Clinical use and toxicity of local anaesthetics

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Summary

Local anaesthetics are widely used in contemporary clinical practice. Regardless of their specific physicochemical properties and chemical structures, all local anaesthetic agents block neuronal voltage-gated sodium channels, suppressing conduction in peripheral nerves. Furthermore, these agents are characterised by numerous (sub-)cellular effects. Despite the fact that local anaesthetics with markedly decreased toxic potential have been developed, systemic intoxication still may be life-threatening. Amongst other things, this severe complication is the result of an unselective block of neuronal and cardiac sodium channels following excessive systemic accumulation, impairing central nervous and cardiac function. In contrast, the clinical impact of local anaesthetic tissue toxicity is controversial, as in many cases there is a lack of clinical symptoms.

Historic aspects

Just a short while after local anaesthesia was first successfully performed in 1884 by Karl Koller, an ophthalmic surgeon from Wien, it became apparent that cocaine – which he had used as a local anaesthetic – was not an ideal substance for the job. Complications – some of them fatal – were noted more and more often, dashing hopes that an alternative to contemporary ether anaesthesia could be established. It was for this reason that toxic complications of local anaesthesia were an early driving force in the development of new substances [1,2]. Once the chemical structure of cocaine had been established, attempts were made to reduce its toxicity by changing the molecular structure – an undertaking which succeeded in 1905 when procaine, a synthetic amino ester local anaesthetic, was synthesised. To this day, that substance is used as a reference standard for local anaesthetic potency. A further milestone was reached when in 1943 lidocaine, one of the first amino amide type local anaesthetics, was introduced into clinical practice. Amino amide type local anaesthetics provide a longer duration of action and are chemically more stable than ester types and so gained increasing clinical significance in the decades that followed. In 1979, however, toxicity hinted at a renewed setback for local anaesthesia when George A. Albright was able to show that a series of fatal complications during obstetric anaesthesia had been caused by the administration of high-dose bupivacaine or etidocaine [3]. In the aftermath, intensive efforts were undertaken to determine the pathogenic mechanisms of local anaesthetic toxicity in detail, and so to develop less toxic substances [4]. One important finding was that optical isomers of the same substance showed different affinities to voltage-gated sodium channels (Na^+ channels) and as such possess differing toxic potentials [5]. This finding resulted in the introduction of the "pure" local anaesthetic isomers ropivacaine and levobupivacaine into clinical practice.

Keywords
Local Anaesthetics – Sodium Channel Block – Alternative Effects – Toxicity – Neurotoxicity – Myotoxicity – Chondrotoxicity

Structure and mechanism of action

Structure

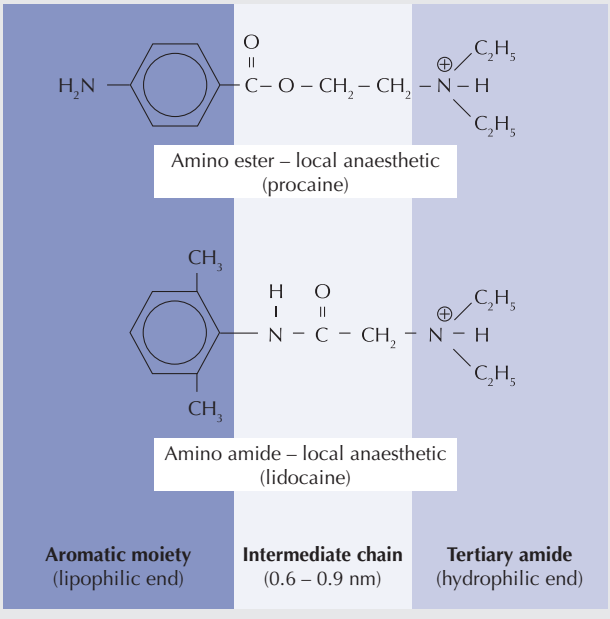
Although a number of organic chemical compounds display local anaesthetic properties (ketamine is one example), only amino esters and amino amides are used in clinical practice. These two classes of substance share a characteristic molecular structure made up – as described by the so called Löfgren schematic (Figure 1) – of three sections [2,6]:

- The **aromatic moiety** primarily determines the lipophilicity of the local anaesthetic.
- The **tertiary amide** of the **amino group** (substituted amino-nitrogen) is present either in its protonated or deprotonated (base) form and when positively charged constitutes the hydrophilic end of the molecule.
- The **intermediate chain** connects the aromatic moiety to the amino group and determines the categorisation of the substance as an amino amide or amino ester, whilst also influencing the pharmacokinetics of the substance, amongst other things.

The local anaesthetic potency of a substance and the toxicity of that substance are determined by its specific physicochemical properties, in particular by the type of substituent on the aromatic moiety and by its optical activity [2,6].

- The influence of the **substituents** can be shown using the example of the three pipecoloxylidide derivates mepivacaine, ropivacaine and (levo-) bupivacaine. If the methyl group on the aromatic moiety of mepivacaine is replaced by a higher alkyl chain, ropivacaine (propyl moiety) or bupivacaine (butyl moiety) is synthesised. This modification of the substituents increases the specific lipophilicity [2,7], which in turn increases the analgesic potency, duration of action but also the systemic toxicity of the substance. When the length of the alkyl chain on the aromatic moiety exceeds four carbon atoms the local anaesthetic potency will increase further – but systemic toxicity increases so abruptly that clinical use of the substance forbids itself.
- The **optical activity** of some local anaesthetics results from an asymmetrical carbon (C) atom with four different ligands which can take on varying spatial configurations. This results in the formation of two stereoisomers (or enantiomers) per asymmetrical C atom. These are identical in their chemical structure, but their ligands are spatially distributed in such a fashion that they cannot be converted into one another by rotation. Instead, the isomers behave as image and mirror image to one another or as the right to the left hand, so that the term chirality (handedness) is used in describing the relationship. Stereoisomers distinguish themselves by their ability to rotate polarised light within an aqueous solution – those which are optically active will rotate the plane of light by the same angle, but to the right or the left, clockwise or anticlockwise. Racemates – which contain an equimolar mixture of stereoisomers – are, however, optically inactive because the deflection of light cancels itself out. Optical activity is clinically relevant because the pharmacodynamics of the stereoisomers can differ significantly when they interact with other chiral molecules such as membrane-bound proteins (ion channels, receptors etc.) [6,8,9]. For example, laevorotatory S(-)-isomers of bupivacaine and ropivacaine show significantly smaller effects on cardiac Na^+ channels than do the racemates or dextrorotatory R(+)-isomers, and as such are less cardiotoxic. It was for this reason that the use of S(-)-ropivacaine and levobupivacaine was introduced into clinical practice – a first for pure stereoisomers – whilst the other optically active local anaesthetics are currently still used in their racemic form.

Figure 1



Schematic of the molecular structure of local anaesthetics.

Mechanism of action

On a molecular level, the mechanism of action of local anaesthetics essentially rests on the reversible blockade of Na^+ channels in neuronal membranes, inhibiting the formation and propagation of action potentials [6,10].

Na^+ channels consist of at least two subunits, namely the larger α-subunit and the smaller β-subunits. The α-subunit forms the transmembrane core of the channel, whilst the β-subunits are mainly responsible for anchoring the channel within the cell membrane. To date, ten different α-subunits have been identified, nine of which functionally act as sodium channels; they have been named Nav1.1 to Nav1.9 [6,11]. The α-subunits are made up of four domains with six transmembrane segments each. Every organ system is characterised by a specific pattern of distribution of α-subunits. As an example, peripheral nerves express every type of α-subunit bar Nav1.4, whereby this diversity is seen less in motor and proprioceptive A fibres but rather in nociceptive C fibres. Nav1.7 and Nav1.8 are almost exclusively expressed in nociceptive fibres and seem to have a central role in pain perception – these α-subunits are therefore seen to be potential targets for new analgesics and selective local anaesthetics.

Current knowledge tells us that local anaesthetics interact with all the α-subunits of the Na^+ channels in an identical fashion [10], whilst **intracellular** amino acid moiety between segments 5 and 6 of domains 1, 3 and 4 constitutes the actual target area. As such, the local anaesthetic molecules have to cross the cell membrane and diffuse into the inside of the cell before their effect can set in. This works because a local anaesthetic in an aqueous solution will rapidly form an equilibrium between the protonated and deprotonated forms (classic acid-base balance according to Brønsted), the position of which is defined by the substance-specific equilibrium constant (pK_a value = negative decadic logarithm of the relationship between deprotonated and protonated molecular forms in equilibrium) and which is also pH-dependent [12]. Because only deprotonated (uncharged) molecules can traverse the cell membrane, it is assumed that these molecules are activated by protonation following diffusion into the cell and then interact with intracellular receptors on neuronal Na^+ channels. The binding affinity to closed active channels is relatively low, whereas it is high to closed inactive and to open channels. Other than this classic mode of hydrophobic block other blocking mechanisms are currently being postulated [13].

Pharmacokinetic aspects

Systemic absorption

The extent and kinetics of systemic absorption are dependent on the perfusion and density of the capillary network at the injection site and on the physicochemical properties of the local anaesthetic (Table 1).

Plasma concentrations are highest following intrapleural, intercostal or peritonsillar administration, and lowest following subcutaneous or intraarticular injection.

Lipophilic local anaesthetics accumulate in the epidural space and in perineural fat, meaning that following epidural anaesthesia or peripheral nerve blocks peak plasma concentrations are delayed [7,12]. When perfusion at the injection site is unphysiologically increased, however, systemic absorption may be unexpectedly rapid and peak plasma concentrations reached early.

The **perfusion at the injection site** is increased by vasodilatory effects of the local anaesthetics. Co-injection of vasoconstrictors (e.g. adrenaline 1:200,000) can counter the vasodilatory effect and increase the clinical duration of action of the anaesthetic [14].

Following absorption into the bloodstream, local anaesthetics are transported bound to varying degrees to plasma proteins – a dynamic equilibrium between free molecules and those bound to plasma proteins ensues. Whilst many drugs bind to albumin, local anaesthetics primarily interact with alpha-1-acid glycoprotein. This acute phase protein reacts rapidly to pathological conditions and, as such, its plasma concentration varies significantly (reference range 550 to 1,440 mg/l) leading to considerable inter- and intraindividual variations in the proportion of free local anaesthetic molecules. The extent of protein binding is also influenced by temperature and pH [12].

Table 1

Pharmacokinetic properties of local anaesthetics in clinical use.
Potency = potency relative to procaine; **pK_a** = equilibrium constant; **$t_{1/2}$** = elimination half-life; **VD** = volume of distribution in equilibrium; **Cl** = clearance; **PC** = partition coefficient of octanol : buffer (at pH 7,4) as a measure of lipophilicity; **PB** = protein binding rate; **Extraction** = rate of hepatic extraction; **C_{tox}** = systemic toxic threshold concentration; **n/a** = not available; *Prilocaine undergoes both hepatic and pulmonary extraction. Based on [12].

Property	Procaine	Lidocaine	Prilocaine	Mepivacaine	Ropivacaine	Bupivacaine	Levobupivacaine
Potency	1	4	4	4	14	16	16
pK_a	9,05	7,9	7,9	7,8	8,1	8,1	8,1
$t_{1/2}$ (min)	1–3	96	96	114	111	162	162
VD (l)	k. A.	91	200–260	84	47	73	60–70
Cl (l/min)	k. A.	0,95	2,37	0,8	0,44	0,58	0,6
PC	0,02	2,9	0,9	0,8	6,1	27,5	27,5
PB (%)	5,8	64	40–50	78	94	96	96
Extraction	k. A.	0,65	k. A.*	0,5	0,4	0,4	0,4
C_{tox} (µg/ml)	k. A.	>5	>5	5–6	4	1,5	?

Elimination

The type of degradation and the elimination of local anaesthetics are determined by the basic chemical structure of the respective substance.

Amino amide local anaesthetics are predominantly hepatically metabolised with renal excretion of the unchanged drug responsible for only approximately 5% of elimination (this proportion of primary renal excretion can be increased to approximately 20% if protonation of the tertiary base to the more water-soluble quaternary form is accelerated by acidifying the urine). Hepatic metabolisation is via microsomal enzyme systems, which degrade amino amides via several steps to amino acid and a cyclic aniline derivative, followed by N-dealkylation or hydroxylation and conjugation with glucuronic acid, and finally renal elimination. The elimination half-life correlates well with hepatic perfusion and rate of metabolism. Prilocaine exhibits the highest and ropivacaine and (levo-)bupivacaine the lowest rates of elimination, with lidocaine and mepivacaine taking up positions in the midfield [12].

Following systemic absorption, amino ester local anaesthetics are rapidly inactivated by nonspecific plasma esterases; the half-life is usually less than 1 minute. Hydrolysis leads to formation of amino alcohols and carboxylic acids which are easily water-soluble and undergo renal elimination. Due to the rapid inactivation, intoxication caused by amino esters is uncommon; a genetic predisposition to decreased plasma esterase activity can, however, increase the elimination half-life significantly, leading to accumulation. Newborns can be presumed to be especially vulnerable because they exhibit a physiological 50% reduction in plasma cholinesterase activity [12].

Patient factors

Besides the aforementioned elementary mechanisms, a multitude of patient factors (such as age, weight and organ function) have direct influence on the pharmacokinetics of local anaesthetics [2,7,12].

Newborns exhibit a physiological reduction of alpha-1-acid glycoprotein concentration by about half meaning that, for example, a single dose of caudal ropivacaine in a newborn or infant up to 3 months of age leads to a higher free plasma concentration than in an older child. In addition, total clearance of local anaesthetics is reduced, which can be particularly relevant when long acting substances are applied continuously. Despite these facts the incidence of toxic complications is no higher in this age group than in an adult population.

The organism of the elderly person is characterised by reduced organ perfusion and function, leading to reduced metabolism and increased duration of action of many drugs including local anaesthetics. All in all, however, peak plasma levels and plasma protein binding in the elderly only deviate insignificantly from levels seen in younger adults. What is clinically more relevant is the fact that the morphology and function of neuronal structures change with increasing age, and nerve conduction velocity decreases. Moreover, a reduction in perineural fat means a reduction in an important storage compartment for local anaesthetics. The elderly person will therefore react more sensitively to local anaesthetics, a fact that can be inferred from animal research and which has been shown to be true clinically in epidural and plexus blocks [12].

Significantly decreased liver function will influence the pharmacokinetics of many local anaesthetics directly through reduced metabolism and indirectly through changes in haemodynamics and decreased protein synthesis. It is also the case that liver disorders are often associated with decreased function of other organs (especially the kidneys). In patients awaiting liver transplantation the total clearance of ropivacaine was reduced by approximately 60%, although no differences in plasma concentrations were seen when compared with healthy individuals [15]. As such, whilst a one-off bolus administration of a local anaesthetic in a patient with decreased liver function can be assumed to be largely safe, when long acting local anaesthetics are administered – especially continuously – accumulation of the substance and its metabolites has to be expected.

In advanced kidney failure total clearance of local anaesthetics will, as a rule, be reduced. Moreover, uraemic states are often associated with hyperdynamic circulation which can influence the rate of absorption and the time required to reach peak plasma levels. Due to the decreased renal excretory function, repeated or continuous administration of long acting local anaesthetics in particular is likely to lead to accumulation of the substances and their metabolites. As some of these degradation products bear a considerable systemic toxic potential, the risk of precarious complications increases significantly when drug doses are not appropriately adjusted. Kidney disease is also often characterised by a loss of protein. However, the relative proportion of alpha-1-acid glycoprotein increases in kidney disease, which at least in theory offers protection from excessively high free plasma concentrations of local anaesthetics, even though the total binding capacity of the plasma proteins is reduced [7].

Advanced heart failure leads to decreased perfusion of the liver and kidneys, reducing the rate of metabolism and excretion of some amino amides. In patients with profound heart failure, the plasma concentrations achieved by injecting 0.5 mg/kg body weight (BW) of lidocaine are equal to those achieved by injecting a healthy individual with twice that dose [16]. Whilst lidocaine – which shows a low degree of plasma binding – experiences an approximately 75% extraction from the hepatic artery with every liver passage, less than half of substances with higher degrees of protein binding such as bupivacaine and ropivacaine is removed [5]. For this reason, reduced cardiac output with correspondingly reduced liver perfusion will primarily influence the plasma levels of those local anaesthetics which display a low

degree of plasma binding. In cases of low-cardiac-output syndrome the perfusion at the (peripheral) injection site is often decreased, leading to the delayed absorption of local anaesthetics. However, a haemodynamic state entailing a shift of blood volume to the central circulation will lead to a relatively larger proportion of systemically absorbed substances reaching the central nervous system (CNS) and heart, increasing the risk for systemic intoxication [2,7].

Pregnancy leads to meaningful haemodynamic and circulatory changes as well as to relevant fluid shifts. This leads to increased perfusion of the peripheral areas of the body in the second half of pregnancy in particular, and with that to a more rapid systemic absorption of local anaesthetics. In addition, protein binding of many of these substances decreases significantly during the course of pregnancy. Because progesterone causes the heart to become more sensitive to local anaesthetics, pregnant women are particularly at risk of systemic toxic effects. What is more – again to due hormonal effects – neuronal structures react more sensitively to local anaesthetics, particularly in the last trimester.

Alternative effects of local anaesthetics

Basic principles

Local anaesthetics don't just block Na^+ channels, but also interact with a number of other channels and receptors such as potassium and calcium channels but also N-Methyl-D-aspartate (NMDA) and G protein-coupled receptors [6,13,17]. The resulting effects are termed the alternative effects of local anaesthetics.

These alternative effects result from subtoxic systemic drug levels and encompass a wide spectrum including increased intestinal motility, systemic analgesic, anti-inflammatory and anti-infective effects. Discussions regarding possible effects of local anaesthetics on the recurrence rates of certain tumours are ongoing [6,17,18,19].

Increased intestinal motility and systemic analgesic effects

Intestinal motility disorders including paralytic ileus are feared complications of major abdominal surgery. A number of articles suggest that intravenous administration of lidocaine reduces not only the duration of decreased intestinal motility but also time to hospital discharge [17,20]. It was shown that the systemic administration of lidocaine (1 mg/min for 24 hours) following open and laparoscopic abdominal surgery lead to a decrease in the duration of motility disorders with low pain intensity and reduced the length of hospital stay by 1 day [21]. A further trial [22] also showed a reduction in the length of hospital stay following the postoperative administration of lidocaine 2 mg/min for 4 hours. A meta-analysis [23] was able to confirm these results: patients receiving intravenous lidocaine showed initial intestinal motility 28 hours sooner than patients in the control group and were discharged from hospital 1.1 days earlier. The available research doesn't, however, permit us to assume the validity of these promising results seen in general surgical patients in other patient collectives.

Anti-inflammatory and anti-infective effects

With respect to **anti-inflammatory effects**, in vitro findings show that local anaesthetics influence the inflammation cascade at the levels of leucocyte adhesion, transendothelial migration, phagocytosis and cytokine liberation [6, 13,17]. In vivo, systemic administration of lidocaine lead to reduced plasma levels of proinflammatory cytokines, correlating with a more rapid onset of bowel function in the postoperative phase.

Certain local anaesthetics seem to exhibit **anti-infective effects** (antibacterial, antiviral and antimycotic) even at low doses [6, 24]. The degree to which the effect is seen is dependent on the substance; bupivacaine is effective against Staphylococcus aureus, Escherichia coli and Enterococcus faecalis when used in clinically relevant concentrations, whereas no such effect could be shown for ropivacaine and levobupivacaine [25]. Topical anaesthetic preparations (e.g. EMLA-cream, a mixture of lidocaine 2.5% and prilocaine 2.5%) also seem to demonstrate bactericidal effects comparable with alcoholic disinfectants [6,24]. The clinical significance of this aspect remains to be seen.

Influence on the recurrence rate of certain tumours

Whether or not the choice of anaesthetic or anaesthetic technique can influence the recurrence rate of tumours or the outcome of patients being treated for malignant disease is the subject of controversial discussions [6,17,18,19]. Whilst animal research has shown positive effects of local anaesthetics or regional anaesthesia, clinical results in humans have been inconsistent and contentious. A retrospective analysis [26] came to the conclusion that neuraxial anaesthetic techniques used in breast cancer surgery reduced the risk of postoperative metastatic spread. Another trial [27] showed a significantly lower rate of recurrence when radical prostatectomy was performed in general anaesthesia augmented by epidural anaesthesia. However, when looking at colon and prostatic cancers, other papers failed to demonstrate a positive effect of combining general with epidural anaesthesia [6,18]. It remains to be hoped that current randomised multicentre trials will provide an answer to the question of whether or not local anaesthetics or regional anaesthesia can influence the rate of recurrence of certain carcinomas.

Toxicity of local anaesthetics

Basic principles

Following injection, local anaesthetics reach their target neuronal structures by means of diffusion, crossing a number of barriers (peri-, epi- and endoneurium). At the same time, they are absorbed into the blood stream – the concentration at the site of action decreases and the plasma concentration increases.

- **Systemic toxicity** correlates closely with the plasma concentration [28, 29,30]. Because Na^+ channels are not only involved in neural conduction but are the central functional unit in all excitable membranes, adverse effects on other excitable cells have to be reckoned with when systemic concentrations become excessive.
- **Systemic toxic effects** have to be differentiated from local tissue toxicity, which predominantly affects neuronal and musculoskeletal structures as well as hyaline cartilage tissues. These can all be damaged irreversibly [7].
- Substance-specific **haematological toxicity** is a form of local anaesthetic toxicity.
- **Allergic reactions** – which are relatively uncommon and are usually to amino esters – are not the subject of this paper. The emergency treatment of such reactions is described in the pertinent guidelines [31].

Systemic toxicity

General aspects

Systemic toxic complications due to regional anaesthesia are uncommon, occurring for example, 1 to 10 times for every 100,000 **epidurals** [32]. Approximately 10 years ago, the incidence for **peripheral nerve blocks** was in the range of 100 to 200 per 100,000 but has fallen drastically following the introduction of ultrasound guidance. Currently, an incidence of 0.8 to 0.9 per 100,000 is assumed [32–38].

Systemic toxic effects arise when the free plasma concentration rises excessively and exceeds a substance- and patient-specific threshold [2,7, 29]. The most common cause is accidental intravascular injection, but overdose and unexpectedly rapid absorption can also occur.

As a rule, any local anaesthetic can cause systemic intoxication, although the symptoms correlate well not only with the plasma concentration but also with the potency of the local anaesthetic, which in turn is determined by the lipophilicity of the substance [6,7]. Freely lipid-soluble substances accumulate in neuronal structures and are relatively slowly absorbed systemically, exhibiting a long duration of action. However, when larger quantities reach the blood stream, diffusion into well-perfused organs and tissues – such as the CNS and myocardium – occurs, and substances may accumulate there. As such, it is the **highly potent, long acting amino amide local anaesthetics** which are problematic in this respect [5].

Defining substance-specific **maximum doses** is to be seen as an attempt to reduce the incidence of toxic reactions, albeit a controversial one [39]. However, these maximum doses have been almost arbitrarily defined on the basis of animal research, experimental results and case reports. Systemic toxic effects can arise following unintentional intravascular injection of just small quantities though, bringing into question the value of recommended maximum doses, which may actually provide a feeling of false security when administering local anaesthetics. Furthermore, the recommendations fail to take perfusion and absorption conditions at the injection site and individual pharmacokinetic characteristics into account [39].

Central nervous system toxicity

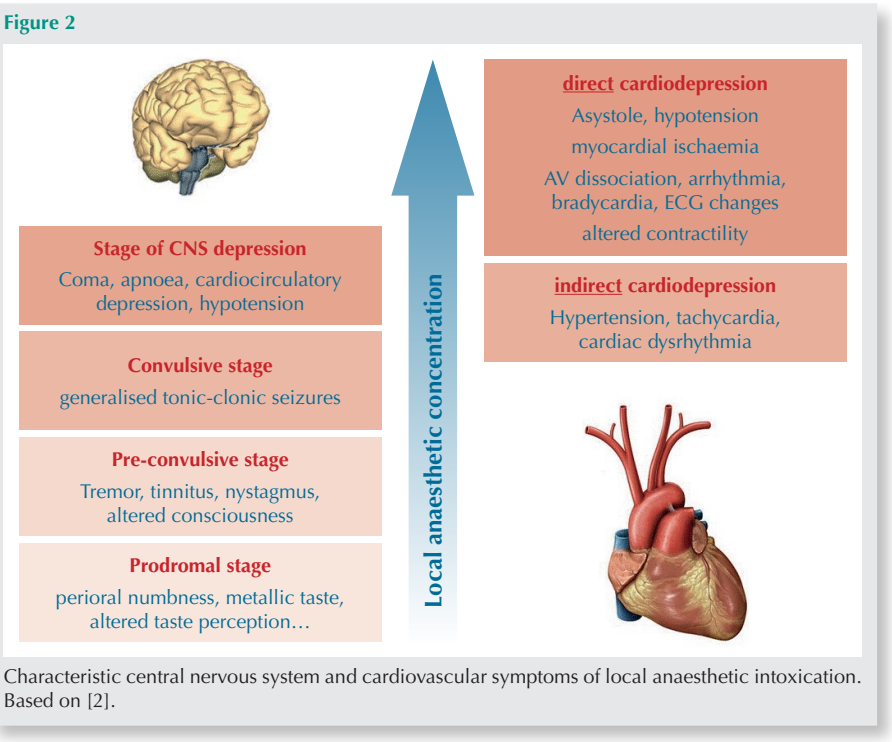
In general, the CNS reacts more sensitively to systemic accumulation of local anaesthetics than the cardiovascular system does [6,7,28].

As such, plasma levels leading to central nervous system symptoms are usually lower than those causing relevant cardiovascular impairment (Figure 2).

The clinical ramifications of central nervous system intoxication are divided into the following stages [2]:

- The **prodromal stage** is characterised by perioral numbness and dizziness, altered taste perception ("metallic" taste), hyperacusis of varying degrees and anxiety extending to panic attacks.
- During the **pre-convulsive stage** patients complain of tinnitus, reduced visual acuity and increasing loss of control over voluntary motor acts combined with tremor and uncoor-

Figure 2



Characteristic central nervous system and cardiovascular symptoms of local anaesthetic intoxication. Based on [2].

dinated motor function. Nystagmus may occur. Altered consciousness up to comatose states can arise.
- The subsequent **convulsive stage** is characterised by tonic-clonic seizures.
- If plasma levels rise further, a stage of **central nervous system depression** ensues. Seizures are self-limiting at this point. In this life-threatening stage, patients are deeply comatose, no longer display spontaneous breathing and become bradycardic. Failure of the vasomotor centres leads to hypotension.

Symptoms do not necessarily arise in the illustrated chronological order – accidental intraarterial injection of the local anaesthetic may, for example, abruptly block central nervous system structures, shortening the pre-convulsive and convulsive stages or even leapfrogging them altogether.

The biphasic course beginning with excitation of the central nervous system followed by depression can be explained on a pathophysiological basis: ultimately inhibitory neurons react more sensitively to local anaesthetics than excitatory neurons do [2,6,7]. The symptoms of the pre-convulsive stage are thus explained by functional predomination of excitatory neurons, with central nervous system depression ensuing when excitatory neurons associated with higher cerebral functions then also become suppressed. From an electrophysiological point of view, this condition is characterised by a flat-line EEG as a correlate of total lapse of neuronal activity.

Cardiocirculatory toxicity

As opposed to CNS symptomatology, signs and symptoms of cardiovascular intoxication (Figure 2) are rather less specific [2,7].

- Initially, a hyperdynamic circulatory state dominates, eliciting tachycardia and hypertension. At this point in time the cardiac effect is indirect and based upon the central nervous system effects of local anaesthetics, which lead to an increased sympathetic tone [4,6,8,9,40].
- The further course brings about various forms of cardiac dysrhythmia (including AV dissociation), hypotension and myocardial ischaemia. The ECG shows wide QRS complexes, prolongation of the QT interval, and unspecific repolarisation abnormalities. Ultimately cardiac arrest – which may be difficult to treat – ensues. These direct cardiac effects are caused by direct interaction with cardiomyocytes with negative chronotropic, dromotropic and inotropic ramifications (Figure 3).

The pathophysiological mechanism behind the negative chronotropic and dromotropic effects is a blockade of cardiac Na^+ channels, which in turn demonstrates substance-specific kinetics [8,9,40].

- For example, lidocaine and bupivacaine very rapidly block Na^+ channels. Whilst the block caused by bupivacaine only regresses slowly (approx. 1.5 s), the effect of lidocaine is short lived (approx. 0.1 s), leading to the terms "fast in – fast out" kinetics being used to describe lidocaine and "fast in – slow out" kinetics used to describe bupivacaine. Ropivacaine is characterised by "fast in – medium out" kinetics (duration of block approx. 1.0 s).
- The block is subject to **stereoselective influences** – suppression of sodium influx by R(+)-ropivacaine is significantly more pronounced than for S(-)-ropivacaine or the racemate [17].
- Furthermore, membrane bound L-type $Ca2^+$ channels are blocked in a concentration dependent fashion both in vitro and in vivo [4,6,9]. Because the extent of intracellular calcium liberation is mainly dependent on the influx of extracellular $Ca2^+$, the block results in a negative inotropic effect.
- In addition, local anaesthetics influence **mitochondrial energy metabolism** and intracellular second messenger systems [4,13,41]. An uncoupling effect on the mitochondrial respiratory chain impedes oxidative phosphorylation, with the degree of inhibition correlating with the lipophilicity of the local anaesthetic [41]. As such, lidocaine only produces a minor reduction in intracellular adenosine triphosphate (ATP) levels, whereas bupivacaine blocks mitochondrial energy metabolism to a greater degree.

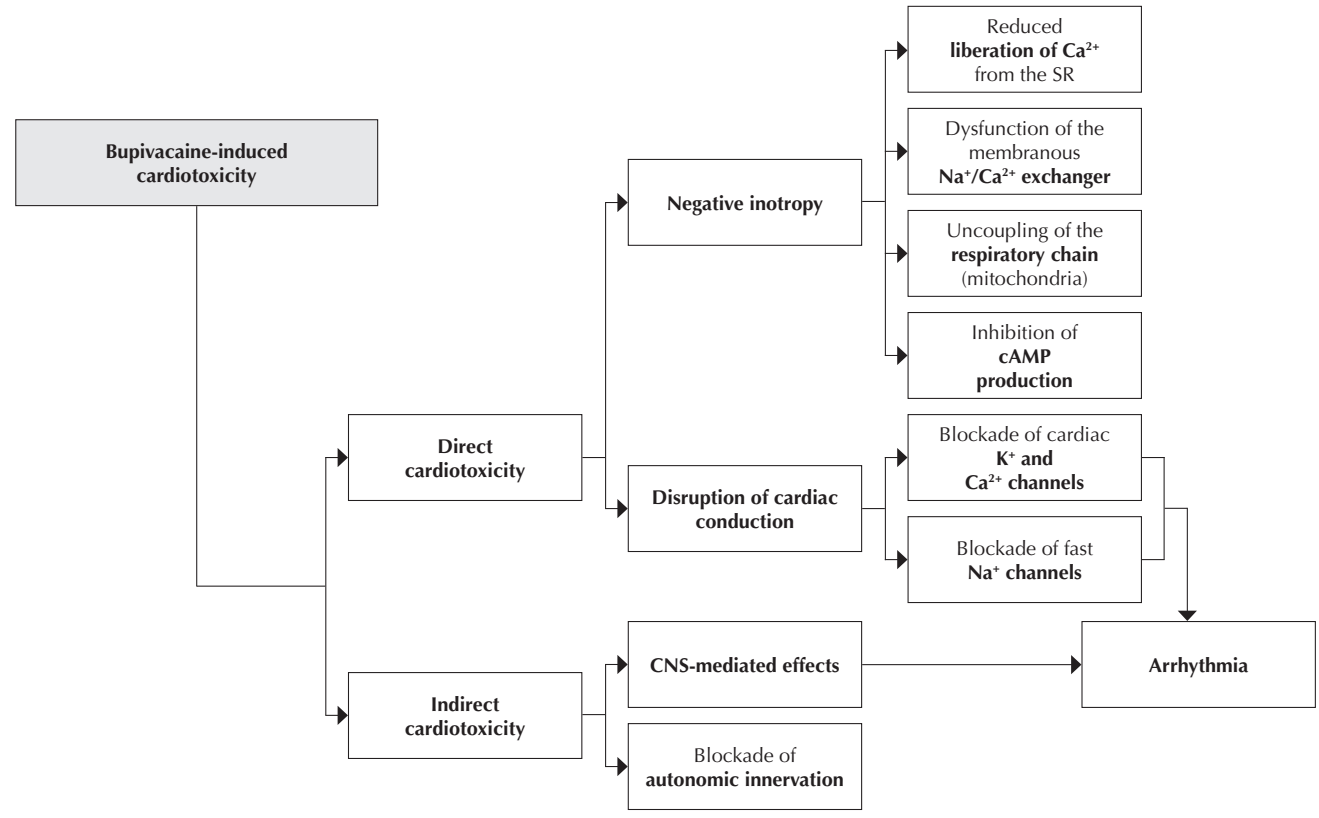
These mechanisms explain the varying degrees of cardiotoxicity of local anaesthetics [2,5,19]. When those substances which are commonly used today are considered, racemic bupivacaine has the greatest cardiodepressive potential. As such, the development of the two isomers levobupivacaine and ropivacaine was an improvement from a toxicological perspective. Due to its low lipophilicity, ropivacaine currently exhibits the most favourable spectrum of action when compared with other long acting local anaesthetics. Nevertheless, despite its moderate cardiotoxic potential the substance can still cause cardiac arrest, although successful resuscitation is more likely in these cases than when bupivacaine has been used [19].

Prevention of intoxication

Systemic intoxications are most commonly caused by inadvertent intravascular injection or administration of inappropriately high doses. As such, local anaesthetics should be applied slowly and in fractionated doses. Intravascular administration can be avoided with relative certainty by repeated aspiration [2,30].

From a toxicological viewpoint, the **use of ultrasound** [42] in regional anaesthesia is a major step forward because it reduces the requisite local anaesthetic doses significantly [33,35,36]. In addition, co-administration of marker substances (such as 5–10 µg of adrenaline in

Figure 3



Pathophysiological mechanisms behind cardiac toxicity using bupivacaine by way of example. Based on [7,9,12].
cAMP = cyclic adenosine monophosphate; **SR** = sarcoplasmic reticulum.

combination with 3 µg of isoproterenol) is touted, especially in English-speaking countries. These substances are intended to make intravascular injection immediately apparent [2,12].

The simplest and most important factor in increasing patient safety is sensitisation of the user for the toxic potential of local anaesthetics. Putting blind trust in adherence to maximum doses is a strategy that can only be warned against.

Treating intoxication – lipid infusions

When first symptoms of toxicity become apparent, the administration of local anaesthetics must be terminated immediately [30,42–44].

- In the case of **central nervous system symptoms**, recognition of the prodromes may be hampered in sedated patients, as well as in infants, small children and the elderly. Avoiding hypoxaemia, hypercapnia and acidosis with associated "ion trapping" (intracellular accumulation of protonated "active" local anaesthetic molecules) by means of adequate ventilation takes on a priority [2] – as such, the decision to perform endotracheal intubation and ventilation should be taken liberally. In the convulsive stage, seizures must be terminated immediately by (preferably intravenous) administration of barbiturates, benzodiazepines or propofol.
- When **cardiocirculatory symptoms** arise, ventilation with avoidance of acidosis again takes on a priority [30, 42–44]. Hypotension should primarily be treated with volume loading, although use of vasopressors (e.g. adrenaline 1:100,000 iv titrated to effect) may be necessary. Haemodynamically relevant bradycardia can be treated using atropine (up to 3 mg iv titrated to effect) and adrenaline iv. Use of transcutaneous or transvenous cardiac pacing should be considered on an individual basis, although bradycardia caused by long acting local anaesthetics is known to be relatively resistant to treatment by pacing.
- Cardiac arrest is treated in accordance with current guidelines [44], noting that prolonged resuscitation efforts may be required.

Current research comes to the conclusion that the probability of successful resuscitation can be increased by infusion of lipids [9,44–48].

Animal research has shown that infusion of lipid solutions reduces the systemic toxic effects of bupivacaine, both when given prophylactically and therapeutically [46–48]. These rather promising initial results could not, however, be uniformly reproduced in subsequent research [45,49,50]. Various mechanisms of action have been postulated for "lipid rescue therapy". The "lipid sink" effect assumes that lipophilic local anaesthetic molecules are incorporated into the intravascularly infused fat micelles, reducing the fraction of free local anaesthetic molecules in the blood stream and creating a concentration gradient which leads to diffusion from the extravascular to the intravascular space, away from the heart and CNS. A second mechanism is purported to be based on increased mitochondrial uptake of the infused lipids, which are then metabolised as energy substrates.

Numerous case reports support the notion of the clinical effectivity of lipid infusions – the type of infusion and the optimum dose, however, remain unclear. Uncertainty also remains over the effectivity of the measure when intoxication has been caused by local anaesthetics less lipid-soluble than bupivacaine. Despite the limited evidence and open questions, a number of national professional societies have chosen to recommend the administration of lipids when toxicity has been caused by local anaesthetics, amongst them the German Society of Anaesthesiology and Intensive Care Medicine (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin) [43]:

- An initial bolus of 1.5 ml/kg BW of a 20% lipid solution should be injected iv, followed by continuous infusion of 0.1–0.5 ml/kg BW for 10–30 minutes.
- The administration of lipids should augment but must not delay resuscitation measures.
- During resuscitation and as a measure of last resort, the patient may be placed on extracorporeal support where available.

It should be noted that the American Society of Regional Anesthesia and Pain Medicine recently revised their recommendations [51] and now focuses on early use of lipids at the first sign of systemic intoxication, whilst also having increased the maximum permissible initial dose of a 20% lipid solution to 12 ml/kg BW.

Tissue toxic effects

Neurotoxicity

When compared with nerve injury secondary to patient positioning and surgical as well as anaesthesiologic manipulation, direct nerve injury attributable to local anaesthetics is very uncommon but should be considered when postoperative neurological dysfunction is incurred [7, 52,53].

Symptoms incurred following peripheral blocks are diverse and can range from temporary numbness to persistent neuropathic pain with altered motor function; they may manifest themselves within hours but also with a latency of up to three weeks following the intervention [2,7]. The pathophysiological process underlying the complaints is often an endoneurial oedema, the mechanisms of which remain largely unclear [6,53], although local dysfunction of the blood-nerve barrier, increased hydrostatic pressure within the nerve and the specific neurotoxic potential of the local anaesthetic – which may correlate with the anaesthetic potency or lipophilicity – are being discussed [53,54]. Moreover, amino esters appear to bear a greater risk of nerve damage than amino amides, with addition of adrenaline or sodium bicarbonate increasing the extent of nerve damage. The gravest damage is caused by higher concentrations of lidocaine (2%–5%) [6,7].

Symptoms following central blocks range from temporary sensory disturbances to irreversible sensory or motor deficits. Two clinically defined entities play a major role:

- **Transient neurologic symptoms** (TNS) almost exclusively arise following "single shot" spinal anaesthesia – they are characterised by dull back ache radiating to the gluteal region and the backs of the thighs down to the calves [2,53,55]. TNS typically manifest themselves within the first 24 hours and regress completely within a few days. The aetiology and pathogenic mechanisms are unclear. In principle, all intrathecally administered local anaesthetics can trigger TNS, although there are significant substance-specific differences: lidocaine and mepivacaine show the highest incidence (up to 37%), whereas bupivacaine and prilocaine are considered to be the safest substances [55].
- The **cauda equina syndrome** with flaccid paresis of the legs, asymmetrical paraesthesia of the saddle area and bladder and bowel dysfunction was observed following continuous administration of hyperbaric 5% lidocaine via spinal microcatheter, but only has historical significance now that this technique has become obsolete [7].

Myotoxicity

As a rule, all local anaesthetics can cause concentration-dependent damage to skeletal muscle fibres, even extending to myonecrosis [56].

The **substance-specific myotoxic potential** varies greatly between substances. Whilst procaine and tetracaine only cause discrete structural changes, bupivacaine leads to the most extensive damage to skeletal muscle, including myonecrosis [56].

The **clinical presentation** of local anaesthetic induced myotoxicity is heterogeneous and dependent on the site of injection.

- Reversible dysfunction of ocular motility following **peri- or retrobulbar blocks** is particularly relevant. This is unequivocally caused by direct damage to the extraocular muscles.
- Moreover, there are anecdotal reports of clinically relevant damage to muscles following **wound infiltration** and **trigger point injections**.
- The relevance of myotoxic effects following **peripheral nerve blocks** is unclear. Symptomatic tissue damage (such as muscle degeneration with formation of scar tissue leading to functional impairment) has been described – but even though it is currently believed that local anaesthetics ordinarily cause lesions in those muscles in close proximity to the nerve, these generally appear to remain clinically inapparent [7,56].

From a **pathophysiological point** of view, the central issue is an excessive increase in the free Ca^{2+} concentration in multinucleate myocytes in which it is, above all, mepivacaine, ropivacaine and bupivacaine which induce the liberation of Ca^{2+} from the sarcoplasmic reticulum (SR). At the same time, they block the reuptake of Ca^{2+} by blocking Ca^{2+} ATPases residing in the SR [56,57]. This increases the Ca^{2+} level until ultimately cytotoxic concentrations are reached, triggering the activation of autolytic enzyme cascades.

Chondrotoxicity

Local anaesthetics can – both in vitro and in vivo – damage human chondrocytes irreversibly [14,58,59].

Bupivacaine and lidocaine appear to have the greatest chondrotoxic potential, whilst ropivacaine used in typical clinical doses only causes moderate damage to cartilage. There are increasing indications from animal research at least, which suggest that tissue damage (extending to total articular chondrolysis) increases with longer duration of contact and higher concentration of the local anaesthetic, although morphological and functional changes to chondrocytes and a loss of protective cartilage matrix have been shown even following single bolus injections with short duration of exposure. Previously damaged and aging hyaline articular cartilage appears to be particularly vulnerable [14,58,59].

The **clinical relevance** of these findings is unclear. Future research will have to show whether local anaesthetics can spare cartilage and be safely administered by intra-articular injection (e.g. following arthroscopy) and whether or not this procedure is suitable for postoperative pain relief. Whether or not intra-articular injections of local anaesthetics should be forgone in the meantime is the subject of controversy.

Haematologic toxic effects

Use of benzocaine, tetracaine and lidocaine but especially of prilocaine causes formation of methaemoglobin (Met-Hb) [2,7].

Oxidation of the central bivalent iron (Fe^{2+}) ions to their trivalent Fe^{3+} form alters haemoglobin (Hb) to Met-Hb, which cannot bind or transport oxygen. Methaemoglobinaemia is defined as a Met-Hb concentration exceeding 1–2% of total Hb.

The **clinical signs and symptoms** of methaemoglobinaemia are cyanosis from approximately 15% and headache, dyspnoea and tachypnoea, and increasing degrees of altered consciousness from approximately 30% upwards, although these levels are dependent on total Hb.

The use of higher doses of **prilocaine** is particularly relevant, because this substance induces formation of Met-Hb via two of its metabolites. Infants and small children are particularly at risk following uncritical use (e.g. as a topical mixture with lidocaine).

- Foetal Hb – still present in infants – can be oxidised particularly easily, a fact which is aggravated by reduced activity of nicotinamide adenine dinucleotide hydride (NADH) methaemoglobin reductase, catalase and glutathione peroxidase.
- Moreover, the local anaesthetic dose relative to body weight is generally higher in infants and small children than in adults.
- In adults, co-medication (sulphonamides, malaria drugs), glucose-6-phosphate dehydrogenase deficiency and haemoglobinopathies seem to favour the development of methaemoglobinaemia.

Treatment entails stopping the administration of the causative local anaesthetic, provision of supplemental oxygen and – where clinical signs and symptoms are marked – iv injection of tolonium chloride (2–4 mg/kg BW) or methylene blue (1–5 mg/kg BW), both of which activate Met-Hb reductase, rapidly converting Met-Hb to Hb. Haemodialysis is a measure of last resort.

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