Maximum recommended doses of local anaesthetics

The recommendations regarding maximum doses of local anaesthetics presented in physicians’ pharmaceutical reference books or in anaesthesiology text books are not evidence based. As a matter of fact, most of the recommendations are published by the manufacturer and are often very conservative.

Usually, the recommendation of a maximum dose is expressed as the total amount of the local anaesthetic, e.g. 200 mg for lidocaine in an adult. The site of administration, size and age of the patient, concomitant diseases and medications are not taken into account. This controversy has been pointed out several times, and most strongly by Daniel C. Moore and co-workers 1 and by Bruce Scott 2. They questioned the validity of maximum dose recommendations because of the completely ignored consideration of the various factors known or suspected, to affect absorption, metabolism and elimination of the drug.

Drug-related factors

Influence of site injection

The vascularity and the binding of the local anaesthetic to the tissues will influence the rate of absorption into the circulating blood. Absorption from richly vascularized regions such as the pleura, the bronchial mucosa, and the scalp occurs rapidly 3.

Intrinsic vasoactivity of the local anaesthetics

The vasoactive potency of the clinically used amide-linked local anaesthetics varies. The effect is dose-dependent and as a rule, high concentrations cause dilatation and low concentrations cause constriction. The intrinsic vasoactivity of the local anaesthetic does not play any greater role in influencing its absorption. Ropivacaine has been found to produce less vasodilatation than other commonly used amide-linked local anaesthetics 4, or even vasoconstriction, but whether this has any clinically beneficial consequences remains open. As an example, plasma concentrations of ropivacaine in epidural anaesthesia are similar to those measured after a similar dose of bupivacaine 5, 6.

Adrenaline

Adrenaline slows the absorption of local anaesthetic and prolongs the anaesthetic action and increases the duration of the block. A suitable adrenaline concentration is 5 µg/ml which reduces the peak plasma concentration of the local anaesthetic, depending on the local anaesthetic, by 30–60 %. Higher adrenaline concentrations are commonly used in dentistry, but if one aims primarily at reducing the uptake of the local anaesthetic into blood, as low adrenaline concentration as 1.7 µg/ml (1:600,000) has been shown to be effective with lidocaine 8.

Patient-related factors

Age

Deterioration in morphology and nerve conduction by aging may increase the sensitivity to local anaesthetic block 8. In addition, because of reduced clearance, the doses of local anaesthetics need to be reduced in adults, age-dependently between 10–20 % 9.

In the newborn less than 4 months old, the low plasma concentrations of α1-acid glycoprotein (AAG), the local anaesthetic-binding acute phase protein, is related to an enhanced risk of toxicity.
When large doses of local anaesthetic are used in this group of patients, the dose per kilogram should be about 15 % lower than in older infants.9

Size
Extremes in size need to be considered when regional anaesthetic blocks are used, both from the performance point of view and the pharmacokinetic/toxicity point of view. There is no evidence based recommendation or rule for proportional reduction of doses according to the weight but, obviously, dosing on milligram-per-kilogram basis would be dangerous.10

Renal dysfunction
In renal dysfunction, the clearance of local anaesthetics has been found to be lower than in nonuraemic patients.11 The concentration of AAG is usually increased in uraemic patients and this offers an important protection against toxicity. The initial absorption of local anaesthetic in uraemic patients is rapid and the dose of a local anaesthetic should be reduced by 10–20 % when large doses are planned to be used. Furthermore, due to reduced elimination of the local anaesthetic and its metabolites, the doses used for continuous infusions should also be reduced by 10–20 %, according to the degree of renal dysfunction.9

Hepatic dysfunction
The pharmacokinetics of the majority of local anaesthetics is affected by a poorly functioning liver associated with concomitant alterations in circulation and body fluids. In end-stage liver dysfunction, the clearance of ropivacaine has been found to be about 60 % lower than in healthy volunteers.13

Patients with severe liver dysfunction often have other concomitant diseases (renal and cardiac), which may be even more important indications to reduce the dose of the local anaesthetic. In mild liver dysfunction due to alcoholism, there is only minor alteration in the clearance of lidocaine.14

Single-dose local anaesthetic blocks can be performed without dose reduction in liver dysfunction. However, in repeat blocks (within short interval) and during continuous infusion blocks, the dose needs to be reduced by 10–50 %, depending on the stage of liver dysfunction.9

Heart failure
In mild cardiac disease, there may be no reason to reduce the local anaesthetic dose in single-dose blocks. Due to decreased liver and kidney blood flow in advanced heart failure, causing slow elimination of drugs and metabolites, the dose of the local anaesthetic should be reduced at least in continuous infusion blocks, e.g., by 10–20 %.9

Large doses of adrenaline should be avoided in patients with cardiac disease with arrhythmias or hypokalaemia. Obviously, lidocaine should not be used to treat local anaesthetic-provoked ventricular dysrhythmia because cardiac toxicity of local anaesthetic is additive.15

Pregnancy
Regional anaesthetic blocks requiring large doses (e.g., brachial plexus block, epidural block) should be avoided during the first trimester of pregnancy.

Dose reduction in epidural or spinal anaesthesia for caesarean section is necessary because of anatomical and physiological changes in the late stages of pregnancy and the enhanced sensitivity of nerves to local anaesthetics. Continuous infusion blocks are rarely used during pregnancy but, in principle, low doses for short periods could be used postoperatively, with the aim to reduce the need for analgesics such as opioid and cyclooxygenase inhibitors.9

Drug interactions
The cytochrome P450 (CYP) isoenzymes primarily involved in the metabolism of local anaesthetics are CYP 3A4, CYP 2D6 and CYP 1A2.16,17 In single dose blocks the impact of drug interactions (CYP enzymes) for toxicity of local anaesthetics is theoretical. In continuous infusions, however, the decreased clearance of bupivacaine by strong CYP3A4 inhibitors (e.g., itraconazole and other conazole antimycotics) and of ropivacaine by strong CYP1A2 inhibitors (e.g., fluvoxamine, which also inhibits CYP 3A4) needs to be considered. If the patient receives such medication the continuous infusion doses of bupivacaine or ropivacaine needs to be reduced by 10–20 %.9

Conclusion
None of the above mentioned recommendation is based on evidence classified higher than grade C (case series or poor quality cohort studies).9 Therefore, exact recommendations regarding highest allowable dose of the local anaesthetics cannot be given. Recommendations regarding which factors need to be considered...
for the reduction of the dose are given in this presentation.

The choice of a suitable (sufficient) dose for a particular type of regional anaesthetic block can be made with the guidance of modern high-quality textbooks of regional anaesthesia. When large doses are needed, the addition of low concentrations (1.7–5 µg/ml) of adrenaline is most useful in reducing the absorption of the local anaesthetic.

The local anaesthetics are potentially toxic agents and, therefore, everyone who uses them must know which a suitable dose for a particular block in normal conditions is. In order to adjust the local anaesthetic dose properly one must also know how the drug-related factors and the patient-related factors can influence the absorption, distribution, metabolism and elimination.

Finally, the maximum milligram dose recommendations for local anaesthetics by the pharmaceutical companies are illogical and needless.

References