The half-life is approximately 12 hours. Apixaban is 27% cleared by the kidney. Apixaban is only excreted by the kidney to a small degree, therefore impaired renal function does not significantly prolong the T ½.
Edoxaban	The half-life is 10 - 14 hours. Edoxaban is 35% cleared by the kidney; in practice the T 1/2 is hardly prolonged if renal function loss occurs.

Because there is a delay of 2-3 days before an effect is seen, heparin (which has an immediate effect) is commenced concurrently with DOACS. This heparin course is usually prescribed for 7 days.

2. Indications

Objectives: DOACs are indicated in patients with non-convulsive atrial fibrillation, a CHA2DS2-VASc score greater than 1, deep venous thrombosis or pulmonary embolism.

The indications for DOACs overlap with the indications for vitamin K antagonists. DOACs are currently not prescribed for patients with a mechanical valve prosthesis, atrial fibrillation with a concurrent valve abnormality, mitral stenosis, kidney insufficiency (eGFR<30ml/min) or patients undergoing haemodialysis. Studies assessing the efficacy of DOACs in the primary and secondary prevention of heart and vessel disease are still ongoing.
Disadvantages of DOACs are a reduced ability to monitor therapy adherence, the relative unfamiliarity of the doctors with these drugs and the fact that no antidote is available for DOACs. Benefits are ease of use, shorter duration of action and fewer interactions with food and medications.

A further advantage with DOACs is that intracranial bleeding occurs less frequently compared to vitamin K antagonists. A choice is made based on patient characteristics.

3. Side effects

Objectives: The main side effect is the risk of bleeding. The risk of haemorrhage whilst using dabigatran is greater if there is renal impairment, e.g. as a result of nephrotoxic medication. The level of apixaban, edoxaban and rivaroxaban in the blood may also rise with concomitant use of verapamil or itraconazole. This occurs due to enzyme inhibition by verapamil and itraconazole. To prevent the bleeding occurring in these situations, the dose should be adjusted, or the DOAC should be switched to a vitamin K antagonist.

The main side effect of DOACs is the occurrence of bleeding. With dabigatran use, the risk of bleeding is greater if there is a renal insufficiency. Dabigatran is 80% renally excreted and renal function loss thus has a major effect on clearance. To prevent the occurrence of bleeding, a dose adjustment is therefore required or the DOAC should be switched to a vitamin K antagonist. The remaining DOACs are only 30% renally cleared, so the effect of renal function loss on clearance is limited.

4. Interactions

The blood level of dabigatran may be higher when prescribed concomitantly with nephrotoxic medications. Verapamil and Itraconazole cause a higher blood level of apixaban, edoxaban and rivaroxaban due to enzyme inhibition. In the above cases, the dose of DOACs should be adjusted to prevent bleeding, or be switched to a vitamin K antagonist.

5. Bleeding while on DOACs

Bleeding during treatment with dabigatran can be stopped with idaruzicimab. In case of bleeding as a result of apixaban, rivaroxaban or edoxaban, four factor concentrate (Cofact®) may be given, however, its effect is limited.

An antidote is available for dabigatran, namely idaruzicimab. If bleeding occurs under apixaban, edoxaban or rivaroxaban, four-factor concentrate may be given, however its effect is limited.

Objectives: The following drugs should be known: acenocoumarol, warfarin, phenprocoumon, aspirin, clopidogrel, heparin, nadroparin, protamine, vitamin K, co-trimoxazole, prednisone, paroxetine, carbamazepine, dabigatran, apixaban, edoxaban, and rivaroxaban.

C. Cardiovascular agents

Cardiovascular agents are divided into the following groups of medications:

A. Diuretics:
   - A.1. Thiazide diuretics
   - A.2. Loop diuretics
   - A.3. Potassium-sparing diuretics

B. β-adrenergic receptor blockers:
   - B.1. Selective β-blockers
   - B.2. Non-selective β-blockers

C. Calcium channel blockers (CCBs):
   - C.1. Dihydropyridines
   - C.2. Other calcium antagonists (diltiazem, verapamil)

D. RAS-inhibitors:
   - D.1. ACE-remmers
   - D.2. Angiotensin II (AT_1)-antagonists or Angiotensin receptor blockers (ARBs)

E. Cardiac glycosides

F. Nitrates

The cardiovascular agents discussed in this chapter are mostly used for their anti-hypertensive effect. For the lowering of blood pressure, roughly three mechanisms can be distinguished:

1) Promoting arterial vasodilatation, which will lead to a reduction of the total peripheral resistance (calcium antagonists, RAS inhibitors, ARBs)
2) Decreasing the preload by venous vasodilation (nitrates, RAS inhibitors) or absolute decrease of circulating volume (diuretics)
3) Reducing the contraction force of the heart or frequency of the heartbeat (β-blockers, diltiazem, verapamil)

A. DIURETICS

Diuretics increase the excretion of sodium chloride and water by reducing the reabsorption of these electrolytes in the kidneys. There are several types of diuretic, namely loop diuretics, thiazide diuretics and potassium-sparing diuretics. They exert their effect on different parts of the kidney. (Fig. 10, Table 24).

Table 24: Mechanism of action of diuretics

Diuretics	Mechanism of action	
Loop diuretics *(bumetanide, furosemide)*	Loop of Henle: • Inhibition of $Na^+/K^+/2Cl^-$ cotransporter • A higher concentration of Na^+ in the distal tubule and the first part of the collecting duct activates the Na^+/K^+ -counter transport with increased K^+ excretion	
Thiazide diuretics *(chlorothiazide, hydrochloro-thiazide)*	Distal tubule: • Inhibition of Na^+/Cl^- cotransporter • The presence of larger amounts of Na^+ in the distal tubule and the first part of the collecting duct activates the compensating Na^+/K^+ exchange transport leading to more K^+ excretion	
Potassium-sparing	Cortical collecting duct:	

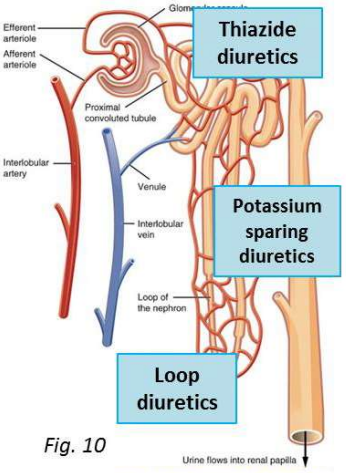


Fig. 10

OpenStax College: http://cnx.org/content/col11496/1.6/

diuretics *(Spironolactone, amiloride, triamterene)*	• Blocking of the aldosterone receptor (spironolactone, eplerenone) thereby limiting Na^{+}/ K^{+} exchange (in/out). • Inhibit cortical Na^{+} channels (triamterene, amiloride) • Weak diuretic effect	

1. Medicinal properties

Objectives: Diuretics inhibit tubular electrolyte reabsorption and increase their excretion in the urine. Loop diuretics are indicated in heart failure, thiazide diuretics are indicated in hypertension and mild heart failure. Potassium-sparing diuretics are used in addition to a loop or thiazide diuretic to prevent hypokalemia. Spironolactone is indicated in NYHA III heart failure, it limits adverse remodeling of the heart and hypokalemia. The diuretic efficacy of spironolactone is small. Renal impairment decreases the effect of loop and thiazide diuretics.

Table 25: The indications and pharmacology of diuretics

Diuretics	Indication		Kinetics
Loop diuretics	• Heart failure (oedema, dyspnoea caused by congestion) • Cirrhosis (oedema, congestion)		Effect duration of furosemide is 6 hours (Lasix = lasts for six hours). For patients with renal impairment, doses should be raised because the target (Na^{+}/K^{+}/2CL^{-} ion channel) is on the luminal site of the tubule.
Thiazide diuretics	• Hypertension • Dyspnoea and oedema in mild heart failure		When renal function is impaired, thiazides are less effective and a loop diuretic is thus indicated.
Potassium-sparing diuretics	Amiloride, triamterene	Preventing K+ depletion when using loop / thiazide diuretics	
	Spironolactone	• Heart failure NYHA 3, due to its positive effect on adverse cardiac remodeling • Avoiding K+ depletion • Be aware of the development of hyperkalemia	

2. Side effects

Objectives: Loop and thiazide diuretics can lead to dehydration, hypokalaemia (resulting in e.g. arrhythmias, muscle weakness) and hypotension (dizziness, especially when standing up, tendency to fall). When using thiazide diuretics, there is a risk of hyponatraemia (resulting in nausea, confusion, tendency to fall). Loop diuretics can also cause renal failure. Potassium-sparing diuretics can cause hyperkalaemia. This risk is increased in patients with diabetes mellitus, renal failure or heart failure.
Adding a potassium-sparing diuretic or a RAS-inhibitor can prevent hypokalaemia. Hyperkalaemia can be treated by adding calcium gluconate (this reduces the severity of arrhythmia but does not lower plasma potassium), insulin/glucose or sodium polystyrene sulfonate. The risk of falling is increased in elderly patients. With fever, diarrhoea and vomiting, there is an increased risk of dehydration, which can be treated with an intravenous saline infusion.

The side effects of diuretics are usually limited to disturbances of the water and electrolyte balance (Table 26). In elderly patients a higher dose of loop and thiazide diuretics is sometimes prescribed; since these agents act as they are being cleared by the kidneys, and renal function is often decreased in elderly patients, a higher dose is required to achieve the required effect.

Table 26: Common side effects as a result of diuretic therapy				
Side effect	**Medication**	**Risk-factors**	**Clinical symptoms**	**Management**
Reduced effective circulating volume	Thiazide diuretics Loop diuretics	Old age (greater risk of falling). Fever, diarrhoea, vomiting and anorexia increase the risk of dehydration.	Hypotension (tendency to fall, dizziness) dehydration	- Regularly monitor hydration state - Rehydration with physiological saline - Stopping the medication
Hypokalaemia	Thiazide diuretics Loop diuretics	Old age, reduced intake of potassium through diet, diarrhoea.	Arrhythmias, muscle weakness	- Potassium supplementation (drink/tablets) - Potassium-sparing diuretic - RAS-inhibitor
Hyponatraemia	Thiazide diuretics	Old age, reduced intake of protein and salt	Nausea, confusion, tendency to fall. Hyponatraemia can occur within two weeks, but also after one or two days, or after a single dose. Correcting this too rapidly can cause central pontine myelinolysis.	Check sodium levels 5 to 9 days after start of the diuretic if patient is > 80 years, > 70 years + SSRI or has ongoing illness (vomiting, diarrhoea)
Hyperkalaemia	Potassium-sparing diuretics	Diabetes mellitus, heart failure, renal failure and old age	Dizziness while standing or getting up, tendency to fall, dehydration, hypotension, renal failure.	- Prevent by checking the K^+ level before and after adding the diuretic; if patient is > 70 years + has risk factor, limit K^+ intake. - Calcium gluconate, insulin/ glucose sodium polystyrene sulfonate. - Dialysis

3. Interactions

Table 27: Common drug interactions with opioids	
Interaction with medication	**Side effect**
• Blood pressure lowering agents • Opiates • Benzodiazepines	Tendency to fall
• SSRIs (SIADH)	Hyponatraemia
• NSAIDs • RAS-inhibitors	Renal failure and/or hyperkalaemia

• NSAIDs	Reduced effect

B. β-ADRENERGIC RECEPTOR BLOCKERS

There are two types of β-receptors: β1- and β2-receptors (Table 28). The blocking of β1- and β2-receptors may lead to a fall in blood pressure, a decrease in cardiac output and to an increase of bronchial secretion and constriction of the bronchioles (Fig. 9). Drug therapy with β-blockers is aimed at improving ventricular filling during diastole, and reducing cardiac ischemia. β-blockers can also be classed according to whether they are selective or non-selective.

Table 28: Pharmacological properties of the β-Adrenergic Receptors

Receptor	Location
β1-receptor	Located mainly in the pacemaker cells of the myocardium. Stimulation causes: • Tachycardia • Increase in cardiac output by increasing heart rate and stroke volume • Accelerated impulse conduction in the heart
β2-receptor	Located in the walls of certain blood vessels and airways. Stimulation causes: • Bronchodilation • Vasodilation of blood vessels in striated muscle (reflex tachycardia)

Table 29: Selective Vs Non-selective β-blockers

Non-selective β-blockers (propranolol, labetalol, sotalol)	Selective β-blockers (atenolol, bisoprolol, metoprolol) XR= extended release = long acting
Blockade of β1- and β2 receptors will diminish heart rate and oxygen use by the heart. β2 blockade will impair smooth muscle relaxation in the respiratory tract. Sotalol is also a Class III antiarrhythmic. Labetalol is also an alpha-blocker (and therefore a vasodilator).	The selective β-blockers act mainly on the β1-receptors.

1. Indications

Objectives: β-blockers will lower the heart rate, blood pressure and decrease cardiac contractility. They are indicated for atrial fibrillation, hypertension, heart failure and secondary prevention after a myocardial infarction.

β-blockers are useful in the treatment of circulatory disorders particularly for the following indications:

- Atrial fibrillation (rate control achieved by all β-blockers, sotalol also causes rhythm control)
- Angina pectoris, secondary prevention after acute myocardial infarction
- Hypertension
- Stable chronic heart failure with reduced systolic ventricular function

2. Side effects

Objectives: The main side effects of β-blockers are: hypotension, bradycardia and increased tendency to fall. Sotalol can cause arrhythmias; this risk is increased if a patient has hypokalemia and/or an impaired renal function, because sotalol is excreted by the kidneys.

The main side effects that occur with the use of β-blockers are: hypotension, bradycardia and increased tendency to fall. With β-blockers one should mainly be aware of orthostatic hypotension in elderly patients, combined with an increased risk of falling. Arrhythmias may occur with the use of sotalol (QT prolongation and torsades de pointes). In patients with hypokalaemia and/or loss of renal function, there is a greater risk of arrhythmias. Sotalol is renally cleared and has a narrow therapeutic index. In elderly patients this medication must therefore be prescribed with caution.

3. Interactions

Table 30: Common drug interactions with β-blockers

Drug interaction	Side effects
• Verapamil, diltiazem, other negative chronotropic drugs	Bradycardia
• Agents that lower potassium levels (thiazides, loop diuretics) • Agents that decrease renal function (NSAIDs) • Agents that prolong Q-T interval (some antipsychotic drugs)	Arrhythmia (interaction occurs predominantly with sotalol use)

C. CALCIUM CHANNEL BLOCKERS

Objectives: Calcium channel blockers can be divided into dihydropyridines (amlodipine, nifedipine) and other agents (verapamil, diltiazem). Dihydropyridines block L-type calcium channels on smooth muscle cells, thereby reducing vascular tone. This causes relaxation of coronary as well as peripheral blood vessels. The latter effect explains why CCBs are used to treat hypertension. The main side effects are hypotension and risk of falling. Verapamil and diltiazem are more cardiac specific, cause bradycardia, and need to be prescribed with great caution when combined with a β-blocker due to the risk of slowed conduction and even heart block.

Calcium channel blocking agents can be classified according to their chemical structure and effect:

C.1. Dihydropyridine compounds, including nifedipine, amlodipine, and barnidipine.
C.2. Other calcium channel blockers, such as verapamil and diltiazem

1. Mechanism of action

For the contraction of muscle cells, calcium ions need to be mobilised from intra- and extracellular stores. Free calcium ions are also required for the conduction of impulses in the SA and AV node of the heart. Calcium channel blockers block the inflow of extracellular calcium in vascular smooth muscles as well as myocardial cells leading to vascular relaxation and reduction in cardiac conduction velocity.
This results in the following effects:

- Reduction in heart rate by delaying the conduction in SA and AV nodes
- Vasodilatation (coronary and systemic)

Calcium channels located in the vessel wall differ from those present in the heart. This is why dihydropyridines and other calcium channel blockers have organ specific effects (Table 31).

Table 31: Pharmacological properties of calcium channel blockers

	Dihydropyridines (amlodipine, nifedipine)	**Other calcium channel blockers** (verapamil, diltiazem)
Mechanism	Vasodilating effect in particular. Dihydropyridines have hardly any effect on the SA and AV conduction.	Influence the SA and AV conduction and have a vasodilating effect. Verapamil and diltiazem can be included in the treatment of atrial fibrillation in order to decrease the heart rate.
Indications	Hypertension	Hypertension and atrial fibrillation

Side effects	Unwanted vasodilatory effects such as headaches, flushes, dizziness and reflex tachycardia. This may give rise to hypotension, increased tendency to fall and peripheral oedema. Constipation (smooth muscle relaxation).	In addition to the vascular side effects listed for dihydropyridines, verapamil and diltiazem also block cardiac specific calcium channels, causing bradycardia negative inotropy.
Interactions	Inhibitors or inducers of CYP3A4 may increase or diminish the effects of some dihydropyridines respectively.	Caution should be exercised when simultaneously using β-blockers, because of the risk of bradycardia and AV conduction disorders.

D. RAS-INHIBITORS

The renin-angiotensin system (RAS) controls the electrolyte balance and blood pressure (BP). When BP decreases and Na^+ levels in the blood drop, renin is secreted by the juxtaglomerular cells in the kidney. This causes the cleavage of the oligopeptide angiotensin I, which is hydrolysed by angiotensin converting enzyme (ACE) into angiotensin II. This hormone has vasoconstrictive properties and induces the release of aldosterone from the adrenal cortex, resulting in an increase in BP, sodium and water retention and an increased potassium excretion (Fig. 11).

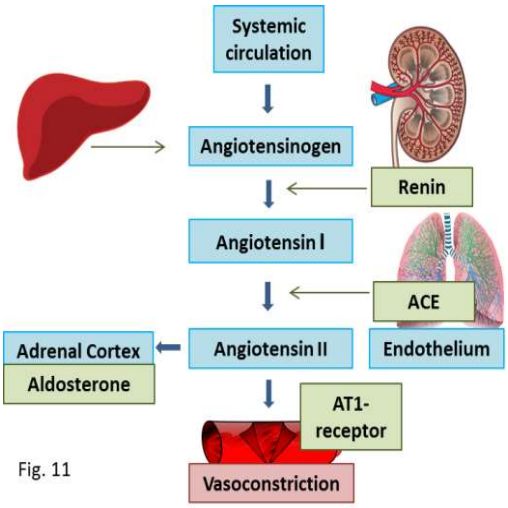


Fig. 11

There are two groups of RAS-inhibitors which each target a different part of the system (all of them inhibit the effects of angiotensin II):

D.1. ACE inhibitors

D.2. AT II receptor (AT_1) antagonists or angiotensin receptor blockers (ARBs).

D.1. ACE INHIBITORS

ACE inhibitors such as captopril, enalapril and lisinopril act on the renin-angiotensin system (RAS). Inhibition of the formation of AT-II by ACE inhibitors results in a lower blood pressure in patients with hypertension, and mediates the regression of cardiac hypertrophy, vasodilation and the reduction of hyperplasia of vascular smooth muscle cells. The perfusion pressure in the glomerulus is also reduced, which is beneficial for patients with diabetic nephropathy.

2. Indications

Objectives: RAS inhibitors act on in the renin-angiotensin system. They are indicated in the treatment of hypertension, heart failure and diabetic proteinuria.

Table 32: Indications and mechanisms of action of beta-blockers

Indication	Mechanism of action
Hypertension	In patients with renal impairment, caution is required, particularly in (double-sided) renal artery stenosis; in this situation, the RAS system is strongly stimulated and ACE inhibitors and ARBs can have a powerful effect (in terms of reduction in blood pressure and renal failure).

Heart failure	Beta-blockers' beneficial effects on the symptoms of heart failure are a result of vasodilation, which reduces both the pre- and afterload. In chronic heart failure, ACE inhibitors and ARBs have a beneficial effect on hypertrophy of the heart muscle, and on the survival of the patient.
Angina pectoris/ acute coronary syndrome	Inhibition of ACE causes, both through an increase in bradykinin and a decrease of AT II, its two most important effects: vasodilation and inhibition of growth of the cardiac ventricle and the smooth muscles in the vascular wall.
Diabetic proteinuria, microalbuminuria	By inhibiting the formation of AT II or blockade of the AT_1 receptor, the arteriolar resistance in the efferent arteriole of the kidney decreases and therefore the pressure in the glomerular capillaries decreases.

3. Side effects

Objectives: The main side effects of ACE inhibitors include: hyperkaliemia, renal failure, hypotension, tendency to fall and angioedema of the pharynx area. It is recommended to start with a low dose and increase it steadily: "start low, go slow". In addition, the risk of falling can be reduced by taking the ACE inhibitors in the evening.

Table 33: Side effects of ACE inhibitor therapy

Side effect	Physiological response
(Orthostatic) hypotension, tendency to fall	Dizziness, weakness, and syncope may also occur. It is recommended to start with a low dose and increase it carefully to avoid hypotensive reactions (especially in elderly patients!).
Renal failure	ACE inhibitors can induce a slight increase in serum creatinine of approx. 10%. With regard to nephrotoxic diseases, these drugs limit proteinuria and slow down the deterioration of renal function. On the other hand, they may cause a severe reduction in renal function, especially when kidney function is already reduced or when a renal artery stenosis is present (Fig. 12). In such conditions, the RAS system is vastly stimulated, and blood pressure and renal function depend heavily on the presence of AT II. If this is the case, ACE inhibitors can have a very powerful effect (in terms of drop in blood pressure and renal function loss).
Hyperkalaemia	The plasma potassium levels may increase due to a reduced aldosterone secretion, especially if renal function is also impaired.
Angioedema of pharyngeal area	Angioedema with a swelling of face, lips, tongue, glottis or larynx is a rare (0.1-0.5%) but potentially fatal side effect.
Tickling cough	In 25% of patients ACE inhibitors may cause a tickling cough.

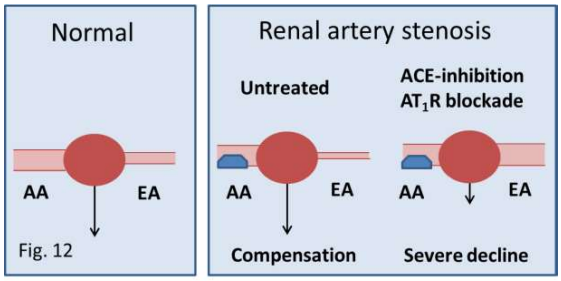


Fig. 12

4. Interactions

Table 34: Common drug interactions with β-blockers		
Interaction with medication	**Side effect**	**Risk factors for adverse effects**
Diuretics, NSAIDs	Renal failure	Dehydration, diarrhoea, vomiting, fever, anorexia
Potassium-sparing diuretics	Hyperkalaemia	Diabetes mellitus, heart failure, renal failure
Diuretics	Hypotension	Old age, dehydration
Antihypertensives Opiates, Benzodiazepines	Risk of falling	Old age, dehydration

D.2. ANGIOTENSIN II (AT_1)-ANTAGONISTS

AT_1 antagonists (losartan, valsartan) affect the RAS system by selectively blocking the AT_1 receptor. This inhibits the action of ATII, a strong vasoconstrictor which also stimulates the release of aldosterone and which further stimulates the proliferation of the smooth muscle cells. AT_1 antagonists are only indicated as an alternative to an ACE inhibitor, if side effects such as a cough (occurring in up to 25% of patients) or angioedema occur.

E. CARDIAC GLYCOSIDES (DIGOXIN)

Objectives: Digoxin increases myocardial contractility, lowers heart rate and slows AV conduction velocity. It is indicated in heart failure and atrial fibrillation with a rapid ventricular response. The half-life is 40-70 hours. Digoxin is renally cleared and has a narrow therapeutic index. As a side effect, it may cause arrhythmias. Patients with hypokalaemia and renal failure have an increased risk of developing these arrhythmias.

The only cardiac glycoside that is currently on the market is digoxin. It increases the contractility of the heart and decreases heart rate by vagal stimulation. Digoxin is indicated in atrial fibrillation with a rapid ventricular response and heart failure. The drug is partially renally cleared and has a half-life of 40-70 hours. Digoxin binds specifically to the cardiac cells, where accumulation of the drug is needed for its action. To achieve sufficient levels in this compartment, the therapy consists of an initial loading dose (digitisation) followed by a maintenance dose: 0.5mg, 0.25mg, 0.025mg. One disadvantage of digoxin is its narrow therapeutic index; severe symptoms such as arrhythmias can arise if levels become too high.

Table 35: Common drug interactions with cardiac glycosides	
Interaction with medication	**Side effects**
• Drugs that lower potassium levels (loop and thiazide diuretics) • Agents that reduce renal function (NSAIDs)	Arrhythmias
• Verapamil, and other negative chronotropic drugs	Bradycardia

F. Nitrates

Objectives: Nitrates (such as nitroglycerin) are indicated for angina pectoris and in pulmonary oedema / cardiac asthma. Different routes of administration are possible, nitrates can also be used topically (in the form of a patch). A problem with nitrate use as a maintenance treatment is that the patient can develop a tolerance to the drug, such that the beneficial effect diminishes. This can be prevented in most cases by intermittent dosing. The most serious side effect that can occur is a nitrate collapse; this mainly occurs in patients using the fast-acting preparation (for acute chest pain), and the risk is yet greater in patients who are dehydrated. Hence, to prevent this side effect occurring, patients should be instructed not to take the medicine whilst standing.

Nitrates (such as nitroglycerin) have a direct vasodilatory effect on venous blood and coronary vessels. At high, usually intravenous doses, nitrates also have a vasodilatory effect on the arterioles.
Nitrates are converted within the smooth muscle cells of the vessel wall into nitric oxide (NO).
In addition to its vasodilatory effect, NO also inhibits platelet adhesion and aggregation. Furthermore it plays a role in the endocardial function and contractility of the myocardium.

1. Medicinal Properties

Table 36: Pharmacological properties of nitrates

Nitrate	Pharmacological properties
Isosorbide dinitrate (ISDN)	Isosorbide dinitrate has a large first-pass effect; the bioavailability varies from 20-30%. The half-life is 30-60 minutes. Via the oromucosal route of administration, it is resorbed quickly and well.
Isosorbide mononitrate (ISMN)	Isosorbide mononitrate is an active metabolite of isosorbide dinitrate. It does not undergo the first-pass effect, meaning that the plasma levels of the drug fluctuate less compared to isosorbide dinitrate. The half-life is 4-5 hours, and it is only administered orally.

There are different routes of administration of nitrates. ISDN is rapidly and well absorbed oromucosally and can be used in this way to treat an attack of angina. Maintenance treatment is usually given orally, intravenous administration is reserved for severe acute heart failure. ISMN is only administered orally.

A disadvantage of nitrate use as maintenance treatment is that the patient can develop a tolerance to the drug, such that the beneficial effect diminishes. A reduction in the effect can sometimes occur after just 6 to 8 hours. The occurrence of tolerance can in most cases be prevented through the implementation of an intermittent dosing regimen, whereby doses are administered every 8-12 hours. Another way to achieve this is through the incorporation of "nitrate-free" or "low-nitrate" days.

2. Indications

Nitrates are indicated for angina pectoris and in pulmonary oedema / cardiac asthma.

3. Side effects

The most serious side effect that can occur with the use of nitrates is a nitrate collapse. This nitrate collapse occurs mainly when using the fast-acting formulation (for acute chest pain), the risk is greater in patients who are hypovolemic. To prevent these side effects, patients should be instructed not to take the medicine while standing.

Objective: The following drugs should be known: chlorodalidone, hydrochlorothiazide, furosemide, spironolactone, triamterene, metoprolol, sotalol, propranolol, carvedilol, atenolol, nifedipine, amlodipine, diltiazem, verapamil, enalapril, lisinopril, losartan, digoxin, isosorbide dinitrate, isosorbide monitrate, paroxetine, sodium polystyrene sulfonate, KCl drink, oxazepam and diclofenac.

D. Antidiabetics

The main feature of diabetes mellitus is the excessively high blood glucose levels. Under normal conditions, the blood glucose levels range between 4-8 mmol/l. In diabetes mellitus type 1, there is an absolute shortage of insulin as a result of auto-immune destruction of the β-cells of the pancreas. Type 1 diabetes is always treated with insulin. This chapter will primarily focus on the treatment of diabetes mellitus type 2.
In type 2 diabetes mellitus, there is a relative insulin deficiency due to increased insulin resistance in the liver, muscles and adipose tissue, as well as a certain degree of dysfunction of the beta cells in the islets of Langerhans. Insulin resistance is associated with obesity. The first line of treatment therefore consists of caloric restriction and promotion of an active lifestyle. If this is not effective, oral antidiabetic agents such as biguanides (metformin), sulphonylureas, α-glucosidase inhibitors, thiazolidinediones (PPAR agonists Y), GLP-1 agonists or incretin enhancers (DPP4 inhibitors) should also form part of the treatment strategy. Of these, metformin or a sulphonylurea derivative is the first choice drug, given the considerable data available on their long-term safety and efficacy. If oral medications are not sufficient, insulin injections are prescribed.

The following hypoglycaemic agents should be studied for the pharmacotherapy safety test:

A. Oral antidiabetic drugs
   A.1. Metformin
   A.2. SU-derivatives (tolbutamide, glimepiride, gliclazide)
   A.3. SGLT2-inhibitors (dapagliflozin)
B. Insulins

A. ORAL HYPOGLYCAEMIC AGENTS

A.1. METFORMIN

Metformin inhibits glucose production in the liver, inhibits glucose uptake by the ileum, and increases peripheral insulin sensitivity. Because it does not stimulate insulin production, it cannot cause hypoglycaemia (Fig. 13).

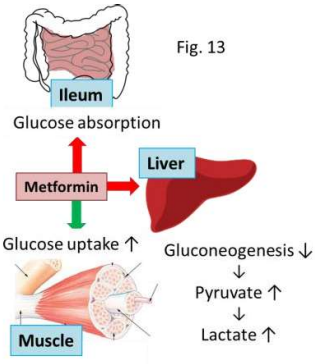


Fig. 13

1. Indications

Treatment of type 2 diabetes with oral antidiabetic agents is not necessary if proper blood glucose control can be achieved through nutritional changes and exercise alone. Metformin is the first choice therapy in the pharmacological treatment of diabetes mellitus type 2 if there is adequate renal function (> 30ml/ min/ 1.73m^2). With a GFR of 30-60ml/min/1.73m^2, the maximum dosage is 1000mg per day (instead of 3000 mg).

2. Kinetics

Objectives: For every patient with type 2 diabetes mellitus and an adequate renal function (>30ml/min/1.73m^2) the first line of treatment is metformin. Metformin is renally cleared; if renal function is impaired half-life will be prolonged and thus the concentration in the blood will increase.

Metformin is excreted solely by the kidneys. This entails that if the patient develops or has renal dysfunction, metformin will accumulate in the body and may cause lactic acidosis (a rare but fatal complication).

3. Side effects

Objectives: Gastrointestinal disorders occur frequently as a side effect of metformin, in particular loose stools and sometimes diarrhoea. Metformin may cause lactic acidosis (happens rarely but can be fatal). Contraindications are renal failure, heart failure, chronic hypoxemia and sepsis.

Especially at the start of treatment with metformin, gastrointestinal symptoms can occur (nausea, vomiting and diarrhoea). This is because the drug also inhibits glucose uptake in the GI system, making more glucose available to bacteria. A rare, but serious side effect is lactic acidosis; this is a particular risk when metformin accumulates in the body, for example, as a result of renal impairment. Due to the latter, metformin is contraindicated in patients with renal or hepatic impairment, heart failure and severe hypoxemia (e.g. caused by severe COPD or sepsis). Other contraindications are diagnostic procedures in which iodinated contrast materials are used or elective surgery under general anaesthesia. The treatment with metformin should be interrupted on the day of the procedure or surgery, and should not be restarted until 48 hours after.

A.2. SULPHONYLUREA DERIVATIVES

Sulphonylurea derivatives (SU-derivatives) stimulate the release of insulin from beta cells, by blocking K^+_{ATP} ion channels; this occurs independently of the glucose concentration. There are short-acting (tolbutamide and gliclazide 80mg) and long-acting agents (glibenclamide, glimepiride). The first choice SU-derivative is gliclazide, because the risk of hypoglycaemia is lowest within this group.

1. Indications

Objectives: If the therapeutic effect of metformin is inadequate, proceed to a combination therapy of metformin and a SU-derivative (gliclazide).

Metformin is the first choice drug therapy in the treatment of DMII. If its effect is insufficient, a short-acting sulfonylurea derivative (gliclazide) may be added.

2. Side effects

Objectives: Hypoglycaemia may occur as insulin secretion is stimulated. This risk is increased by poor/irregular food intake, exercise and renal insufficiency. Hypoglycaemia can be controlled by eating carbohydrates or by the administration of glucose or glucagon. Non-selective beta blockers in particular may mask the early symptoms of hypoglycaemia.

The main side effect of SU-derivatives is hypoglycaemia, since the release of insulin occurs independently of the level of glucose. This complication occurs particularly with the use of the long-acting sulfonylureas. The risk of hypoglycaemia is greater in elderly patients, in patients with hepatic or renal impairment, and in patients under unusual physical stress or who have irregular diet or reduced food intake. A contraindication for glibenclamide is renal impairment because accumulation of active metabolites (which are excreted by the kidneys) may contribute to the increased risk of hypoglycaemia. With gliclazide, the converted substances are inactive, so treatment of patients with renal impairment can be continued.

3. Interactions

Table 37: Drug interactions with SU-derivatives

Drug interaction	Side effect	Mechanism
Beta blockers	Hypoglycaemia	Beta blockers may mask the early symptoms of hypoglycaemia, and they can even delay recovery of blood glucose levels after hypoglycaemia. This occurs particularly with the non-selective beta blockers because in normal conditions beta2 receptor activation results in hepatic glucose release.

4. Hypoglycaemia

The symptoms of hypoglycaemia occur in two phases. A drop in blood glucose level (<4mmol/l) leads first to stimulation of the adrenergic system, with resulting symptoms such as tachycardia, sweating, restlessness and tremors. As the inadequate glucose level begins to affect the brain, the secondary neuroglycopenic symptoms can occur, such as dysarthria, diplopia, headache, impaired concentration and confusion. Mild symptoms can be controlled by the oral administration of carbohydrate or glucose. If this is not possible, due for example to the decreased consciousness of the patient, an intravenous glucose solution should be administered or glucagon 1 mg should be injected subcutaneously or intramuscularly.

A.3. SGLT2-INHIBITORS

SGLT2 (sodium-glucose co-transporter 2) inhibitors selectively and reversibly block the sodium-glucose co-transporter-2 in the kidneys. This inhibits renal glucose reabsorption, leading to excretion of glucose in the urine and a decrease in blood glucose levels.

1. Indications

SGLT2 inhibitors are indicated in the treatment of type 2 diabetes mellitus when neither metformin, SU derivatives nor insulin have resulted in adequate glucose control.

2. Side effects

Objectives: The most important side effect to be aware of when treating patients with SGLT2 inhibitors is euglycaemic diabetic ketoacidosis (EDKA).

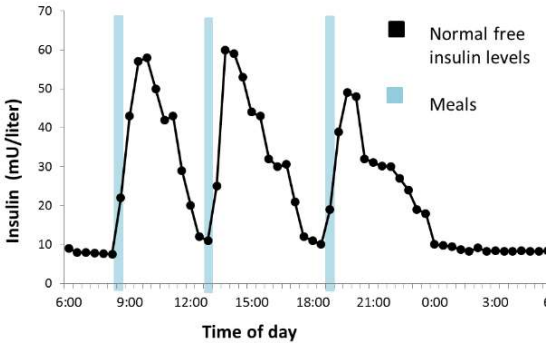
The main side effect of SGLT2 inhibitors is euglycaemic diabetic ketoacidosis (EDKA). This complication mainly occurs in patients who also follow a low-carbohydrate diet. The difference between EDKA and diabetic ketoacidosis (DKA) is that the blood glucose levels are lower than would be expected (less than 14mmol/l, hence the term euglycaemic). This means that the diagnosis can sometimes be missed and hence treatment (the administration of glucose and insulin) is delayed.

B. INSULIN

1. Indications

Insulin is necessary in the treatment of insulin-dependent or type 1 diabetes mellitus. In diabetes mellitus type 2, the use of insulin is indicated if there is an insufficient response to oral antidiabetic agents. The aim of insulin treatment is to mimic normal physiological insulin release as much as possible (Fig. 14).

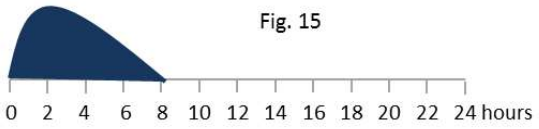
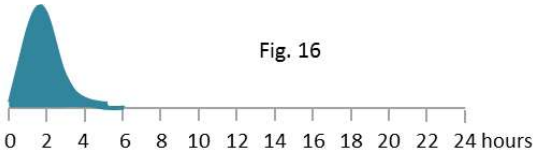
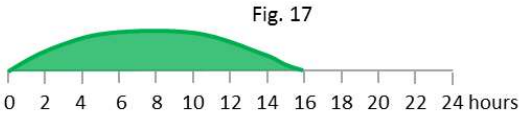
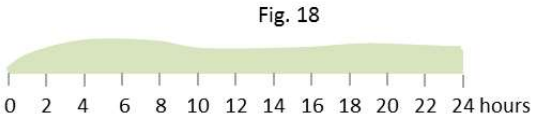
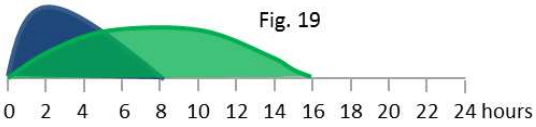
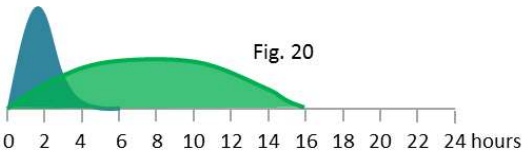
Fig. 14 **Physiological plasma insulin profile**



2. Insulin therapy

Objectives: Patients with DM1 are always treated with insulin. Treatment with insulin in patients with type 2 diabetes mellitus is indicated if diet and oral agents do not achieve proper glycaemic control. Hypoglycaemia usually occurs in patients who are being treated with insulin and who have skipped a meal or have participated in exceptionally vigorous physical activity.

An important consideration when choosing an insulin to treat diabetes is to carefully think about "insulin profiles". An insulin profile refers to the insulin levels in the blood over a certain period of time. Below is an overview of the various insulin preparations. This goes beyond the syllabus of pharmacotherapy safety test.

Table 38: Pharmacological properties of the different insulins		
Insulin type	**Pharmacological properties**	
Short-acting insulin • Humulin Regular • Insuman Rapid	Slightly delayed absorption by s.c. injected hexamers. Max. effect: 2-3 hours after injection. Duration of effect: 6-8 hours Inject 30 minutes before meals.	
Fast-acting insulin analogue • Aspart (Novorapid) • Glulisine (Apidra) • Lispro (Humalog)	Rapid absorption because the insulin enters subcutaneously as a mono/dimer. Max. effect: 45-90 min after injection. Duration of effect: 4-5 hours. Inject immediately before, during or immediately after a meal.	
Intermediate acting NPH-insulin • Humulin NPH • Insulatard • Insuman Basal	Delayed release because of the binding of NPH to insulin. Max. effect: 4-8 hours after injection Duration of effect: 12-16 hours. Inject between dinner and before sleep.	
Long-acting insulin analogue • Glargine (Lantus)	Delayed resorption because of formation of subcutaneous micro precipitates. Duration of effect: ±24 hours or even longer. Inject between dinner and before bed.	
Humane mix-insulin • Humulin NPH 30/70	Biphasic mixture of short-acting insulin + NPH insulin. Inject 30 minutes before breakfast and the evening meal.	
Analogue mix-insulin • Aspart/aspart protamine (NovoMix 30, 50 of 70) • Lispro/lispro protamine (Humalog Mix 25/75, 50/50)	Biphasic mixture of rapid-acting insulin analogue + protamine bound to rapid-acting insulin analogue. Inject directly before breakfast and evening meal	

3. Side effects

The main side effect of insulin is the occurrence of hypoglycaemia. This may be caused by overdose, eating too late, eating too little food, excessive alcohol consumption or physical exertion. The risk of severe hypoglycaemia is significantly increased if the patient has hypoglycaemia unawareness, which means that the patient does not feel the onset of hypoglycaemia. A major benefit of Insulin glargine (Lantus) is that it causes nocturnal hypoglycaemia less often than NPH insulin; this is particularly beneficial for patients with type 2 diabetes mellitus. Patients already being treated with insulin can develop ketoacidosis if they get too little insulin.

4. Interactions

Table 39: Drug interactions with insulin

Interaction with medication	Side effect	Mechanism
Beta blockers	Hypoglycaemia	Beta blockers may mask the early symptoms of hypoglycaemia; they can even delay recovery of blood glucose levels after hypoglycaemia. This occurs particularly with the use of non-selective beta blockers.

Objectives: The following drugs should be known: Insulin (aspart and glargine), metformin, tolbutamide, glimepiride, gliclazide, metoprolol, propranolol, and glucagon.

E. Antidepressants

In this module, the following drug groups are discussed:

A.1. Antidepressants
- Tricyclic antidepressants (TCAs)
- Serotonin Reuptake Inhibitors (SSRIs)

A.2. Lithium

A.1. ANTIDEPRESSANTS

In the Netherlands, antidepressants are frequently prescribed, with currently approximately 1 million people receiving them. All antidepressants cause an increase in the amount of monoamine neurotransmitters (norepinephrine, serotonin, and, to a lesser extent dopamine) in the synaptic cleft. Monoamines play a role in mood disorders, with serotonin being the most important, followed by norepinephrine. Based upon the difference in chemical structure and mechanism of action, antidepressants are divided into tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) (Table 40).

Table 40: Mechanism of action of TCAs and SSRIs

Antidepressant	Mechanism of action
Tricyclic antidepressants (TCAs): • Amitriptyline • Nortriptyline	Amitriptyline inhibits both the reuptake of serotonin and norepinephrine. Nortriptyline, a metabolite of amitriptyline, inhibits the reuptake of norepinephrine and, to a lesser extent, also inhibits that of serotonin.
Selective serotonin reuptake inhibitors (SSRIs) • Citalopram • Fluoxetine • Paroxetine	SSRIs were developed based on the assumption that potentiation of neuronal serotonin signalling was the most important therapeutic mechanism in treating depression.

1. Indications

Objectives: Antidepressants are indicated for moderate depression. TCAs can furthermore be used for treating neuropathic pain. SSRIs also have a pronounced anxiolytic activity, which is why they are indicated in the treatment of anxiety disorders. They can also be used in the treatment of obsessive-compulsive disorders.

Treatment with antidepressants is indicated in patients with moderately severe depression. For mild depression, the effect is no better than placebo. It is generally assumed that these drugs are prescribed too easily and too often for depression. SSRIs are also indicated for a variety of anxiety disorders due to their panic- and anxiety-reducing action. A non-registered use of TCAs is for neuropathic pain.

2. Side effects

Objectives: Because of their broad pharmacological profile, the use of TCAs is associated with a wide range of adverse effects. TCAs have anticholinergic, antihistaminic, anti-noradrenergic (be aware of the orthostatic hypotension risk) and quinidine-like properties (beware of the risk of arrhythmias). TCAs in combination with antihypertensive medication may amplify orthostatic hypotension. SSRIs have side effects due to their strong serotonergic potentiation. SSRIs can cause SIADH (syndrome of inappropriate (release of) anti-diuretic hormone) after approximately 1 week, and thereby may cause hyponatraemia. This risk is increased when thiazide diuretics are also used. Another important side effect of SSRIs is thrombocytopathy. SSRIs in combination with NSAIDs result in an even more increased risk of bleeding.
A rare but serious adverse effect of medications that raise the serotonin concentration within the synapse is serotonin syndrome. This complication is characterised by symptoms such as agitation, fever and hyperreflexia.

Many side effects of TCAs are related to unintended effects on the cholinergic, histaminergic, noradrenergic system, or as a result of quinidine-like effects (Table 41). Anticholinergic side effects are most common. In elderly patients in particular, central side effects such as cognitive dysfunction and confusion may occur. Nortriptyline results in fewer anticholinergic side effects, making this the preferred agent for elderly patients. Orthostatic hypotension, dizziness, and a tendency to fall are the result of the anti-noradrenergic activity. The risk of these side effects is increased in patients with dehydration, e.g. as a result of diarrhoea, fever or vomiting. The antihistamine effect results in drowsiness, which is why TCAs are preferably taken in the evening. The quinidine-like effect is responsible for cardiac conduction disturbances, which is why the use of this agent is contraindicated after a myocardial infarction. If a patient overdoses (e.g. in a suicide attempt), this property of TCAs can cause arrhythmias and may be life threatening. The risk of these side effects can be minimised by prescribing these drugs only after critical assessment of their need has been made and by starting with a low dose.

The adverse effect profile of the SSRIs is caused by the amplification of serotonin (5-HT) signalling, and is characterised by gastro-intestinal disorders, headache, anorexia or weight gain, insomnia and agitation. An increased tendency to bleed has also been reported in patients using fluoxetine and paroxetine. Furthermore SSRIs may cause the syndrome of inappropriate ADH secretion (SIADH), resulting in hyponatraemia - this side effect can occur after approximately one week, and is characterised by drowsiness, confusion and nausea. This cause of hyponatraemia is treated with fluid restriction. The combined prescription of SSRIs and thiazide diuretics increases the chances of hyponatraemia. Other risk factors for the development of SSRI side effects include pneumonia, older age, low intake of protein and salt, salt loss (through diarrhoea or sweating), and excessive drinking.

A rare but serious adverse effect of medications that raise the serotonin concentration within the synapse is serotonin syndrome. This complication is characterised by symptoms such as agitation, fever and hyperreflexia. The risk of this complication is increased by concurrent use of an SSRI with oxycodone or tramadol. This potentially fatal adverse effect is treated by administering insulin and, if the patient is suffering from hyperthermia, by cooling the patient.

Table 41: Pharmacological properties and side effect profile of antidepressants

Type of antidepressant	Pharmacological property	Side effects
Tricyclic antidepressants (TCAs)	anticholinergic (muscarinic receptor blockade)	• Visual disturbances, reduced accommodation ability of the eye and deterioration of a glaucoma • Dry mouth • Micturition disorders • Constipation • Sexual dysfunction • Confusion, delirium (elderly patients)
	antihistaminic (histamine H_1 receptor blockade)	• Sedation, drowsiness
	anti-noradrenergic (alpha-1 receptors blockade)	• Postural hypotension, tendency to fall
	Quinidine-like	• Conduction disorders
Selective serotonin reuptake inhibitors (SSRIs)	Mainly due to serotonin potentiation	• Hyponatraemia • Thrombocytopathy (haemorrhages) • Gastrointestinal symptoms • Headache • Insomnia • Sexual dysfunction • Serotonin syndrome

3. Interactions

The risk of orthostatic hypotension, a side effect of TCAs, is increased with the use of diuretics and antihypertensive drugs. NSAIDs in combination with SSRIs result in an increased risk of gastrointestinal bleeding. With concomitant use of an SSRI and an NSAID, it may be useful to reduce the dose of the NSAID and to start gastric protection (proton pump inhibitor) or to replace the NSAID with a selective COX-2 inhibitor. The indications for using these preventive measures are described in the module on analgesia.

Table 42: Drug interactions with antidepressants

Type of antidepressant	Drug interactions	Side effects
Tricyclic antidepressants (TCA's)	Antihypertensives Diuretics	Orthostasis
Selective serotonin reuptake inhibitors (SSRIs)	Thiazide diuretics (hydrochlorothiazide, chlorothalidon)	Hyponatraemia
	NSAIDs	Risk of haemorrhage

4. Treating depression

The antidepressant effect, thus the normalisation of mood and other features of depression, such as loss of interest and guilt, is usually noticeable after two to four weeks, while side effects can occur a few hours after ingestion (Fig. 21). It is important to prevent lifelong use of this medication and to evaluate the effects regularly. A successful treatment should be continued for at least six months after recovery. When stopping treatment, the dose should be reduced very slowly to avoid 'antidepressant discontinuation syndrome' (sleeping problems, agitation and anxiety). If this approach does not prevent antidepressant discontinuation syndrome, the antidepressant should be replaced with fluoxetine, which has a lower chance of causing this syndrome due to its long half-life.

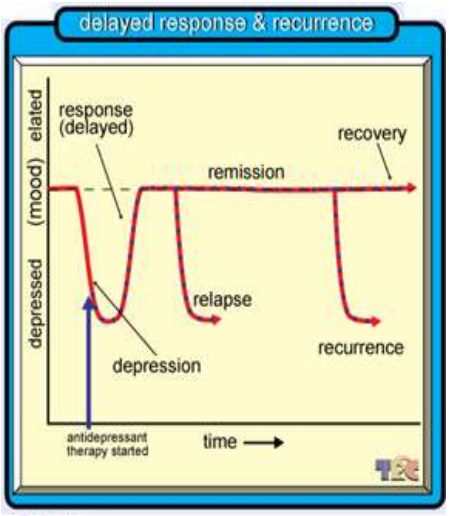


Fig. 21

A.2. LITHIUM

1. Indications and kinetics

Objectives: Lithium has anti-manic and anti-depressive effects, and is indicated for the treatment of bipolar disorders. Lithium is cleared by the kidney and is reabsorbed proportionally with sodium and water. It has a narrow therapeutic index and there is an increased risk of lithium toxicity in patients with renal impairment and those suffering from dehydration. Its dosage is determined by monitoring the lithium levels in the blood and adjusted accordingly.

Mood stabilisers are drugs used to suppress and prevent the occurrence of mania and depression in patients with bipolar disorders. Several types of drugs have a mood stabilising effect, including lithium, anticonvulsants and antipsychotics. For the medication safety test, you are only expected to have studied lithium. Lithium has anti-manic and anti-depressive effects and is used for the treatment of bipolar disorders (as monotherapy) and is a complementary drug in the treatment of treatment-resistant unipolar depressive disorder.

Lithium is excreted primarily through the kidneys and approximately 75% of the filtered lithium is reabsorbed again in the proximal tubule, in proportion to the levels of sodium and water reabsorption. Lithium has a narrow therapeutic index (0.4-1.2 mmol/l) and should be dose-adjusted according to blood levels to prevent an overdose occurring. Since lithium interacts with sodium, inadequate fluid and salt intake or excessive sweating can easily lead to toxic levels of the drug in the blood. The risk of lithium toxicity is increased in patients with renal impairment.

2. Side effects

Objectives: Side effects of lithium are renal dysfunction, diabetes insipidus, thyroid problems (often hypothyroidism), nausea and vomiting.

In 10-20% of the patients using lithium, there is a decrease in thyroid gland function. Because of the possibility of iatrogenic hypothyroidism, thyroid function (TSH) should be measured periodically. Prolonged use of lithium may cause nephrogenic diabetes insipidus, leading to polyuria and thirst. Long-term use can have detrimental effects on the kidney. Therefore, patients should be instructed to take their medication regularly, drink plenty of water (two to three litres per day) and to have their renal function checked at least two to four times per year (serum creatinine), as well as their blood levels of lithium.

3. Interactions

Objectives: When patients concurrently take diuretics, NSAIDs, or RAS inhibitors, side effects or lithium toxicity may occur due to increased plasma levels of lithium.

Table 43: Drug interactions with lithium

Interaction with medication	Side effect
Diuretics NSAIDs RAS inhibitors	Higher lithium levels

Objectives: The following drugs should be known: amitriptyline, nortriptyline, fluoxetine, paroxetine, citalopram, lithium, naproxen, furosemide, hydrochlorothiazide, enalapril.

F. Benzodiazepines

Doctors have contrasting views regarding benzodiazepines ($GABA_A$ receptor agonists). This medication is on the one hand of great value due to both its anti-anxiety and sleep-promoting effects. On the other hand, caution is necessary due to the risk of addiction, the risk of falling in elderly patients, possible cognitive problems and behavioural changes, and the risk of long-term tolerance development. Knowledge of the mechanisms of action and pharmacokinetics of benzodiazepines is required to select the best drug from the many available. The main features of temazepam, oxazepam and diazepam need to be studied for this pharmacotherapy safety test.

1. Mechanism of action and pharmacokinetics

Objectives: Benzodiazepines enhance the inhibitory action of GABA through binding to the $GABA_A$ ion channel and prolonging the influx of chloride leading to neuronal hyperpolarisation. Temazepam and oxazepam are benzodiazepines with a short T½. The T½ of diazepam is long (40-100 hours). Oxazepam, a derivative of diazepam, has a much shorter T½ (4-15 hours).

Benzodiazepines have sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxing effects because they enhance the action of the neurotransmitter gamma-amino butyric acid (GABA) through engaging the $GABA_A$ receptor. Though their mechanisms of action (pharmacodynamics) are identical, benzodiazepines do differ in their pharmacokinetics. Differences in pharmacokinetics largely determine which specific benzodiazepine is most appropriate. The majority of benzodiazepines, such as diazepam, have active metabolites with very long elimination half-lives; these agents are therefore not suitable as sleep medication. Temazepam and oxazepam (a metabolite of diazepam) are on the other hand benzodiazepines with a short half-life, and are therefore suitable as sleep medications (Table 44).
In elderly patients, elimination and conversion of these drugs may be slower than in young people because elderly people generally have a higher body fat percentage and thereby an increased volume of distribution. This slower elimination and conversion can result in a 'hangover' effect. Factors that determine the time before effect onset are the rate of absorption and the distribution of the drug in the fatty tissue. The duration of the effect is predominantly determined by the dosage, but other determinants include the elimination half-life, absorption and distribution.

Table 44: The half-lives of the benzodiazepines

Benzodiazepine	$T_{1/2}$ in hours
Diazepam	40-100 hrs
Oxazepam	4-15 hrs
Temazepam	7-11 hrs

2. Indications

Objectives: The main indications for the use of benzodiazepines include sleep disorders, generalised anxiety disorder and the treatment of withdrawal symptoms. In addition, benzodiazepines are used to treat fever convulsions and seizures. Finally, benzodiazepines play an important role in premedication for surgery.

The main indications for the use of benzodiazepines are insomnia and generalised anxiety disorders (Table 45). In addition, benzodiazepines are used to treat withdrawal symptoms and for stopping febrile convulsions and epileptic seizures. When using benzodiazepines for the treatment of alcohol withdrawal symptoms, it is important to additionally prescribe thiamine as part of the therapy; this is because a thiamine deficiency can present in patients who have been chronically abusing alcohol. For the treatment of seizures clonazepam,

diazepam, or midazolam are available. Diazepam can also be administered as a suppository. Finally, benzodiazepines have an important role as premedication before surgery.
Regarding insomnia, a suitable medication is one that has an effect that sets in rapidly and lasts until the morning, without sedative effects during the day. For this purpose, benzodiazepine agonists with a short elimination half-life, such as temazepam and zolpidem are suitable.

If a benzodiazepine is being prescribed due to its anxiolytic effect, it is important for the drug to work for a sufficiently long time, and for no accumulation or sedation to occur. A less lipophilic benzodiazepine with a long elimination half-life, such as lorazepam, is therefore suitable.

Table 45: Indications for benzodiazepines [3]

Benzodiazepine	Hypnosis	Anxiolysis
Diazepam	-	+
Lorazepam	-	+
Oxazepam	-	+/-
Temazepam	+	+, not registered for this purpose, but often used off label

3. Side effects

Objectives: The main side effects are muscle weakness (tendency to fall, especially in elderly patients), memory loss and decreased alertness, which has consequences when driving a car. Furthermore long-term use may induce tolerance as well as dependence. Rebound phenomena may occur upon abstinence (anxiety, difficulty sleeping). Respiratory depression can occur following a benzodiazepine overdose or if benzodiazepines are prescribed in combination with other CNS depressants. Respiratory depression can also occur in patients with (severe) COPD. In elderly patients and children, administration of a benzodiazepine can result in paradoxical reactions (agitation, restlessness). The most important interactions contributing to the increased tendency to fall are the use of anti-hypertensives, alcohol, and opiates.

Benzodiazepines often affect alertness and motor skills negatively, which reduces driving ability. Anterograde amnesia may occur at therapeutic doses, especially a few hours after intake. 'Paradoxical' reactions such as restlessness, agitation and aggressive behaviour may occur, particularly in elderly patients and children. In older people, muscle hypotonia may occur. Following prolonged use, the efficacy of benzodiazepines may decrease as tolerance develops (there is an increased need to achieve the same effect). Use of benzodiazepines may lead to dependence. Additionally, after discontinuation of treatment rebound insomnia may occur. This is a transient syndrome characterised by amplification of the original sleep complaints. Rebound insomnia may be associated with mood changes, anxiety and restlessness. In such cases the prescription of benzodiazepines is sometimes recommenced too quickly, which can lead to their chronic use.

4. Prevention of adverse events

Objectives: Tolerance and dependency can be prevented by prescribing benzodiazepines only for short periods of time (<2 weeks), and by providing good patient instruction. Dependency can be treated by using long-acting benzodiazepines (diazepam). Doses should be decreased gradually and finally phased out. In the event of respiratory depression, flumazenil ($T_{½}$ ca. 1 hour), a benzodiazepine receptor antagonist, can counteract this.

[3] Christiaan H. Vinkers, Joeri K. Tijdink, Jurjen J. Luykx en Roeland Vis. Kiezen voor de juiste benzodiazepine, werkingsmechanisme en farmacokinetiek. NTVG. 08-2012

Anticipated problems that arise from prolonged use of sleeping pills include tolerance, dependence, withdrawal symptoms and rebound insomnia upon discontinuation of treatment. As a result it is important to prescribe these drugs carefully. These problems are avoided by prescribing benzodiazepines for only for a short time (<2 weeks), preferably intermittently, and by providing good patient instruction. Because of the risk of withdrawal symptoms, it is recommended to switch to a long-acting benzodiazepine (such as diazepam) and then to slowly reduce the dose when stopping the therapy. The risk of withdrawal symptoms and rebound phenomena is in this way minimised.

Toxicity

The toxic effects of benzodiazepines are generally minimal. If a patient overdoses or if benzodiazepines are used in combination with other CNS depressants, respiratory depression may occur. This can be reversed by the intravenous administration of flumazenil (benzodiazepines receptor antagonist). One should be aware that the half-life of flumazenil ($T_{½}$ ca. 1 hour) is much shorter than that of the majority of other benzodiazepines.

5. Interactions

Table 46: Drug interactions with benzodiazepines

Interaction with medication	Side effects
Antihypertensives Alcohol Opiates	Tendency to fall
Opiates Alcohol	Respiratory depression

Objectives: The following medications must be known: diazepam, oxazepam, temazepam, flumazenil.

G. Antibiotics

Antimicrobial agents are divided into several groups:

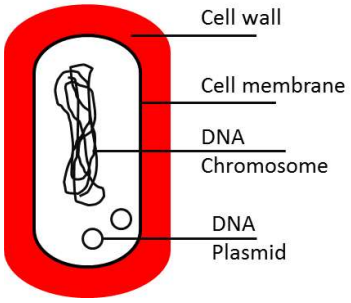
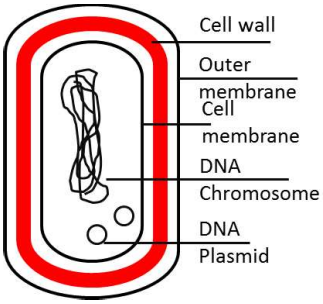
A. β-lactam-antibiotics
   A.1. Penicillins
   A.2. Cephalosporins
   A.3. Carbapenems
B. Tetracyclines (doxycycline)
C. Aminoglycoside (gentamicin)
D. Macrolides (azitromycine, claritromycine)
E. Sulfonamides/Trimethoprim (co-trimoxazol)
F. Quinolones (ciprofloxacin)

For a better understanding of how the various types of antibiotics work, it is essential to first understand the basics about the structure and functioning of bacteria.

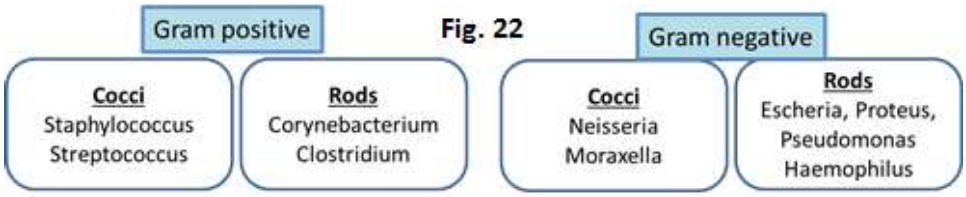
1. Bacteria

Bacteria are classified in cocci and rods, and, subsequently into Gram-positive and Gram-negative bacteria. Gram-positive bacteria have a thick cell wall, which is made up of peptidoglycans (Table 47). Gram-negative bacteria have a much thinner cell wall which is surrounded by an additional outer membrane, which is formed by LPS (lipopolysaccharides).

Table 47: Gram positive vs gram negative bacteria

Gram-positive bacteria	Gram-negative bacteria
	

The figure below provides an overview of the most important bacterial pathogens (Fig. 22).



Some general principles apply to all antibiotics:

- All antibiotics can cause gastrointestinal side effects, in particular abdominal pain and diarrhoea. These side effects arise as a consequence of unabsorbed antibiotics that disturb the microbiotic flora. Most antibiotics are renally cleared, which means that the dose has to be adjusted in patients with reduced kidney function. This can be achieved in two ways, either by directly decreasing the dose or extending the interval between doses.
- All antibiotics have a clinically relevant interaction with coumarins. The effect of coumarins is indirectly enhanced by antibiotics (when the patient is feverish, breakdown of coagulation factors is also enhanced). Since the clotting time may increase when a patient is being given this combination of drugs, it is important to consult the thrombosis specialist before initiating treatment.

A. β-LACTAM-ANTIBIOTICS

β-lactam antibiotics are characterised by a β-lactam ring which is essential for their anti-microbial activity. The cleaving of this ring makes these drugs ineffective. Several bacteria have enzymes (β-lactamases) which cleave these rings, and thus confer resistance against β-lactam antibiotics. Drugs that belong to the class of β-lactam antibiotics include penicillins, cephalosporins, and carbapenems.

A.1. PENICILLINS

Penicillins are divided into narrow spectrum (penicillin and flucloxacillin) and broad-spectrum penicillins (amoxicillin).

1. Mechanism of action

Penicillins affect the synthesis of the bacterial cell wall (Fig. 23). This explains why they are highly potent against rapidly-growing bacteria, and also explains their reduced efficacy against dormant pathogens involved in chronic infections. It also explains why anti-microbial agents with a bacteriostatic function reduce the bactericidal efficacy of β-lactam antibiotics.

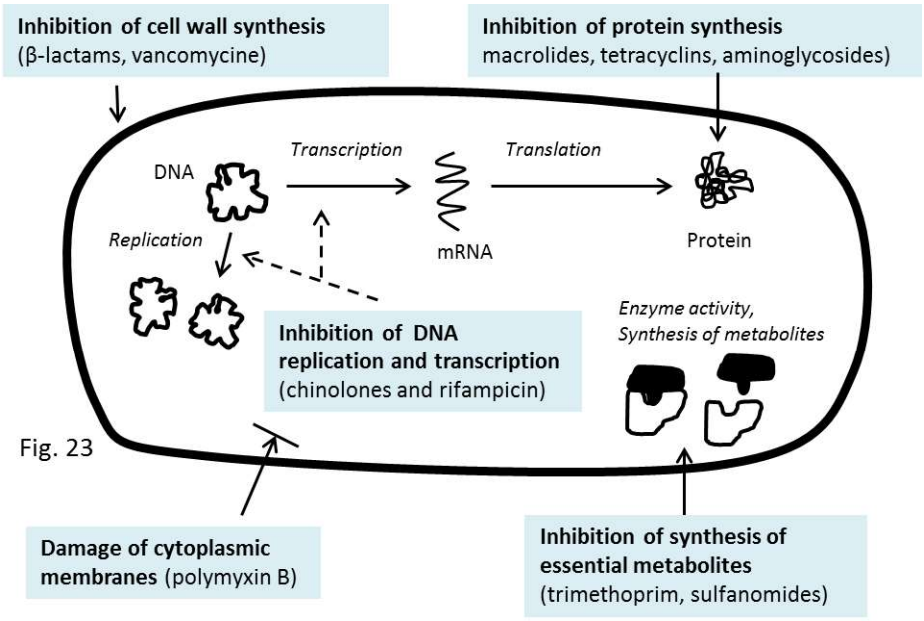


Fig. 23

2. Indications

Penicillins are particularly effective against Gram-positive bacteria (Table 48). 80-90% Of the Staphylococcus aureus strains are now resistant to benzylpenicillin and amoxicillin. Especially in hospitals outside the

Netherlands, infections of methicillin-resistant Staphylococcus aureus (MRSA) are a major problem. In such cases, treatment with the non-beta-lactam antibiotics vancomycin or teicoplanin is indicated. The disadvantages of vancomycin however are that it can only be administered intravenously and that it is nephrotoxic. Certain enterococci, particularly vancomycin-resistant enterococcus (VRE), are resistant to vancomycin.
Flucloxacillin is a β-lactamase-insensitive penicillin with a narrow-spectrum of action (effective against gram-positive organisms). Flucloxacillin can be combined with broader spectrum antibiotics (also effective against Gram-negative organisms), such as amoxicillin or piperacillin. Piperacillin is also effective against pseudomonas aeruginosa.
Penicillins can also be combined with a β-lactamase inhibitor, such as clavulanic acid or tazobactam. This may overcome the resistance conferred by the bacterial β-lactamase production. Examples of these combinations are amoxicillin with clavulanic acid and piperacillin with tazobactam.

Table 48: Characteristics of common Gram positive bacteria

Gram positive bacteria	Relevant characteristics
Enterococcus faecalis	Belongs to genus Enterococcus, is susceptible to amoxicillin.
Staphylococcus aureus β-lactamase-producing	Virulent skin bacteria resistant to benzylpenicillin and amoxicillin through the production of β-lactamase. Flucloxacillin or amoxicillin with clavulanic acid are indicated.
Staphylococcus epidermidis coagulase negative	Commensal, non-virulent bacterium. This usually indicates contamination in culture bottle. If pathogenic, this bacterium is very difficult to eradicate.

3.Side effects

Objectives: The most common side effects of penicillins are drug eruptions (dermatitis medicamentosa) and diarrhoea. There is also a risk of anaphylactic shock if the patient is allergic to such antibiotics. Amoxicillin causes skin eruptions more frequently (7-8%) than other penicillins do (1% of cases); in most cases these skin eruptions are not immunologically mediated. The incidence of anaphylactic shock is 0.01 – 0.04%; in approximately 5% of cases, there is cross sensitivity within the cephalosporin group.

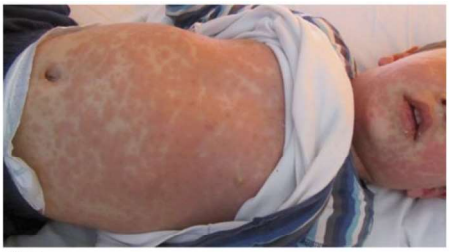


Fig. 24
http://www.medischcontact.nl/Kennis-1/gezien2/Gezien-aflevering/127292/Reactie-op-penicilline-bij-EBV infectie.htm

Penicillins regularly result in drug eruptions as a side effect, occurring with amoxicillin in 7%, and with other penicillins in 1% of cases. In infectious mononucleosis and lymphocytic leukaemia, 90% of patients develop skin eruptions (Fig. 24). The incidence of anaphylactic shock is 0.01 – 0.04%. Cross-sensitivity amongst the penicillins is often the case. In about 5% of cases, there is also a cross-sensitivity with cephalosporins.
Gastro-intestinal reactions in the form of diarrhoea also frequently occur, which are caused by a disturbance of the intestinal flora by non-resorbed antibiotics. Sometimes the diarrhoea is caused by a Clostridium difficile infection, which may progress into pseudomembranous colitis. In this case, it is necessary to immediately discontinue the therapy and, if possible, to treat the patient with metronidazole.

A.2. CEFALOSPORINS

There are three generations of cephalosporins (Table 49).

Table 49: The properties of cephalosporins

Cephalosporin	Properties
1e generation: *Cefazolin*	The 1st generation has a narrow spectrum and is especially effective against Gram-positive bacteria.
2e generation: *Cefuroxime*	The 2nd generation is β-lactamase-insensitive and is more effective against Gram-negative organisms.
3e generation: Ceftazidime	The 3rd generation has a broader spectrum and must often be administered parenterally. These are particularly effective against Gram-negative bacteria (including Pseudomonas).

A.3. CARBAPENEMS

The carbapenems include imipenem and meropenem. They have the same mechanism of action as the penicillins, interfering with the permeability of the cell wall and thereby causing autolysis of the bacterium. The spectrum of imipenem and meropenem is very broad. They are active against nearly all types of Gram positive, Gram negative and anaerobic bacteria. They are 'last choice' antimicrobials, used to treat infections caused by highly resistant gram-negative microorganisms, such as extended spectrum beta-lactamase-producing bacteria (ESBL).

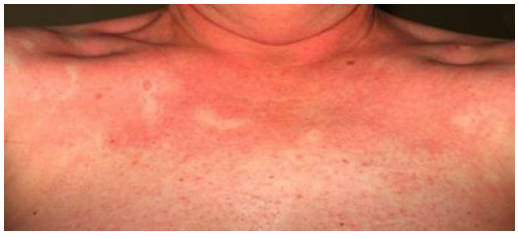
B. TETRACYCLINES

Tetracyclines (minocycline, doxycycline, tetracycline) work by inhibiting protein synthesis (Fig. 23). Tetracyclines cause bacteriostasis, and may therefore impede the action of bactericidal antibiotics, such as penicillins and cephalosporins. They should not be used during pregnancy neither should they be prescribed to young children (<8 years) whose teeth are not yet fully developed (Table 50).

1. Side effects

Objectives: Discolouration of the teeth in children and photosensitivity are side effects of tetracyclines (Table 50). Because of the harmful effects of these drugs on bone tissue, the use of tetracyclines during the whole period of pregnancy and in children under the age of 8 years is contraindicated. Given the risk of skin photosensitivity, exposure to sun light is discouraged during the treatment period. When administered in combination with aluminium, calcium, iron and magnesium containing compositions (such as antacids and milk), the absorption of these agents is reduced because of the formation of insoluble complexes of quinolones with these elements.

Table 50: Side effects associated with tetracyclines

Discoloration of teeth, stunted growth	Photosensitivity
Tetracyclines are absorbed in bone tissue and can have adverse effects on growth. This drug can also interfere with the calcification of the teeth during the odontogenesis, which can result in teeth discoloration and enamel hypoplasia.	

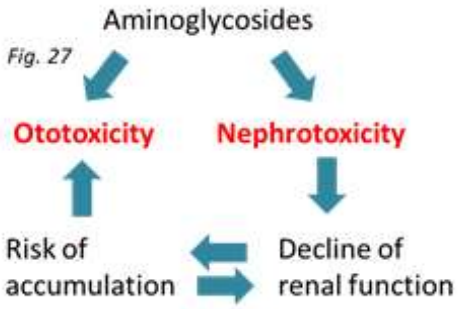
2. Interactions

Table 51: Drug interactions associated with tetracyclines		
Interaction with medication	**Side effects**	**Consequences**
Iron preparations, milk or antacids	Decreased absorption of tetracyclines	The combination of tetracyclines with iron, calcium, magnesium or zinc causes insoluble complexes to form.

C. AMINOGLYCOSIDES

Objectives: Aminoglycosides (gentamicin, tobramycin) are particularly effective against Gram-negative microorganisms. They have important and very serious side effects (irreversible deafness and reversible renal impairment) and should therefore be used for as short a period as possible.

Aminoglycosides interfere with the bacterial protein synthesis (Fig. 23). They block the interaction between mRNA and ribosomes and have a bactericidal effect. They work especially well against gram-negative rods. Aminoglycosides are not absorbed by the intestines and can therefore only be administered parenterally. They have a narrow therapeutic index, being particularly ototoxic and nephrotoxic. The renal toxicity is usually reversible, however any ototoxicity is permanent. Determination of serum levels is therefore recommended with administration of these agents, in order to prevent ototoxic and nephrotoxic dosages being administered. One danger is that it becomes a vicious circle: the nephrotoxicity reduces kidney function, causing a risk of accumulation. The result is a further decreased kidney function and increased risk of ototoxicity (Fig. 27).



D. MACROLIDES

Objectives: Macrolides (e.g. clarithromycin) inhibit protein synthesis of bacteria and are effective against atypical and gram-positive pathogens. The disadvantage with these antibiotics is that they inhibit the degradation of many other medications (e.g. statins) through CYP3A4 inhibition, and thus can cause serious drug interactions.

Macrolides (erythromycin, clarithromycin, azithromycin) inhibit protein synthesis and are therefore bacteriostatic (Fig. 23). They are especially effective against gram-positive bacteria, such as S. aureus, pneumococcus and intracellular micro-organisms (Legionella, Chlamydia, Mycobacteria). Erythromycin and clarithromycin inhibit CYP3A4 enzymes and are CYP3A4 substrates. Potent inhibitors of CYP3A4 therefore increase plasma levels of these antibiotics, and should therefore not be administered simultaneously. The combination of macrolides with statins (which are also metabolised by CYP3A4, e.g. simvastatin) increases the risk of statin toxicity (rhabdomyolysis). Macrolides can increase the QTc interval; in combination with other QTc-prolonging agents the risk of torsade de pointes is further increased.

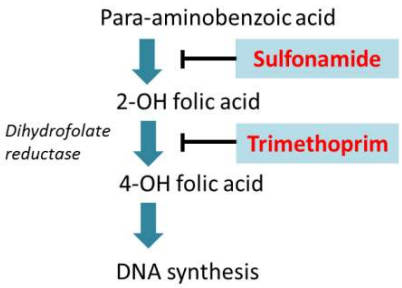
E. SULPHONAMIDES/TRIMETHOPRIM

The combination of trimethoprim and a sulphonamide is called co-trimoxazole. This combination is synergistic; the efficacy is five to ten times greater than that of trimethoprim alone. Furthermore, the combination has bactericidal activity and there is a decreased risk of developing resistance. However the disadvantage with this combination is that the patient is at risk of developing toxic effects due to a double inhibition of folic acid synthesis.

1. Mechanism of action

The bacteriostatic action of sulphonamides is based on the inhibition of bacterial synthesis of dihydropteric acid by blocking the incorporation of para-aminobenzoic acid (Fig. 28). Trimethoprim inhibits the conversion of dihydrofolic acid to tetrahydrofolate. Humans also possess this enzyme, however in bacteria, this enzyme (dihydrofolate reductase) is much more sensitive (> 10,000 x) for trimethoprim than the corresponding enzyme in humans.

Fig. 28



2. Interactions

Objectives: The effects of methotrexate may be increased with the simultaneous use of trimethoprim or co-trimoxazole. This is because all of these medications suppress the activity of the dihydrofolate reductase, which can lead to potentially life-threatening bone marrow suppression. Also, co-trimoxazole can inhibit the breakdown of vitamin K antagonists (e.g. warfarin), which can lead to an increase in the INR and severe haemorrhage. This combination should therefore be avoided.

Trimethoprim inhibits dihydrofolate reductase in bacteria. To inhibit this enzyme in humans, a 50,000x higher concentration of the drug is needed. Hence the use of trimethoprim does not lead to serious changes in blood count. However, the combination of trimethoprim and methotrexate increases the risk of megaloblastic anaemia due to the dual inhibitory effect on folic acid metabolism. Concomitant use of trimethoprim-sulfamethoxazole and trimethoprim with methotrexate should therefore be avoided. Co-trimoxazole enhances the effect of vitamin K-antagonists, which may lead to elevated INR levels and potential haemorrhage (Table 52). The latter interaction is due to three mechanisms. Firstly, vitamin K antagonists are mainly metabolised by CYP2C9. Illness/fever decreases CYP2C9 activity. Secondly, sulfamethoxazole (part of co-trimoxazole) inhibits CYP2C9, which results in an increased plasma concentration of vitamin K antagonists. Finally, sulfamethoxazole displaces vitamin K antagonists from transport proteins. As a result, a larger free fraction of vitamin K antagonists is present in the blood, which temporarily increases the effect of vitamin K antagonists.

Table 52: Drug interactions with co-trimoxazol

Antibiotic	Interaction with medication	Side effects
Trimethoprim, co-trimoxazol	Methotrexate	Leukopenia
Co-trimoxazol	Coumarins (e.g. Acenocoumarol, phenprocoumon, warfarin)	INR levels substantially increase

F. QUINOLONES

Objectives: Quinolones (ciprofloxacin and levofloxacin) are particularly effective against gram-negative organisms. Just like tetracyclines, quinolones form insoluble complexes with aluminium, calcium, iron and magnesium, which means that the absorption of these minerals and the absorption of the quinolones into the blood is severely hampered. To prevent this occurring, it is recommended to select an alternative antibiotic, or at the very least, to ensure that a certain amount of time elapses between the ingestion of the two compounds. If a patient is taking two QT-prolonging medications there is an increased risk of Torsades de Pointes occurring.

The quinolones include ciprofloxacin, levofloxacin, moxifloxacin and norfloxacin. They are especially effective against gram-negative bacteria. Quinolones have a bactericidal activity; they will affect the DNA synthesis by inhibition of bacterial DNA gyrase, an enzyme that winds the long DNA chains around a histone core (Fig. 23) Ciprofloxacin and norfloxacin bind to zinc, calcium, magnesium and iron in the gastro-intestinal tract. This creates insoluble complexes, so that absorption of these minerals and the absorption of the quinolones into the blood is severely hampered.

G. MEDICATIONS FOR URINARY TRACT INFECTIONS

Objectives: This section describes the current treatment guidelines for urinary tract infections. Antibiotic therapy for urinary tract infections is not among the goals of pharmacotherapy safety test and should be regarded as optional material.

An uncomplicated urinary tract infection is defined as cystitis in a healthy, non-pregnant adult woman. The majority of urinary tract infections are caused by Escherichia coli. If the infection spreads to the tissue of the kidneys or to the prostate, a pyelonephritis or acute prostatitis respectively may occur. These infections may be associated with signs of tissue invasion, such as high fever, chills, nausea, and pain in a flank or perineum. It is important to determine whether the urinary tract infection is uncomplicated or complicated, as the treatment options are different. Underlying conditions may play a role in the development of urinary tract infections, such as prostatic hyperplasia, prostatitis, reduced immune resistance (e.g. by diabetes mellitus), having kidney stones or a neurogenic bladder.

1. Treatment

For the treatment of uncomplicated urinary tract infections, there are several medications available (Table 53). These agents need to reach high concentrations in the urine, and most preferably low concentrations in the blood. This is different in complicated urinary tract infections, where antibiotics need to penetrate into tissues (and for which longer drug therapy is needed).

Table 53: Uncomplicated vs Complicated cystitis[4]

Cystitis *Healthy non-pregnant women*	**Cystitis with signs of tissue invasion** *Non-pregnant women*
1st choice: nitrofurantoin 2dd 100mg, 5 days 2nd choice: phosphomycin 3 grams, single dose 3rd choice: trimethoprim 1dd 300mg, 3 days	1st choice: ciprofloxacin 500mg 2dd, 7 days 2nd choice: amoxicillin/clavulanate dd 500 / 125mg, 10 days 3rd choice: co-trimoxazole 2dd 960mg, 10 days
In men: antibiotic selection same as in women, however treatment duration is 14 days	

H. MEDICATIONS FOR ANAEROBIC INFECTIONS

Of the different medications available, only metronidazole needs to be known for the medication safety test. Metronidazole can be used either to treat an infection caused by an anaerobic bacteria, or prophylactically against these microorganisms. Examples of bacteria which are sensitive to treatment with metronidazole include Bacteroides fragilis, Clostridium difficile and Clostridium perfringens.

[4] NHG standaard – urineweginfecties. 2013 NICE Guidelines UTI

Metronidazole can increase the effect of vitamin K antagonists. Another important property of this drug is that it has disulfiram-like effects. This means that it can affect the metabolism of alcohol by inhibiting the enzyme aldehyde dehydrogenase. As a result, if someone taking metronidazole consumes alcohol, the concentration of acetaldehyde in their blood will significantly increase. This leads to symptoms such as nausea, vomiting, a flushed face and headache. As a result alcohol consumption is not recommended for at least 48 hours following discontinuation of metronidazole.

I. INSTRUCTIONS WHEN CHOSING AN ANTIBIOTIC

Objectives: For a targeted therapy, when pathogen and its sensitivity are known, prescribing antibiotics with a narrow spectrum is preferred over those with a broader spectrum. The policy is to treat very severe infections intravenously for a few days and then to proceed with oral therapy as soon as possible (within three to four days). Reasons not to start antibiotic therapy are: resistance, a different pathogen or febrile non-infectious disease. The infection can be difficult to reach due to an abscess or empyema, foreign body (prosthesis, catheter, IV cannula) or it may be located in an inaccessible location, such as in a heart valve, the meninges, bones or joints.

As soon as the causative pathogen and the sensitivity pattern are known from the microbiological examination, it is necessary to adjust the initial, blind, "broad" therapy, and to switch to a "narrower", more targeted therapy in order to reduce the likelihood of resistance developing. The policy is to treat very severe infections for only a few days intravenously and to proceed with oral therapy as soon as possible (within three to four days). If the isolated micro-organism is indeed the causative agent of the infection, and the sensitivity determination is correct, a good response to antimicrobial therapy can usually be expected within one to three days. If the treatment response is not consistent with what is expected, the cause for this should be sought (Table 54).

Table 54: Causes of inadequate response to therapy

Resistance	Examples of highly resistant bacteria are extended-spectrum beta-lactamases (ESBL), vancomycin-resistant Enterococci (VRE) and methicillin-resistant Staphylococcus aureus.
Viral infection/other bacteria	The clinical diagnosis is incorrect or the selected antibiotic is ineffective.
Non-infectious aetiologies of fever	For example, a malignancy (lymphoma, Grawitz tumour), auto-immune disease (Still's disease), side effect of drug (penicillin, isoniazid, nitrofurantoin).
Source of infection difficult to reach	The source of infection is difficult to access because of a vascularisation disturbance (diabetes mellitus), abscess or empyema, foreign body (prosthesis, catheter, infusion), difficult-to-reach compartment (heart, bone, brain).

Objectives: The following drugs should be known: β-lactam antibiotics (penicillins: penicillin, amoxicillin, amoxicillin clavulanic acid, cephalosporins: ceftriaxone), aminoglycosides (gentamicin), quinolones (ciprofloxacin), macrolides (azithromycin), tetracyclines (doxycycline), trimethoprim / co-trimoxazole, nitrofurantoin, fosfomycin.

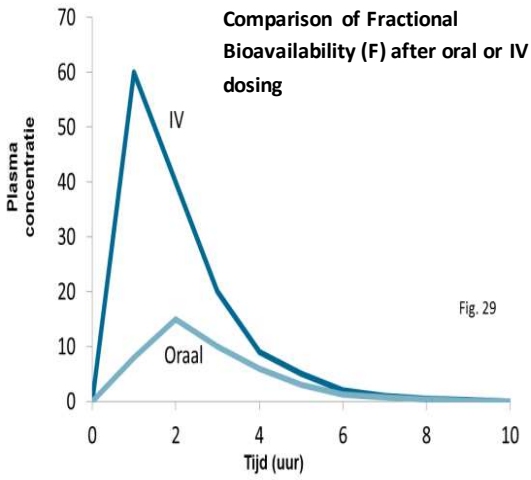
H. Pharmacokinetics

Pharmacokinetics describes the interactions of a drug with the human body, namely its absorption, distribution, metabolism, and excretion.

1. Absorption

Objectives: The bioavailability (F) is the fraction of the administered dose of a drug that reaches the general circulation in unchanged form. Following oral administration of a drug, a portion of the absorbed substance can be metabolised by enzymes in the intestines or liver before it reaches the circulation (a phenomenon known as the first-pass effect). When the same drug is administered intravenously however, the bioavailability is always 100%.

In defining absorption one distinguishes the speed at which the active substance is absorbed and the degree to which it is absorbed. The degree of absorption determines the bioavailability. The bioavailability describes the fraction (F) of the administered substance that reaches the general circulation over time (area under the curve) in comparison to the amount that is available after intravenous administration (AUC_{oral}/AUC_{IV}). F ranges from 0 (no active ingredient available) to 1 (all of active substance available). The percentage of active substance lost after oral dosing is (1-F) x 100; this loss occurs, for example, because a percentage of the active substance undergoes biodegradation in the gastro-intestinal tract or in the liver (the first-pass effect). The Area Under the Curve (AUC) is the integral of the drug concentration over time. This variable provides information regarding the total exposure of the patient to the medicine.



2. Distribution

Objectives: The volume of distribution (Vd) is the ratio between the amount of drug taken up in the body and the (estimated) plasma concentration immediately (t=0) after administration. This is represented in the formula $Vd=F \times D / C_0$. The volume of distribution determines the size of the loading dose. The volume of distribution may be larger than the volume of all body compartments, and is therefore often referred to as the fictitious volume of distribution.

In pharmacokinetics, the parameter describing the distribution of a substance throughout the body is the volume of distribution (V_d). The Vd represents the apparent volume into which the drug is distributed to provide the same concentration as it currently is in blood plasma. The Vd can be calculated if one knows how much of a drug has entered the systemic circulation of the patient and the corresponding plasma concentration at t=0. The Vd of a drug, after an oral dose (D) is defined by the formula: $V_d = F \times D / C_0$. A drug which has a high affinity for plasma proteins will have a small volume of distribution, given that a large proportion of the total amount of drug will be located in the plasma. A large volume of distribution is seen when a drug has strong lipophilic properties and thus accumulates in fat or other tissue compartments. The volume of distribution is of practical importance for the determination of the loading dose required to achieve a desired plasma concentration quickly and is often expressed relative to body weight (L/kg).

3. Metabolism

The metabolism of a drug takes place in the liver through type I and type II reactions (Table 55). Both of these types of reactions generally result in an increased water-solubility of the molecule, which can then be excreted by the kidneys or via the bile.

Table 55: Type I vs type II conjugation reactions

Reaction type	Biochemical effect
Type I	In phase I, the molecules are chemically activated for phase II through: • Hydrolysis • Oxidation • Reduction
Type II	In phase II, the molecules are made more water-soluble, for example by: • Acetylation • Glucuronidation • Sulfation

The CYP450 enzyme system is essential for biotransformation of drugs. Many drugs are substrates for the CYP3A4 and CYP2D6 enzymes. Certain medicines or food constituents may cause CYPP450 enzyme inhibition or induction, resulting in a delayed or increased degradation rate respectively when such substances are combined. This may particularly cause problems if drugs have a narrow therapeutic index.

Table 56: Enzyme inhibitors vs enzyme inducers of CYP3A4

Type of medication	Effect
Enzyme inhibitors	The following enzyme inhibitors of CYP3A4 cause higher levels of medications in the blood; this effect occurs immediately. • Azoles (ketoconazole, itraconazole, miconazole) • Clarithromycin, erythromycin • Verapamil • Grapefruit juice
Enzyme inducers	The following medications are inducers of CYP3A4; when taking these, drugs are broken down faster, so higher doses must be taken for the same effect. This induction effect occurs within days to weeks. N.B. The dosage should be adjusted again when the inducing agent is stopped! • Rifampicin (main enzyme inducer) • Anti-epileptic drugs (carbamazepine, phenytoin) • St John's wort

4. Elimination

Objectives: Clearance is the volume of plasma that is cleared of a substance per unit time. It describes the capacity of elimination by the liver and kidneys. In steady state (SS) conditions where input equals output, the maintenance dose depends only on the clearance. Enzyme inhibitors can lead to accumulation of a drug in the body; examples of such substances include azoles, grapefruit juice, clarithromycin, erythromycin and verapamil. When enzyme inducers are taken, drugs are broken down faster (rifampicin, carbamazepine, St. John's wort). However, this effect develops more gradually over time, usually days or weeks.

The two main ways by which the body can eliminate a substance are through the liver and the kidneys. The kidneys can excrete water soluble substances by filtration and through active tubular secretion. A substance

that is less hydrophilic, needs to be converted into hydrophilic derivatives through type I and type II reactions in the liver before elimination via the kidneys or bile/faeces is possible.

Clearance

The clearance (Cl), a measure for the elimination capacity of the liver and kidneys, is defined as the volume of plasma which is completely cleared of a drug per unit of time (volume/time). In steady state conditions, where input equals output, the quantity of a drug that needs to be given per unit of time (T) is equal to the amount that is excreted per unit of time. So for oral dosing schedules this means that F x D/T = Cl x Css, with F being the first pass effect, D/T (dose/time) being the maintenance dose, Cl being the clearance and Css being the drug concentration in steady state conditions. Thus, in steady state, the maintenance dose should equal the clearance (per unit of the same time). When a rapid effect is desired with a medication that has a high Vd and long $T_{½}$, a loading dose must sometimes be administered. The loading dose itself is independent of the clearance. It is the volume of distribution that determines how much should be given in order to achieve a certain initial concentration. Clearance determines how much drug should be given in order to keep this concentration stable.

Renal impairment

If the glomerular filtration is decreased, for example in kidney disease, there is a risk of accumulation of drugs. Usually, renal clearance declines by the same factor as the GFR. Renal impairment is an important consideration when administering medications that are more than 50% cleared by the kidney; the doses of these drugs should be adjusted accordingly.

Half-life ($T_{1/2}$)

Objectives: The half-life ($T_{½}$) is the time taken for the drug plasma concentration to halve. The time it takes to reach 'steady state' is only dependent on the half-life. The half-life of a drug determines whether there is a need for a loading dose or not. A long half-life may be caused both by a low clearance and a large volume of distribution.

The half-life is the amount of time it takes for the body to reduce the plasma concentration of a substance by 50%. The half-life is proportional to the volume of distribution, and inversely proportional to the clearance: $T_{½} = 0.7 \times V_d/Cl$.

If, upon repeated administration, the daily absorbed fraction of the dose is equal to the amount eliminated, the plasma concentration fluctuates around a constant value. This plateau is reached after approximately five half-lives. In general, clinical effects of a drug should be assessed when the plateau phase (steady state) has been reached after repeated dosing (see Fig. 30).

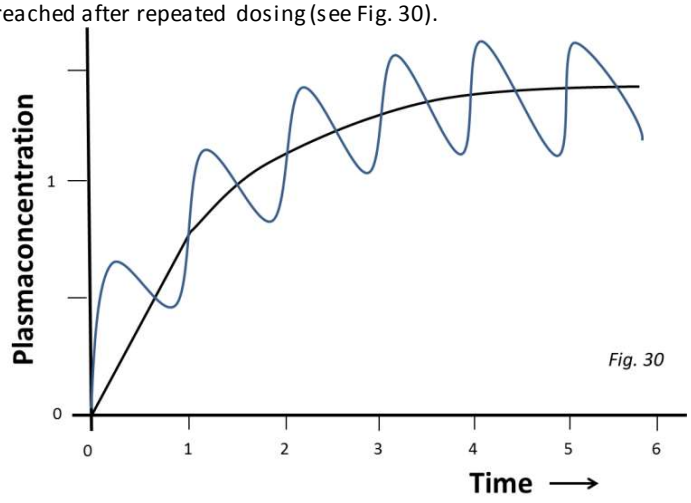


Fig. 30

I. Drug allergies

Hypersensitivity reactions to drugs are common. A drug can cause an immunological hypersensitivity reaction which may present as a fever, rash, impaired hepatic and renal function, pneumonia, mucosal lesions, and/or haematological abnormalities such as auto-immune haemolytic anaemia or autoimmune thrombocytopenia.

When a hypersensitivity reaction is suspected, the particular drug should immediately be stopped:
A. Anaphylaxis (immune/non-immune)
B. Thrombocytopenia/haemolytic anaemia
C. Severe skin reactions (Severe Cutaneous Adverse Reactions (SCAR))
   C.1. Stevens Johnson Syndrome (SJS)
   C.2. Toxic epidermal necrolysis

Objectives: For the pharmacotherapy safety test, the following topics should be known: the types of allergic reactions, the main drugs that provoke these reactions, the risk and the prevention and treatment thereof. This information is summarised in Table 57. The remaining information is supplementary and will not be assessed in the exam.

Table 57: Drug reactions that necessitate immediate withdrawal of the drug [5]

	Anaphylactic /anaphylactoid reaction	**Thrombocytopenia / haemolytic anaemia**	**Serious skin reactions: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)**
Frequently responsible drugs	β-lactam antibiotics NSAIDs Muscle relaxants	Heparins β-lactam antibiotics	Antibiotics Carbamazepine Allopurinol
Risk factors	Frequent exposure, immune activation (chronic viral infections), asthma/atopy (pronounced course)		
Preventative measures	Prescribe with caution - check for the presence of allergy prior to prescribing		
Treatment	STOP suspected drug/replace by chemically unrelated drug		
	Grade III or higher: Adrenaline 0.5-1.0mg IM Clemastine (Tavegil) 2mg IV Dexamethasone 0.1mg/kg IV If bronchospasm present, nebulisation with salbutamol	(platelet) Transfusion	Pain Relief Infection control If> 30% of surface area of is body affected -> burn centre.

[5] Acute boekje NIV. 2009

A. ANAPHYLAXIS

In anaphylaxis, there is a systemic, severe, and rapid manifestation of a type I IgE-mediated hypersensitivity reaction. Both allergic and non-allergic reactions may be the underlying cause (Table 58). Symptoms may be mild, such as pruritus, urticaria, angioedema and erythema, but severe life-threatening anaphylactic shock can also occur (Table 59). Non-immunologically mediated mast cell activation results in the same clinical symptoms as IgE-dependent mast cell activation, and can be induced, amongst others, by aspirin, NSAIDs and opiates.

Table 58: Anaphylactic vs Anaphylactoid reactions[6]

Anaphylactic reaction	Anaphylactoid reaction
Anaphylactic reactions present only after sensitisation has occurred. The reactions only manifest themselves 7-21 days after the first exposure to the drug. Following repeated exposure an allergic reaction can be induced, either within minutes of the last administration (type I, IgE-mediated response), or after a few days (type IV T-lymphocyte mediated response).	Anaphylactoid reactions are similar to IgE-mediated responses, but are not due to specific recognition of an antigen by the cells of the immune system. Through interaction with the membranes of mast cells, opiates can evoke the release of histamine. Reactions following aspirin and other NSAID administration are probably related to COX mediated overproduction of leukotrienes over prostaglandins (which are inhibited by the NSAIDS). These reactions are dose-dependent and may occur after the first dose.

Table 59: The different degrees of anaphylaxis

Degree	Symptoms
First Degree	Pruritus, erythema and urticaria
Second Degree	+ Generalised oedema and gastrointestinal symptoms: nausea, abdominal cramps and diarrhoea.
Third Degree	+ Stridor, dysphagia, hoarseness and dyspnoea. In more serious cases, dyspnoea with oedema in the upper airways or bronchoconstriction occurs. Hoarseness and stridor are indicative of obstruction at the level of the larynx. In addition to symptoms of dyspnoea and wheezing, patients often experience tightness in the chest.
Fourth Degree	+ Cyanosis, hypotension, syncope, unconsciousness, incontinence, and severe cardiac arrhythmias. These circulatory complications are life-threatening. Through vasoplegia, loss of plasma and cardiac arrhythmias, a cardiovascular collapse may develop in a short time.

[6] W.M.C. Mulder, M.M.H.M. Meinardi, D.P. Bruynzeel. Cutaneous reactions to drugs. The Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde, 2004.

B. THROMBOCYTOPENIA/HAEMOLYTIC ANAEMIA

1. Heparin-induced thrombocytopenia (HIT)

Heparin Induced Thrombocytopenia (HIT) is a relatively uncommon yet very serious complication. Patients treated with heparin may produce antibodies against the complexes of heparin and platelet factor-4 circulating in the blood. The binding of this antibody to platelets causes potent platelet activation, which leads to platelet depletion and consequently thrombocytopenia. In many cases, severe arterial or venous thrombosis also occurs. Because this thrombosis occurs in patients when they are treated with heparin, it is called paradoxical thrombosis. There are two types of HIT. Type I is a non-immune-mediated thrombocytopenia, whereas type II is an immune-mediated form (Table 60). HIT typically occurs when using unfractionated heparin, but it can also occur with the use of LMWH (although less frequently). Although HIT occurs in less than 1% of patients treated with heparin, it is nevertheless required to monitor the platelet count every week during heparin treatment. In HIT type II, administration of heparin should be discontinued immediately, whereas in type 1 this is not necessary.

Table 60: Heparin-induced thrombocytopenia (HIT): type I vs type II

HIT type I	HIT type II
1-4 days after starting heparin Platelets $100x10^9$/L No anti-HEP/PF4 antibodies No thrombosis, no bleeding complications Continue heparin	5-10 days after starting heparin Platelet count $30\text{-}55x10^9$/L Positive anti-HEP/PF4 antibodies 30% of patients develop thrombosis; bleeding complications are rare. DISCONTINUE heparin!

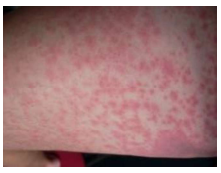
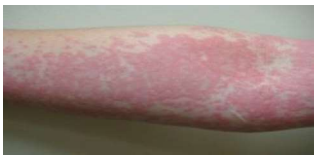
2. Haemolytic anaemia associated with medication use

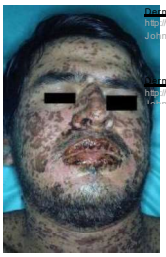
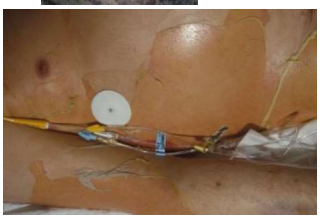
A major cause of drug-induced haemolytic anaemia is β-lactam antibiotics. In penicillin-induced haemolytic anaemia for example, IgG antibodies bind to a penicillin derivative which is bound to the erythrocyte membrane. This type of haemolytic anaemia occurs approximately one week after the start of the β-lactam antibiotics. After discontinuation of the causative drug, recovery is usually seen within a few days.

C. SKIN REACTIONS

Skin reactions are among the most common side effects of medication use. These are seen frequently when patients are treated with penicillins, cephalosporins, allopurinol, or carbamazepine. Common skin lesions are exanthema, maculopapular eruptions, urticaria and angioedema. Serious skin reactions (referred to as "severe cutaneous adverse reactions', or SCAR) include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); these two complications are however relatively rare (Table 61).

Table 61: Skin lesions caused by medication

Lesion	Presentation	
Maculopapular eruptions	Maculopapular eruptions are the most frequently occurring drug-associated skin eruptions. They are mainly observed during treatment with penicillins, carbamazepine, or allopurinol.	
Urticaria	Urticaria is a slightly elevated, itchy skin eruption. Usually there is a white-coloured central spot. This may be the result of an IgE-mediated, allergic reaction, but it can also be caused by a non-allergic reaction.	

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) Life-threatening! STOP IMMEDIATELY!!	These serious skin reactions are relatively rare. In SJS, <10% of the body surface is usually affected. It is regarded as an extensive form of erythema multiforma, as one or more mucous membranes may be affected. Patients with SJS usually present also with conjunctivitis and oral mucositis. Progression of the disease may result in a clinical presentation similar to that of severe burns, which may necessitate treatment in a specialist burns centre. The skin surface area that is affected then is larger (> 30%) and skin shed in large lacerations / lesions / plaques. Both SJS and TEN are characterised by necrolysis of mucosa and skin. In addition to the symptoms in the skin, both conditions can also induce a systemic reaction in the patient. This may manifest as a prodromal stage where the patient experiences fever and general malaise. SJS and TEN are both life-threatening, so early recognition is very important.	 Dermnet.com / http://www.dermnet.com/Stevens-Johnson-Syndrome/picture/14975  Dermnet.com / http://www.dermnet.com/Toxic-Epidermal-Necrolysis/picture/14991

J. Laws and regulations

!TO BE ADAPTED BY EACH INDIVIDUAL COUNTRY!

It is of great importance for the prescribing process to adhere to the necessary procedures and regulations. Drugs can, if they are not prescribed competently, harm the patient. This chapter is divided into the following subheadings:
A. Writing prescriptions
B. Driving while taking medication

A. WRITING PRESCRITPIONS

Objectives: Every prescription must adhere to the Medications Act and must include the following information: the name and date of birth of patient, the physician's name, the name / strength / dose / method of usage, initials and the date. It is also mandatory to state the kidney function of the patient and whether the medication is one of the 23 mediations requiring special attention (according to the Medications Act).

Objectives: Every prescription must adhere to the Medications Act and must include the following information: the name and date of birth of patient, the physician's name, the name / strength / dose / method of usage, initials and the date. It is also mandatory to state an abnormal kidney function (< 50 (MDRD/e-GFR)) of the patient and whether the medication is one of the 23 mediations requiring special attention (according to the Medications Act).

It is important that no data is missing on the prescription. The Medications Act states what is required. Each prescription must contain the following information:

- Name of authorised physician, preferably with address and telephone number
- Date of prescription
- Name, sex, date of birth and address of the patient (in children, indicate the body weight or height)
- Signature with doctor's initials (Full signature with Opium Act drugs) and Method of administration

Please note that since January 1, 2014, electronic prescriptions have been compulsory in the Netherlands.

1. Prescription structure

A prescription always starts with the designation R / ("R" is derived from the Latin verb recipere which means to take). The order in which the drug-related information is to be put on a prescription consists of three parts (Table 62).

Table 62: Guidelines when prescribing

Principle	Description	Example
Rule 1	On the first line you state the name of the substance and strength (in mass per dosage, try to avoid decimals).	R/ Paracetamol 500mg

Rule 2	On the second line you state the dosage form (tablets, capsules) to be delivered and in what quantity. This is indicated by: d.t.d = Da tales doses = give such doses.	Dtd tablet no 15
Rule 3	On the third line you state what must be written on the label; this line begins with the letter S (= signa, write on the label). Consider in particular the time of ingestion; when to stop; whether driving is allowed etc. With regards to non-oral medications, provide directions regarding the particular route of administration.	S. 4dd 1, take with water

2. Name of the drug

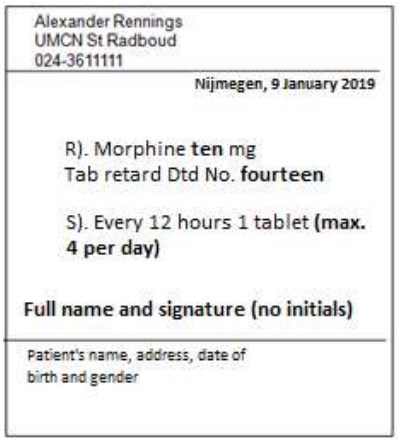
Medicines can be prescribed using their generic name or by their brand name. The generic name only gives information about the nature of the active substance. The brand however also provides information about the manufacturer. It is advised to only use generic names when prescribing. The advantage is that generic names are internationally recognised and that the pharmacist can choose the cheapest option.

3. Opium Act Drugs (Dutch regulations)

Objectives: Each opioid prescription is required to adhere to the Opium Act. This requires the inclusion of the following information: the name, date of birth and full address of the patient; the full address and telephone number of the physician; the strength and amount of the drug written in words; the date the prescription is being written and; the physician's signature.

Prescribing of Opium Act drugs is regulated by the Opium Act. The aim of this Act is to restrict the use of opium and other narcotics. Opiates should be prescribed according to a special format:

- The strength of the composition and number of units to be delivered should be written in words
- The name, initials and full address must be given of the doctor and patient, as well as the gender of the patient
- The maximum daily dose should be written out in full
- The number of repetitions must be written in words
- The prescription must be signed with the full signature of the prescriber
- Each prescription note should only account for one preparation
- The prescription must be written in indelible ink



B. DRIVING A VEHICLE WHILE USING MEDICATION

Objectives: A number of drugs are known to influence the reaction time. They are included in the list of "danger-to-driving" drugs, which are classified into three categories: Category 1 = safe; category 2 = mild to moderate negative impact, which users generally adapt to; category 3 = severe, potentially dangerous influence. Hazardous drugs include: benzodiazepines, opioids, TCAs, certain anti-epileptic drugs, certain antipsychotics and certain antihistamines (clemastine). To protect the prescribing physician and the pharmacist from liability lawsuits, the patient must be informed of any effect the drug may have on their ability to drive. According to road traffic law, a driver is committing a criminal offence when driving under the influence of a drug which they know or reasonably should know can affect their driving abilities.

Certain drugs or their side effects can affect driving ability of the user. This usually relates to symptoms such as dizziness, drowsiness, decreased concentration or reduced attention

1. Three categories

The drugs that affect driving abilities are classified into three categories on the basis of their initial effect upon their commencement (Table 63). After a few hours, days or weeks of use, a different warning level may be applicable, depending on how much tolerance (to the initial sedative side effect) the patient has developed.

Table 63: The drug impairment classification

Category	Description
0	Safe to drive a vehicle.
1	Little effect on the ability to drive. This is comparable to a blood alcohol concentration of <0.5‰.
2	Mild to moderate adverse effect on driving. This is comparable to a blood alcohol concentration of 0.5 to 0.8%. Patients should not drive when commencing the drug.
3	Serious or potentially dangerous influence on driving. This is comparable to a blood alcohol concentration of> 0.8‰. This category includes benzodiazepines, opiates (including tramadol), some anti-epileptic drugs, some antihistamines (clemastine), TCAs and some antipsychotics. The patient may only drive again when the drug is stopped or if the side effects diminish after a period of time (this varies per medication, see http://rijveiligmetmedicijnen.nl).

2. Regulations for doctor and patient

Drugs that affect a patient's response time have a yellow sticker that states: "This medication can diminish reaction times". Doctors and pharmacists, when prescribing and dispensing these drugs, have a duty to inform the patient about the relevant side effects, and also possible alternatives, for example there may be a drug available whose effect on a patient's driving ability may be less severe but whose overall efficacy is also less.

According to road traffic law, a driver is committing a criminal offence when driving under the influence of a drug which they know or reasonably should know can affect their driving abilities.

K. Appropriate use of medication

Efficient prescribing of medication is of great importance. Efficiency entails, besides acting in the best health-related interests of patients, acting with the costs of treatment in mind, following guidelines (and deviating from them when required), and prescribing the cheapest variant of drug available (generic prescribing). This chapter is divided into the following subheadings:

A. Pharmacotherapeutic plan: the WHO six-step method
B. Old or new medications?
C. Generic prescribing
D. Transfer and logistics

A. PHARMACOTHERAPEUTIC PLAN: WHO 6-STEP

Objectives: For optimal treatment, one is advised to employ the 6-step method developed by the WHO (Table 64). An important factor determining the success of a treatment is the compliance of the patient to the therapy. By providing clear instructions with regard to the taking and use of the medication, the compliance can be improved. Also, it is important to explain the expected effect(s) and side effects.

The primary learning objective of this chapter is to learn to how solve individual patient problems in a proper and rational way, by asking: why, when and how medicinal therapy should be applied in patients.

1. Six-step plan

The *WHO Guide to Good Prescribing* describes the rational prescribing of medications in the format of a multi-step plan (Table 64). This method can be employed when analysing patient problems, leading to a full prescription.

Table 64: The 6-step method for rational prescribing [7]

Step	Description
Step 1: problem	Define a working diagnosis in terms of severity, cause and possible consequences. Also evaluate the ongoing therapies for the problem.
Step 2: treatment goal	Here, the goal of treatment is chosen: curative, symptomatic, preventive or palliative.
Step 3: treatment options	A choice is made for non-pharmacological and pharmacological treatment options. The choice for a particular class of medicines should be founded on evidence based medicine, current guidelines, etc. Once the optimal class of drugs has been chosen (on the basis of mechanism of action) the best particular drug from this class must be selected.
Step 4: check that choice is appropriate for specific patient	In this step, one should consider whether the particular drug of choice is suitable for the particular patient. Factors that should be considered include comorbidities, gender, age, race, preferences and wishes of the patient, pregnancy, expected adherence, co-medication and allergies.

[7] Vries TPGM de, Henning RH, Hogerzeil HV, Fresle DA. Guide to good prescribing, A practical manual.

Step 5: prescription and patient information	A prescription is written and a choice is made for the correct dosage, formulation (tablet, powder, liquid etc.) and route. The patient is informed about the drug therapy (desired effect, side effects, and dosing instructions), while focusing on encouraging adherence.
Step 6: follow-up	A plan for follow-up is made with the effect, side effects and compliance to be checked at an agreed future date.

2. Adherence

According to the WHO, 50% of patients are noncompliant. A decreased compliance can lead to an increased risk of morbidity and mortality, and increased costs of care. Reasons for non-adherence are complex (Table 65). Compliance can be improved in several ways. Examples include simplifying dosing regimens, improving communication between and informing of caregiver and patient.

Table 65: Intentional and nonintentional causes of therapy non-compliance

Non-intentional factors	Intentional factors
Forgetfulness (e.g. because of complex dosing regimens or polypharmacy)	Patient regards treatment as unnecessary (e.g. with asymptomatic disease)
Limited ability to understand treatment	Negative attitude towards specific prescribed drug
Ease of administration of the drug (e.g. pill size)	Concerns about drug (side effects, dependence, addiction)
Cost of treatment	Lack of confidence in treatment
Illiteracy	Lack of knowledge
Visual impairment	Disease concerned has a stigma attached to it

B. OLD OR NEW MEDICATIONS?

Objectives: The selection of a drug must take place on the basis of the following factors: efficacy, safety (newer vs older medication), costs and efficiency. This should in principle result in a prescribing policy that states: "cheap if possible, expensive when needed".

Newer medications are often relatively expensive. The question is whether it is justified to prescribe these new drugs when older, cheaper medicines can function just as adequately. Specialists who consider prescribing new preparations should make this assessment and evaluate whether the new product meets expectations.

- "Me too's" are new versions of drugs that closely resemble the original medications but rarely offer additional advantages. There is also a risk of unknown idiosyncratic adverse reactions with these drugs. Benefits of "Me-too's" can include more favourable pharmacokinetics, fewer interactions and increased applicability of the new drug e.g. in patients with hepatic or renal dysfunction.
- 'New Chemical Entity (NCE)' is the name for a medicine with a new chemical moiety. The assumption is that such new chemicals add to the therapeutic array of available treatments. Due to the novelty of the drug, particular attention is required to monitor unexpected side effects. Adverse reactions should be reported to agencies recording these side-effects (In the Netherlands this is the LAREB).

C. GENERIC SUBSTITUTION

Objectives: Drug substitution is an important means to reduce costs in health care. Generic substitution is the substitution of medicines with other medicines with the same active substance, the same strength and the same pharmaceutical form. The registration of generic medications does not require repetition of pre-clinical research; the only requirement is that it must be demonstrated that the active ingredient acts in the body in the same manner as the original drug and that it reaches the same site of action with the same speed.

To keep health care affordable and of the highest quality possible, work within the healthcare sector needs to be done as effectively as possible. With a generic substitution, a branded drug is replaced by a drug with the same active ingredient. Upon registration of medicines, it must be demonstrated by means of a bio-equivalence study that the active substance works in the same manner and arrives at the site of action at the same time as the registered drug. Generics are considered bioequivalent if the 90% confidence interval of the AUC ratio and C_{max} is within 80-125% of the reference product. For agents with a narrow therapeutic index, these values should be between 90-111.11%. Generic prescribing is achieved by prescribing a drug using the generic name rather than by the branded name; the pharmacy can then, wherever possible, supply a generic version (generic substitution). The doctor may also choose the cheapest variant from a group of drugs characterised by a similar pharmacological profile. An important limitation when prescribing by generic name is that small variations in drug characteristics can have considerable consequences in the effect. This may apply to situations where the therapeutic index is small or bioavailability is low. The reason for choosing a branded version, as sometimes said, is to avoid confusion for the patient. Allergic reactions to adjuvant components (components other than the active ingredient in the preparation) are very rare.

D. TRANSFER AND LOGISTICS

Objectives: At any time of prescribing, a patient's current medication list should be available. Consent from the patient is needed when obtaining, viewing, using and updating of medication data by clinicians (Personal Data Protection Acts).

The guidelines regarding the transfer of medication data throughout the health care chain state that an overview of the patient's current medication list should be available at any time in the process of writing prescriptions. The purpose hereof is to prevent errors and to increase patient safety with the transfer of medication data. The guidelines are applicable to any situation in which medication is prescribed, modified or stopped. In table 66, the responsibilities of the different stakeholders in the transfer of medication information are described.

Table 66: Responsibilities of different care givers with regards to the patient's medication list

Care giver	Responsibility
The prescriber	The prescriber himself is responsible for ensuring that he has the patient's current medication list during a consultation. He is also responsible for registering all changes instigated by him to the medication.
The pharmacist	The pharmacist is responsible for the secure dispensing and monitoring of the medications prescribed to the patient. He must take all the necessary steps to ensure that the patient's medication list is always up to date when patient data is transferred from one prescriber to another.

L. Pregnancy and breastfeeding

During pregnancy many changes occur in the mother's body which can influence the mechanism, side effects and toxicity of medications. Therefore medications are only prescribed to pregnant patients if there is an absolute indication. The use of medications during pregnancy and breastfeeding is not always preventable; in such cases decisions are made regarding which medications, when and in which dose the medication will be prescribed.

Information over the use of medications during pregnancy can vary between sources. The best Dutch source of information regarding this subject is the Teratologie Informatie Service from Lareb.

1. Medication and pregnancy

Objectives: The best source of information over this topic is the Teratologie Informatie Service from Lareb. The use of medications during pregnancy is sometimes unavoidable. Medical management is often necessary in the treatment of infections or chronic illnesses such as diabetes, asthma, epilepsy or hypertension. This should be done in such a way that risk to the foetus is minimised.
Certain medications (such as nadroparin or heparin) do not cross the placental barrier and are therefore safe. The risks for the foetus differ depending on the stage of the pregnancy. In the first trimester the main concerns are miscarriage and genetic disorders. In the second trimester the main concerns are growth and developmental delays. In the third trimester the main concerns are the pharmacological effects of the medication on foetal growth e.g. insulin and thyroid hormone inhibitors. One should be aware that there may be a heightened risk of a complicated birth (for example due to anti-coagulants, opiates or NSAIDs).

Medical management is often required in the treatment of infections or chronic illnesses such as diabetes, asthma, epilepsy or hypertension. In such cases medications are prescribed in such a way as to minimise the risk to the foetus. Certain medications (such as nadroparin or heparin) can cross the placenta and are therefore not safe.

A medication is considered teratogenic if its use during pregnancy causes a (structural) developmental disorder. Certain medications are considered toxic to the embryo or foetus; this means that these medications have a toxic effect on fertilisation and/or on embryological or foetal development. The pathogenesis behind these effects is not always known, however what is clear is that adverse effects are often dependent on the specific medication and the point in time during pregnancy in which it is used.

- In the first trimester the main risks include miscarriage and genetic disorders, such as spina bifida.
- In the second trimester the main risks are growth and developmental disorders.
- In the third trimester the main risks are the pharmacological effects of the medication on development (especially insulin and thyroid hormone inhibitors).
- One should be aware that the use of medications can increase the risk of a complicated birth, for example there may be an increased tendency to bleed (due to anti-coagulants), or the birth itself may be more difficult (due to contraction inhibitors, e.g. opiates or NSAIDs).

2. Classification of Medications during Pregnancy (Teratologie Informatie Service – Lareb)

Objectives: The classification system helps us to consider the advantages and disadvantages of prescribing a medication and decide whether to actually prescribe it.

- **Most safe:** these drugs may be used by a pregnant woman (e.g. paracetamol, nadroparin, amoxicillin, clarithromycin and acetylsalicylic acid (maximum dose 160 mg/day)).
- **Probably safe:** these drugs may be prescribed, however if possible choose an alternative drug from the "most safe" category (e.g. metoprolol, metformin, diclofenac and ibuprofen).
- **Possible risk:** these drugs should be prescribed only after careful consideration of the benefits and risks of these medications. Regular check-ups are necessary.
- **Risk of congenital abnormalities:** only prescribe these medications in exceptional circumstances (e.g. carbamazepine, acenocoumarol, phenprocoumon, doxycycline, gentamicin, enalapril).
- **Unknown risk:** insufficient information available. Choose a medication where more is known regarding the safety (e.g. ciprofloxacin).

The following classification system helps us to consider the advantages and disadvantages of prescribing a medication and decide whether to actually prescribe it:

- **Most safe:** these drugs are the safest and hence may be used during pregnancy (examples of drugs in this category are: paracetamol, nadroparin, amoxicillin, clarithromycin and acetylsalicylic acid (maximum dose 160 mg/day)). Data collected in research studies and/or in clinical practice has demonstrated that there is no increased risk of congenital defects or harmful effects during pregnancy.

- **Probably safe:** these drugs may be prescribed, however if possible choose an alternative drug from the "most safe" category (examples of drugs in this category are: metoprolol, metformin, diclofenac and ibuprofen (probably safe during the first and second trimester of the pregnancy)). A reason why a drug may be classified as "probably safe" and not as "most safe" may be because there is currently insufficient data regarding its safety.

- **Possible risk:** these drugs can have potentially harmful effects on the pregnancy or the foetus, and hence should be prescribed only after careful consideration of the benefits and risks. Regular check-ups are necessary.

- **Risk of congenital abnormalities:** these drugs carry an increased risk of causing congenital abnormalities or complications during pregnancy (examples of drugs in this category are: carbamazepine, acenocoumarol, phenprocoumon, doxycycline (from week 16), gentamicin, enalapril (second and third semester)). Only prescribe these medications in exceptional circumstances.

- **Unknown risk:** there is insufficient information available regarding the use of these drugs during pregnancy (examples of a drug in this category is: ciprofloxacin). It is therefore not possible to know for certain if these drugs are safe. Choose a medication where more is known regarding its safety.

3. Medication and Breastfeeding

Objectives: If the use of medication during the breastfeeding period is necessary, then it is important to make a well-considered decision regarding the continuation of breastfeeding. It is always possible to switch to bottle-feeding if necessary.

If the use of medication during the breastfeeding period is necessary, then it is important to make a well-considered decision regarding the continuation of breastfeeding. It is always possible to make a switch to bottle-feeding.
Not all medications can enter the breastmilk; this depends on several factors:

- Pharmacokinetics in the mother: the method, dosage, bioavailability and the half-time.
- Chemical properties of the medication: molecular weight, protein binding, fat solubility and acidity.

The consequences for the breastfed child depend on the quantity of the medication which reaches the child and the period of time during which the child will be exposed to the medication.

4. Classification of Medications during Lactation (Teratologie Informatie Service – Lareb)

Objectives: The following classification is used to assist in deciding whether breastfeeding can be continued:

- **Safe:** Breastfeeding can be continued (examples: paracetamol, ibuprofen, acenocoumarol, nadroparine).
- **Probably safe: I**t is unlikely that there is any risk; adopt a watchful waiting approach (examples: diclofenac, acetylsalicylic acid, metoprolol, phenprocoumon, enalapril, metformin).
- **Unknown risk:** There is no, or no relevant, available information regarding the use of these medication in combination with breastfeeding (example: ciprofloxacin).
- **Probable risk:** The medication is likely to be harmful to the child; these risks must be weighed against the mother's own needs and degree of use of the medication (examples: codeine, morphine).
- **Risk, stop:** It is not safe to prescribe these medications and continue breastfeeding (examples: the long term of use of oxazepam and diazepam).

Safe: The medication can be safely combined with breastfeeding. Breastfeeding can be continued (examples: paracetamol, ibuprofen, acenocoumarol, nadroparine).
Probably safe: Based on available information, it is unlikely that there is any risk. Adopt a watchful waiting approach (examples: diclofenac, acetylsalicylic acid, metoprolol, phenprocoumon, enalapril, metformin).
Unknown risk: There is no, or no relevant, available information regarding the use of this medication in combination with breastfeeding (example: ciprofloxacin).
Probable risk: The medication is likely to be harmful to the child. The risks to the child must be weighed against the mother's own needs and degree of use of the medication (examples: codeine, morphine).
Risk, stop: It is not safe to prescribe this medication and continue breastfeeding. If possible a safe alternative should be chosen, otherwise breastfeeding must be (temporarily) stopped (examples: the long term of use of oxazepam and diazepam).

Objectives: The following drugs should be known: Paracetamol, nadroparin, amoxicillin, clarithromycin, metoprolol, acetylsalicylic acid, diclofenac, ibuprofen, phenprocoumon, doxycycline, gentamycin, enalapril, metformin, ciprofloxacin.

Overview of drugs

This overview lists all drugs mentioned in the various chapters. Where possible, the summary includes direct links to the e-learning tool TRC Pharmacology. Also listed are several important drug interactions that must be known for the medication safety test.

PAIN MEDICATION

- Paracetamol
- Prostaglandin synthetase inhibitors
  - Diclofenac
  - Naproxen
  - Ibuprofen
  - Acetylsalicylic acid
- Opioid receptor agonists
  - Morphine
  - Fentanyl
  - Tramadol
  - Oxycodone
  - Codeine
- Opioid antagonists
  - Naloxon
- (Omeprazol)

Medication that interacts with pain medication:

- Lisinopril (ACE-inhibitors)
- Losartan (angiotensin-II-antagonist)
- Acenocoumarin (vitamin K-antagonist)
- Paroxetine (SSRI)
- Furosemide (loop diuretics)

ANTICOAGULANTS

- Thrombocyte aggregation inhibitors
  - Acetylsalicylic acid
  - Clopidogrel
  - Ticagrelor
- Coumarin derivatives
  - Acenocoumarin
  - Phenprocoumon
- Heparin group
  - Heparin
  - Nadroparin
- Heparin antagonist
  - Protamine
- DOACs
  - Dabigatran
  - Apixaban
  - Rivaroxaban
  - Edoxaban
- Vitamin K

Medication that interacts with anticoagulants:

- Co-trimoxazole (antibiotic)
- Prednisone (corticosteroid)
- Paroxetine (SSRI)
- Carbamazepine (anti-epileptic)

CARDIOVASCULAR DRUGS

- Thiazide diuretics
  - Chlorthalidone
  - Hydrochlorothiazide
- Loop diuretics
  - Furosemide
- Potassium sparing diuretics

Medication that interacts with cardiovascular drugs:

- Paroxetine (SSRI)
- Oxazepam (benzodiazepine)
- Diclofenac (NSAID)

    - Spironolactone
    - Triamterene
- β-receptor blocking sympatholytic
    - Metoprolol
    - Sotalol
    - Propranolol
    - Atenolol
- Calcium antagonists
    - Nifedipine
    - Amlodipine
    - Verapamil
- ACE-inhibitors
    - Enalapril
    - Lisinopril
- Angiotensin II (AT_1)-antagonists
    - Losartan
- Heart glycosides
    - Digoxin
- Nitrates
    - Isosorbide-dinitrate
    - Isosorbide-mononitraat
- Sodium polystyrene sulfonate
- Insulin/glucose
- Calcium gluconate
- KCl-drink

ANTIDIABETIC DRUGS

- Metformin
- SU-derivate
    - Tolbutamide
    - Glimepiride
    - Gliclazide
- Insulin
    - Humuline regular
    - Aspart
    - Glargine
- Glucagon

Medication that interacts with antidiabetic drugs:

- Metoprolol (beta-blocker)
- Propranolol (beta-blocker)

ANTIDEPRESSANTS

- Tricyclic antidepressants
    - Amitriptyline
    - Nortriptyline
- Serotonin reuptake inhibitors
    - Fluoxetine
    - Paroxetine
    - Citalopram
- Lithium

Medication that interacts with antidepressants:

- Naproxen (NSAID)
- Furosemide (lis diuretic)
- Hydrochlorothiazide (thiazide diuretic)
- Enalapril (ACE inhibitor)

BENZODIAZEPINES

- Benzodiazepines
    - Diazepam
    - Oxazepam
    - Temazepam
- Flumazenil

ANTIBIOTICS

- Penicillins (β-lactam antibiotics)
  - Penicillin
  - Amoxicillin
  - Amoxicillin-clavulanic acid
- Cefalopsorins (β-lactam antibiotics)
  - Ceftriaxon
- Tetracycline
  - Doxycycline
- Aminoglycosides
  - Gentamicin
- Macrolides
  - Azitromycin
- Trimethoprim/co-trimoxazole
- Quinolones
  - Ciprofloxacin
- Nitrofurantoin
- Fosfomycin

Interesting websites

For background information, you can consult the following websites:

www.necf.nl (The Nijmegen Expertise Centrum for Complex Pharmacotherapy)

www.farmacotherapeutischkompas.nl (Farmacotherapeutisch Kompas)

Do you want to practice the objectives?
The app "**Battle of the Meds**" is available through the Google Play Store and the App store. In this game, all the objectives described are assessed through different exercises. There are also some questions that assess knowledge that is not mentioned in the objectives, but rather relate to the formulation of an effective treatment plan.