▼ Review Articles

Maximum Recommended Doses of Local Anesthetics: A Multifactorial Concept

Per H. Rosenberg, M.D., Ph.D, Bernadette Th. Veering, M.D., Ph.D., and William F. Urmey, M.D.

The current recommendations regarding maximum doses of local anesthetics presented in textbooks, or by the responsible pharmaceutical companies, are not evidence based (ie, determined by randomized and controlled studies). Rather, decisions on recommending certain maximum local anesthetic doses have been made in part by extrapolations from animal experiments, clinical experiences from the use of various doses and measurement of blood concentrations, case reports of local anesthetic toxicity, and pharmacokinetic results. The common occurrence of central nervous system toxicity symptoms when large lidocaine doses were used in infiltration anesthesia led to the recommendation of just 200 mg as the maximum dose, which has remained unchanged for more than 50 years. In most cases, there is no scientific justification for presenting exact milligram doses or mg/kg doses as maximum dose recommendations. Instead, only clinically adequate and safe doses (ranges) that are block specific are justified, taking into consideration the site of local anesthetic injection and patient-related factors such as age, organ dysfunctions, and pregnancy, which may influence the effect and the pharmacokinetics of the local anesthetic. Epinephrine in concentrations of 2.5 to 5 μg/mL should be added to the local anesthetic solution when large doses are administered, providing there are no contraindications for the use of epinephrine. As a rule, conditions (eg, end-stage pregnancy, high age in epidural, or spinal block) or diseases (uremia) that may increase the rate of the initial uptake of the local anesthetic are indications to reduce the dose in comparison to one normally used for young, healthy, and nonpregnant adults. On the other hand, the reduced clearance of local anesthetics associated with renal, hepatic, and cardiac diseases is the most important reason to reduce the dose for repeated or continuous administration. The magnitude of the reduction should be related to the expected influence of the pharmacodynamic or pharmacokinetic change. *Reg Anesth Pain Med 2004; 29:564-575.*

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Present recommendations for maximum doses of local anesthetics are, in large part, not evidence based. Most recommendations, if not all, are published by the manufacturer. Presumably, the purpose of stating maximum recommended doses for local anesthetics has been to prevent the administration of excessive amounts of the drug, which could result in systemic toxicity. Usually, recommendations are in the form of a total amount of the drug, for example, 200 mg or 300 mg for lidocaine in an adult. More recently, amounts of the drug per body mass of the patient have been given in physicians' drug references. For example, in the case of bupivacaine, 2 mg/kg (FASS Sweden 2004, Pharmaca Phennica, Finland 2004).

Recommendations for a single dose of local anesthetic that do not take into account the site of injection are of little value. There are no controlled data on this issue either. Some rough extrapolation can be made from various pharmacokinetic studies on lidocaine. Similar plasma concentrations of lidocaine are achieved after 300 mg in intercostal nerve

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From the Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital, Helsinki, Finland (P.H.R.); Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands (B.T.V.); and Department of Anesthesiology, The Hospital for Special Surgery, New York, NY.

Reprint requests: Per H. Rosenberg, M.D., Ph.D., Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital, PB 340, Helsinki, FIN-00029 HUS, Finland. E-mail: per.rosenberg@hus.fi

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Table 1. Officially Recommended Highest Doses of Local Anesthetics in Finland (Pharmaca Fennica 2004), Germany (Rote Liste 2004), Japan (Drugs in Japan 2004, Japan Pharmaceutical Information Center), Sweden (FASS 2004), and the United States (Physicians' Desk Reference 2004)

	Finland	Germany	Japan	Sweden	US
2-Chloroprocaine	—	—	—	—	800 mg
With epinephrine	—	—	1,000 mg	—	1,000 mg
Procaine	—	500 mg	600 mg (epidural)	—	500 mg
With epinephrine	—	600 mg	—	—	—
Articaine	7 mg/kg	4 mg/kg	—	—	—
With epinephrine	7 mg/kg	4 mg/kg	—	—	—
Bupivacaine	175 mg (200 mg*) (400 mg/24 h)	150 mg	100 mg (epidural)	150 mg	175 mg
With epinephrine	175 mg	150 mg	—	150 mg	225 mg
Levobupivacaine	150 mg (400 mg/24 h)	150 mg	—	150 mg	150 mg
With epinephrine	—	—	—	—	—
Lidocaine	200 mg	200 mg	200 mg	200 mg	300 mg
With epinephrine	500 mg	500 mg	—	500 mg	500 mg
Mepivacaine	—	300 mg	400 mg (epidural)	350 mg	400 mg
With epinephrine	—	500 mg	—	350 mg	550 mg
Prilocaine	400 mg	—	—	400 mg	—
With epinephrine	600 mg	—	—	600 mg	—
Ropivacaine	225 mg (300 mg*) (800 mg/24 h)	No mention	200 mg (epidural) 300 mg (infiltr.)	225 mg	225 mg (300 mg*)
With epinephrine	225 mg	No mention	—	225 mg	225 mg (300 mg*)

*For brachial plexus block in adults.

block, after 500 mg in epidural block, after 600 mg in brachial plexus block, and after 1,000 mg in subcutaneous infiltration of the skin of the legs.[1,2] To complicate the matter, use of epinephrine and other additive vasoconstrictors may reduce the peak concentrations of local anesthetics in plasma. This also seems to vary from block to block, as well as from agent to agent. For example, epinephrine 5 μg/mL (1:200,000) reduces the peak plasma concentration of lidocaine after subcutaneous infiltration by approximately 50%, whereas after intercostal, epidural, and brachial plexus block, the reduction is only about 20% to 30%.[3-5]

The maximum recommended dose for lidocaine in the European countries is 200 mg without epinephrine (European Pharmacopoeia) and in the United States it is 300 mg. This dose of plain lidocaine may not be sufficient for many regional anesthetic procedures in adults. In both Europe and the United States, 500 mg of lidocaine is allowed if epinephrine (5 μg/mL) is added, and this assumes that epinephrine reduces the peak plasma concentrations by 60%. There is no evidence for this recommendation.

It is illogical that a maximum dose of lidocaine of 200 to 300 mg has been advocated, whereas an allowable dose of bupivacaine is 150 to 175 mg, despite data that in frog sciatic nerve bupivacaine is 4 times more potent.[6,7] A recent extension of this irrational recommendation for bupivacaine is the published maximum dose of 150 mg for levobupivacaine, although levobupivacaine is clearly less toxic than bupivacaine (racemic bupivacaine).[8,9]

It is presently common practice to administer a local anesthetic as a continuous infusion for several days to provide postoperative analgesia, after an initial single large dose for surgical anesthesia. This has boosted pharmacokinetic research, and knowledge has been gathered regarding plasma concentrations of bupivacaine and ropivacaine during continuous infusions. In fact, recommendations of 24-hour doses of 3 local anesthetics have been issued mainly based on experience rather than controlled evidence (Table 1). More importantly, controlled research data are now available regarding the influence of certain disease states and drug interactions on plasma concentrations of the potent local anesthetics, bupivacaine,[10-12] and ropivacaine.[13-15] These influences have been shown to be significant.

The purpose of this review is to convince the anesthesiologist that standard maximum dose recommendations of local anesthetics as exact milligram amounts are inappropriate. As in all medicinal therapy, the dose of a drug should be individualized as clinically indicated. Therefore, this review deals with the factors that must be considered as the basis for clinically necessary modifications of local anesthetic dosing, especially when large quantities of the drug are administered. Appropriate general recommendations that consider these factors are made.

Background: Current Recommendations

The current recommendations of maximum local anesthetic doses in Finland, Germany, Japan, Sweden, and the United States are presented in Table 1.

Table 2. Pharmacokinetic Parameters* of Local Anesthetics in Adults.

	V_{dss} (L/kg)	CL (L/kg/h)	$t_{1/2}$ (h)
2-Chloroprocaine	0.50	2.96	0.1
Procaine	0.93	5.62	0.1
Articaine	approximately 0.7	approximately 7	0.2–0.3[20]
Bupivacaine	1.02	0.41	3.5
Levobupivacaine	0.9	0.3	3.5[12]
Lidocaine	1.30	0.85	1.6
Mepivacaine	1.2	0.67	1.0
Prilocaine	2.73	2.03	1.6
Ropivacaine	0.84	0.63	1.9

*All parameters are from Denson et al.,[19] except those of Palkama et al.[12] and Oertel et al.[20]

Such doses have usually been determined by extrapolating data obtained from laboratory animals to man, followed by clinical investigations in man using these extrapolated doses for peripheral nerve blocks and epidural block. Published case reports of systemic toxicity in patients are also referred to when recommendations have been given.

The problems with recommendations of maximum doses have been dealt with repeatedly. Milestone publications in this respect include the paper by Moore et al.[16] in 1977 and the editorial by Scott[2] in 1989. Both of them question the validity and the logic of maximum dose recommendations because they do not take into consideration factors such as the varying absorption at different sites or patient characteristics (eg, age, disease). In addition, the rather conservative dose recommendations, or modifications given by the pharmaceutical companies, probably reflect an economic interest and protection of the product. These companies are certainly not without bias.

The background for the most conservative maximum dose recommendation (ie, that of lidocaine [200 mg in Europe]) relates back to the first clinical testing of lidocaine in the 1940s and 1950s. At the Karolinska Hospital in Stockholm, Gordh[17] performed clinical tests on patients with lidocaine doses up to, or even exceeding, 1,000 mg, occasionally accompanied by systemic toxicity. His own maximum dose recommendation to the Astra pharmaceutical company was 300 mg (T. Gorgh, personal communication, 2002). However, despite this recommendation, the company decided on 200 mg, which has remained unchanged to this day in most European countries. Whoever was responsible in the United States for having suggested, or having made the decision, that 300 mg is a maximum recommended dose of lidocaine cannot be tracked.

Pharmacokinetics of Local Anesthetics

The pharmacokinetic parameters of local anesthetics depend on the uptake (absorption from the site of injection), distribution (spread in the body fluids and tissues according to lipid solubility and protein binding characteristics), and elimination (metabolism and excretion) of the drug. In the case of ester-linked local anesthetic molecules (eg, procaine and 2-chloroprocaine) the metabolism starts mainly in the blood by esterases before the distribution phase. Thus, from the toxicity point of view, ester-linked local anesthetics are quite safe and relatively high doses may be used. On the other hand, their breakdown into molecules similar to para-aminobenzoic acid[18] is the reason for a relatively high frequency of anaphylactic reaction related to their use.

The important pharmacokinetic parameters of the amide-linked local anesthetics are presented in Table 2. As mentioned earlier, the absorption of the local anesthetic into the circulation depends primarily on the vascularity of the site of deposition (injection) as well as on the structure composition of the surrounding tissues (eg, presence of lipid). Because of the huge interindividual and interblock variations and the fact that systemic toxicity of the amide-linked local anesthetics is caused by the unbound (free) local anesthetic in plasma, the magnitude of a safe dose of the local anesthetic should not be based on the total plasma concentrations of the drug.

The volumes of drug distribution at steady state (V_{dss}) of local anesthetics (when uptake by less-perfused organs, together with simultaneous biotransformation, are matched by drug release from well-perfused organs) clearly exceed the total body volume. This is because local anesthetics are more soluble in fat, liver, and brain and other organs than in water. The low degree of central nervous system toxicity symptoms with prilocaine has been considered to be caused by its relatively great V_{dss} (Table 2), its rapid uptake into the lungs,[21] and its rapid metabolism.[22] The difference in V_{dss} between racemic bupivacaine and its S(−)-enantiomer seems to be because of enantioselectivity in plasma protein

binding.[23,24] Perhaps the most important parameter is the elimination half-life ($t_{1/2}$), which indicates how soon another dose or at which rate a continuous infusion of the local anesthetic can be administered safely. As a rule, 5 half-lives are required for a decline of the plasma concentration to near zero (in practice, a fall to about 3% of the peak concentration). It may be prudent to give some clinical examples with regards to the most toxic of the presently used local anesthetic (ie, bupivacaine with an elimination half-life of about 3 hours). When the administration of a similar dose (2 mg/kg) of bupivacaine with epinephrine for intercostal nerve blocks was repeated after 6 hours, the second peak plasma concentration was, on average, 10% higher than the first one.[25] In continuous interscalene brachial plexus block with 0.25% bupivacaine at a rate of 6 to 10 mL/h, after an initial block for surgery with 150 to 200 mg bupivacaine, the total plasma concentration rose clearly and statistically significantly by about 20%, on average, during the second postoperative day.[26]

The clearance (CL) is the overall efficiency of drug elimination from the body. Because only a very small fraction of nonmetabolized amide-linked local anesthetics is excreted by the kidneys and their biotransformation occurs mainly in the liver, CL of amide-linked local anesthetics is essentially synonymous with hepatic clearance (Table 2). It should be noted that there is an enantioselectivity in clearance also and the CL of S(+)-mepivacaine is clearly lower than that of racemic mepivacaine and R(−)-mepivacaine.[27] There are also some differences in the CL for bupivacaine enantiomers. In humans, the CL of R(+)-bupivacaine is greater than that of S(−)-bupivacaine, but the CL of unbound R(+)-bupivacaine is less than that of S(−)-bupivacaine.[23] In single-dose regional anesthetic techniques, CL does not play a great role with regards to toxicity or maximum dose. In case of renal or hepatic insufficiency (see later), the CL will decrease accompanied by a retention of the local anesthetic and certain metabolites in the body, which assumes great importance in continuous regional anesthetic techniques.

Site of Injection Affects the Absorption of Local Anesthetics. The vascularity (density of capillaries)[28] and the binding of the local anesthetic to the tissues[1,29] will influence the initial rate of absorption into the circulating blood. Additionally, the vasoactive properties (dilatation or constriction) may play a role in further rate of absorption (see later). During end-stage pregnancy[30] and in uremia,[14] when the blood perfusion of the site of local anesthetic injection is enhanced because of a hyperdynamic circulation, the absorption of local anesthetics into the blood occurs rapidly and high early peak concentration may result.

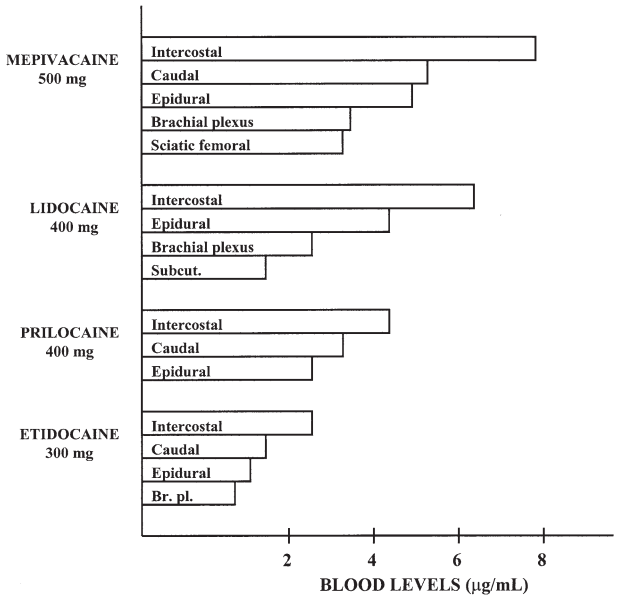

Fig 1. Collection of data of local anesthetic blood levels (mainly plasma concentrations) from various sources,[34-39] indicating the pattern of order of peak concentrations associated with various regional anesthetic blocks.[40]

Absorption from richly vascularized regions such as the pleura, the bronchial mucosa, and the scalp occurs rapidly and high peak concentrations are seen in the blood. Very slow absorption of local anesthetics occurs from the urinary bladder,[31] and intact skin is almost impermeable to regular concentrations of amide-linked local anesthetics as hydrochlorides.[32,33]

Several studies have shown that the blood level of the local anesthetic depends on the total dose and is independent of the the concentration of local anesthetic in the injected solution.[34,35] It is thought that a smaller absorption surface counterbalances a greater concentration so that no alteration in absorbed blood levels occurs.

Studies on peak plasma concentrations of a fixed dose of certain local anesthetics used in various blocks have been performed to a limited extent. A particular pattern of order of peak concentrations has been shown for a number of amide-linked local anesthetics (Fig 1) with the highest after intercostal block and higher after epidural than after brachial plexus block.[35-40] The fact that all studies show that the highest peak concentrations occur after intercostal nerve block independent of the local anesthetic used is thought to be caused by the fact that several injections are made and the absorption area is large. More recently, it has become obvious that

peak concentrations as high as after intercostal nerve blocks may result from a similar dose used for interpleural (intrapleural) regional block.[41,42] This presumably results from the "sheeting" distribution of the drug in the interpleural space, an anatomic potential space with a comparatively large surface area.

After deflation of an arm tourniquet cuff in intravenous regional anesthesia, approximately 30% of the dose is released into the systemic circulation by the first flush of blood.[43] Therefore, the peak concentration is usually not encountered immediately after the cuff release.[44,45] Despite that, mild central nervous system toxicity symptoms often occur soon after the cuff deflation before attaining the peak concentration, in particular by lidocaine.[46] This effective but mechanistically and technically rather complicated technique depends strongly on the awareness of safety precautions regarding cuff functioning and timing of deflation. Ischemia makes up a significant part of the mechanisms of action of intravenous regional anesthesia,[47] and, therefore, a lower dose of a local anesthetic with low toxicity potential should always be considered.

Intrinsic Vasoactivity of Various Local Anesthetics. Although local anesthetics have intrinsic vasoactive effects on blood vessels, the resulting systemic absorption may be difficult to predict. Vasoactivity is both dose dependent (usually high concentrations cause dilatation and low concentrations cause constriction) and organ specific. It should also be kept in mind that the needle stick produces vasodilatation, whereas injection of a large bulk of fluid may cause temporary compression of even large blood vessels.

Clearly, clinically injected anesthetic solutions of bupivacaine and lidocaine cause vasodilation of skin blood vessels while neural blood flow is reduced.[48,49] Lower concentrations may cause vasoconstriction in certain tissues and reduce, for example, muscle blood flow. In man, injection of bupivacaine (0.25%-0.5%) in the skin increases capillary blood flow substantially, whereas ropivacaine (0.25%-0.75%) decreases the flow, as compared with control values.[50]

The vasoactivity of mepivacaine lies in between that of bupivacaine and ropivacaine (ie, in man mepivacaine does not increase skin blood flow beyond that of saline alone, suggesting a mild vasoconstrictive action).[51] This intrinsic vasoactivity of the local anesthetic does not have any significant clinical role in influencing its own absorption; for example, plasma concentrations of ropivacaine (assumed to cause vasoconstriction) in epidural anesthesia[52] are similar to those after the same dose of bupivacaine in epidural anesthesia,[53] and both concentrations are reduced to the same extent if the solution contains 5 μg/mL epinephrine.

Epinephrine. Epinephrine slows the absorption of local anesthetic and thereby prolongs the anesthetic action and also increases the intensity of the block. With medium-duration local anesthetics such as lidocaine and mepivacaine, a suitable epinephrine concentration appears to be 5 μg/mL,[35] but both lower and higher concentrations have been used. Particularly in dentistry, concentrations up to 12.5 μg/mL are used, the aim being a bloodless field (ischemia) for minor surgery in addition to the prolongation of the duration of the anesthetic effect.

It has also been speculated that the α_2-adrenergic action of epinephrine could provide analgesia, at least at the spinal level.[54] Epinephrine is of no significant value in prolonging the effect of long-acting local anesthetics such as bupivacaine and ropivacaine because the epinephrine effect is exceeded by the local anesthetic effect. However, acutely, epinephrine diminishes the peak concentration of both bupivacaine and ropivacaine, and this has been found useful when large doses are used, as with interpleural regional analgesia.[42,55]

Clinically available injectable concentrations of lidocaine may decrease neural blood flow. Laboratory studies have shown that whereas epinephrine 5 μg/mL decreased sciatic nerve blood flow in the rat by 20%, the addition of lidocaine 20 mg/mL synergistically lowered flow by 60%.[49] In another experimental series, this decrease was as great as 78%.[48] Intact nerve can tolerate such intense vasoconstriction, at least temporarily, without any complications. To what extent a continuous infusion of epinephrine-containing local anesthetic solution could reduce nerve blood flow is unknown, and such a situation may be regarded as theoretical.

Large doses of epinephrine injected within a short time interval may cause tachycardia and severe dysrhythmias. Based on clinical experience, Raj et al.[56] recommend that in infiltration for incisional analgesia of the skin, the amount of epinephrine should not exceed 1.5 μg/kg/10 minutes or 8 μg/kg/h. If large amounts of local anesthetic are needed, both the local anesthetic solution and the epinephrine solution should be diluted. In fact, a similar reduction in lidocaine uptake from the epidural space was shown when the epinephrine concentration was reduced from 5 μg/mL to 1.7 μg/mL (1:600,000).[57]

Patient-Related Factors to Be Considered When Large Doses of Local Anesthetics Are Used

In the recommendations, we apply the "Grades of Recommendation" published by the Oxford University Centre for Evidence Based Medicine (available at: http://www.cebm.net/index.asp): A = systematic reviews of randomized controlled trials or prospective good-quality cohort studies with good follow-up; B = systematic reviews of cohort studies, individual cohort studies, low-quality randomized controlled trials, outcomes research; C = case series, poor-quality cohort studies, extrapolations from studies of grade B; and D = evidence from inconsistent or inconclusive studies at any level, expert opinion.

Age. At birth, the plasma concentration of α_1-acid glycoprotein (AAG, orosomucoid) is about half the adult concentration,[58] suggesting that the risk of systemic local anesthetic toxicity would be increased. Probably, because large doses of local anesthetics are not used in obstetric epidural analgesia or for postoperative analgesia in the newborn, toxic reactions are quite rare.

A single caudal injection of ropivacaine in infants resulted in higher free ropivacaine plasma concentrations in infants aged 0 to 3 months compared with older infants.[59] In that particular study, however, both the free and the total ropivacaine concentrations were within the levels reported in adults and in children. In addition to a low AAG level in plasma of the newborn, they seem to have a low intrinsic CL of bupivacaine.[60] Based on studies on continuous caudal bupivacaine infusion in the newborn, Meunier et al.[60] recommend restricting the dosage to less than 0.25 mg/kg/h in infants younger than 4 months and to a maximum of 0.3 mg/kg/h in older infants.

Deteriorating blood flow and organ functions decrease the CL of local anesthetics in the elderly.[61,62] Peak plasma concentrations and plasma protein binding of local anesthetics are similar in elderly people and young adults.[63,64] However, the nerve axon function deteriorates,[65,66] nerve morphology changes,[66] and the surrounding fatty tissue disappears[68] in the elderly who become more sensitive to the blocking action and, therefore, smaller doses of local anesthetics are required in elderly patients, a phenomenon observed in epidural block[69,70] and brachial plexus block.[71] The isolated vagus nerve in young and old rabbits has been found to be more sensitive to local anesthetic–induced nerve conduction blockade than that in adult rabbits.[72]

Recommendation. Deterioration in morphology and nerve conduction by aging is assumed to increase the sensitivity of nerve axons to local anesthetics blockade.[70,71] This, in addition to reduced CL,[61,62] is the main reason for the need to reduce the dose in the elderly (C). In repeat dosing and during continuous infusions, the lower CL of amide-linked local anesthetics easily results in accumulation of the local anesthetic and some of its metabolites, with concomitant rise of the free plasma concentration and an increased risk of toxicity. In nerve blocks, in which large amounts are commonly used (epidural block, brachial plexus block, lower extremity combined bocks, interpleural block) followed by continuous infusion, or as repeated dosing in middle-aged adults with normal organ functions, the doses should be reduced by 10% to 20% age dependently over the age of 70 years (D), mainly because of age-dependent pharmacodynamic and anatomic changes rather than of pharmacokinetic reasons.

In the newborn (<4 months), the low AAG concentration in plasma is related to an enhanced risk of local anesthetic toxicity. When using regional anesthetic blocks with large doses in this age group, the dose per kilogram should be approximately 15% lower than in older infants[58,60] (C).

Renal Dysfunction. In renal dysfunction, the CL of lidocaine has been found to be lower[73] or similar[74] to that of subjects with normal kidney function. Bupivacaine CL[10] and ropivacaine CL[14] in uremia, on the other hand, have been shown to be lower than in nonuremic patients. The elimination half-life of local anesthetics does not seem to change in uremia.[10,14,73,74] The CL of the main metabolites of ropivacaine, 2,6-pipecoloxylidide (PPX) and 3-OH-ropivacaine, is also decreased in uremic patients. Plasma concentrations of bupivacaine and ropivacaine have been shown to rise rapidly in brachial plexus block in uremic patients,[10,14] probably because a hyperdynamic circulation[75] promotes absorption of the drugs into the blood. The concentration of the acute phase protein, AAG, is increased in uremic patients[76] and this may offer important protection against local anesthetic toxicity.

Toxicity may become a real risk in uremic patients when long-term continuous infusions of bupivacaine or ropivacaine are administered because of the accumulation of both the parent drug and its metabolites. The PPX metabolite, the cardiotoxicity of which in anesthetized rats seems to be about half that of bupivacaine,[77] is increasing continuously in plasma during continuous brachial plexus block infusions.[26] Again, the surgery-stimulated increase in the production of AAG[78] functions as a buffer, effectively binding local anesthetic in blood, and that is likely the reason why systemic toxicity is ex-

tremely rare during continuous postoperative analgesic infusions.

Because the initial absorption of local anesthetic is rapid in uremic patients, there is an obvious need for dose reduction in single-injection blocks in which large doses are applied (eg, brachial plexus block, multi-injection paravertebral blocks, interpleural blocks, epidural surgical blocks, and combined lower-extremity blocks).

Recommendation. The hyperdynamic circulation in uremic patients results in enhanced absorption of the local anesthetic from the site of deposition. High peak plasma concentrations may occur early after injection, and the concentrations may remain higher than in nonuremic patients for an extended time[10,14] (C). A small reduction of doses (10%-20%), relative to the degree of renal dysfunction, in those regional anesthetic techniques in which large doses are normally used (eg, brachial plexus block and epidural block) is recommended (D).

The decreased renal function causes a reduction in CL of local anesthetics and some of their metabolites[10,14] (C), and this is the primary reason for the need to reduce the amount of repeat doses administered within the time span of less than 5 half-lives and the doses for the continuous regional anesthetic techniques by 10% to 20%, according to the degree of dysfunction (D).

Hepatic Dysfunction. The pharmacokinetics of the majority of local anesthetics are affected by a poorly functioning liver associated with alterations in circulation and body fluids. In end-stage liver dysfunction (patients being evaluated for liver transplantation), the CL of ropivacaine was found to be about 60% lower than in healthy volunteers,[15] but, interestingly, plasma concentrations were similar. The latter finding may depend on an increased V_{dss} of ropivacaine. The V_{dss} of other drugs, such as rocuronium[79] and propofol,[80] is also increased in patients with hepatic dysfunction. When repeated doses[25] or continuous infusions are used, the accumulation of both bupivacaine and ropivacaine and of their metabolites needs to be considered, and doses should be reduced accordingly. Even in end-stage liver dysfunction, AAG is synthesized[15] and thus provides some protection against local anesthetic toxicity.

It should be kept in mind that patients with severe liver dysfunction may also have other diseases (eg, nephropathy and cardiac disease), which may be even more important indications to reduce the dose of a drug. Conversely, in mild hepatic dysfunction related to alcoholism, there seems to be almost no alteration in the clearance of lidocaine.[73]

Recommendations. In patients with hepatic dysfunction, single-dose blocks can usually be performed safely with normal doses of the local anesthetics[15,73] (C). However, patients with severe liver disease often have renal dysfunction, which also requires dose reduction. The doses for repeat blocks within a short time period (<5 half-lives), and the doses for continuous infusion blocks need to be reduced markedly (10%-50%) (D) in patients with liver dysfunction, mainly because of a significantly reduced CL[15,73] and accumulation of the local anesthetic and its metabolites in the blood[15,26] (C).

Heart Failure. In heart failure, deterioration of the circulation may cause changes in the body clearance of drugs such as lidocaine[73] by reducing blood flow to the liver and kidneys. Indeed, similar plasma concentrations of lidocaine were found in patients with heart failure after injecting 0.5 mg/kg intravenously as after 1 mg/kg in patients without heart failure.[81] Although about three fourths of lidocaine entering the liver via the hepatic artery will be extracted from the circulation, less than half of bupivacaine and ropivacaine will be cleared by the liver per pass.[19] Therefore, lower cardiac output may not greatly affect the blood levels of the strongly protein-bound local anesthetics, bupivacaine, and ropivacaine to any greater extent.

Because of the autoregulation of cerebral blood flow, the proportion of a local anesthetic in the blood that reaches the brain is increased in severe heart failure (low cardiac output), thereby predisposing to acute central nervous system toxicity when a substantial amount of the drug has entered the circulation. On the other hand, because of the low cardiac output perfusion to the site of local anesthetic injection (eg, epidural space) is decreased, which may decrease the rate of further absorption.

Recommendation. In mild and well-controlled cardiac disease, there may not be any reason to reduce the local anesthetic dose (D). However, the substantially lowered total body CL because of reduced blood flow to the liver and kidneys occurring in advanced heart failure is a clear indication for a reduction of local anesthetic dose[73] (C). This should be done also for the intravenous lidocaine dose used for the treatment and prevention of ventricular arrhythmias. Lidocaine must not be used for the treatment of local anesthetic–induced ventricular arrhythmias because the toxicity of the amide-linked local anesthetics is additive.[82] Epinephrine should be avoided in patients with cardiac diseases involving hypokalemia,[83] and its dose should be kept low in other types of cardiac disease (D). Because of reduced CL of local anesthetics[73] (C) and because the metabolites of both bupivacaine and ropivacaine will be eliminated slowly[15,26]

(C), the dosages used for repeat or continuous dosing of local anesthetics need to be reduced by 10% to 20% (D).

Pregnancy. During pregnancy, hormonal (progesterone) mechanisms may increase the sensitivity of nerve axons to neural blockade.[84,85] There seems also to be an enhanced risk of cardiotoxicity by bupivacaine and ropivacaine in pregnancy induced by progesterone.[86] The protein binding of bupivacaine in blood (but not of mepivacaine) is significantly reduced in pregnancy, which also may enhance the risk of toxicity.[87] Therefore, at any stage of pregnancy, it is indicated to reduce the dose in blocks in which large doses would normally be used, such as in brachial plexus block because of an enhanced risk of local anesthetic toxicity.

When pregnancy progresses to the stage in which cardiac output is increased, blood perfusion to the site of local anesthetic injection will increase and the absorption of local anesthetic into the circulation is rapid.[30] This constitutes an independent reason to further reduce the dose of the local anesthetic in blocks with large doses. In cesarean delivery, both hormonal effects[84,85] and the mechanical effect of uterus compression are assumed to have a significant impact on speed and spread of spinal and epidural blocks and therefore markedly reduced doses can be used.

Recommendations. Regional anesthetic blocks in which usually large doses are required (eg, brachial plexus block, epidural block) should be avoided during the first trimester of pregnancy (D). Regional anesthetic blocks where usually small doses are needed (eg, spinal anesthesia, infiltration blocks), the doses can be still reduced because of a hormonally induced increased sensitivity of the nerve axons to sodium channel block[84,85] (C) and can be performed without risk to the mother and the fetus (D). Special precautions need to be taken to avoid unintentional intravascular injection of the local anesthetic because of danger to the fetus and maternal heart. The use of epinephrine in the local anesthetic solutions is not contraindicated in obstetric patients.[88]

Dose reduction in epidural or spinal anesthesia for cesarean delivery is necessary because of anatomic (narrowed spaces) and physiologic changes (greater pressure at the site of injection and enhanced sensitivity of nerves to local anesthetics) in the later stages of pregnancy[84,85,88] (C). In principle, continuous regional anesthetic blocks, with low doses of local anesthetics, may be used for short periods in pregnant patients (D), the aim being to reduce the need for analgesics such as opioids or cyclooxygenase inhibitors.

Drug Interaction. Amide-linked local anesthetics are metabolized mainly in the liver by the cytochrome P450 enzymes (CYP). Several of the isoforms of CYP are involved in the metabolism of local anesthetics. Lidocaine is N-de-ethylated in liver to monoethylglycine xylidide by CYP1A2 and CYP3A4.[89] The metabolism of bupivacaine has been shown indirectly to depend on both CYP2D6 and CYP3A4. Propranolol and cimetidine, inhibitors of CYP2D6, have been found to reduce plasma clearance of bupivacaine by 30% to 35%.[90,91] These drugs also decrease liver blood flow and may therefore have some influence on the clearance of bupivacaine, which has a low-moderate hepatic extraction ratio.[23] Itraconazole, the inhibitor of CYP3A4, decreases the elimination of bupivacaine enantiomers by 20% to 25%.[12]

Ropivacaine is metabolized to 3-OH-ropivacaine by CYP1A2 and to 2′,6′-PPX by CYP 3A4.[92,93] Ciprofloxacin, an inhibitor of CYP1A2,[94] slightly decreased the clearance of ropivacaine,[95] and at the same time the CYP3A4-mediated formation of PPX was increased. On the other hand, fluvoxamine, a strong inhibitor of CYP1A2,[96] reduces the clearance of ropivacaine by approximately 70%.[13,96] Evidence for less significance of the CYP3A4 pathway in ropivacaine metabolism was shown in studies with strong CYP3A4 inhibitors (eg, chlarithromycin, itraconazole, ketoconazole), which only slightly reduced the CL of ropivacaine.[96,97]

Recommendations. The impact of drug (CYP) interactions for toxicity of local anesthetics is theoretical concerning single-dose nerve blocks. On the other hand, in continuous infusions, the decreased CL of bupivacaine by the CYP3A4 inhibitor itraconazole (and possibly other azole antimycotics) and of ropivacaine by the CYP1A2 inhibitors may play a role in increasing the risk of systemic toxicity. In particular, fluvoxamine is a risky drug in this respect because in addition to its major inhibition of CYP1A2, it also causes some inhibition on CYP2D6 and CYP3A4,[98,99] which are involved in the metabolism of ropivacaine and other amide-linked local anesthetics. Patients' use of itraconazole or fluvoxamine should be an indication to reduce the dose (10%-20%) (D) in repeat administration of a large amount within a short interval of bupivacaine and ropivacaine, respectively, and to reduce their doses in long-term continuous regional anesthetic blocks[12,98,99] (C).

Conclusion

None of the recommendations presented in this review is based directly on evidence classified higher than grade C (case series or poor quality cohort studies). Therefore, exact recommendations

regarding highest allowable dose of the local anesthetics cannot be given.

The choice of a suitable dose range for a particular type of block can be made with the guidance of modern high-quality textbooks of regional anesthesia.[100-103] Despite the guidance of experts, surprisingly large doses of local anesthetics are sometimes administered by anesthesiologists, in particular in the types of block in which multiple punctures/injections have been replaced by single-puncture/injection (eg, in brachial plexus block). Adding epinephrine (2.5-5 μg/mL) to local anesthetic solutions is a useful practice for reducing the absorption of the local anesthetic.

As long as a significant dose of local anesthetic is not deposited intravascularly, even relatively high plasma concentrations resulting from injection of large doses do not usually cause systemic toxicity. In normal healthy persons, the binding of amide-linked local anesthetics to AAG in plasma effectively prevents the formation of high concentrations of unbound (free) local anesthetic. Surgery further stimulates the synthesis of AAG in the liver, and, therefore, the local anesthetic binding capacity is enhanced and the risk of toxicity reduced postoperatively.

The CL of local anesthetic from the body is reduced by high age, renal dysfunction, hepatic dysfunction, and cardiac dysfunction. In these circumstances, accumulation of local anesthetic in the body can be expected even in continuous regional anesthetic blocks in which relatively low drug concentrations are used. It should also be kept in mind that in the elderly, several organs may function poorly simultaneously. The current practice of mixing various other types of analgesic drugs in regional anesthetic block infusions has reduced the risk of systemic toxicity by the local anesthetic component in the mixture.

It is concluded that instead of thinking in terms of a standard milligram dose when selecting the dose for a particular regional anesthetic block, the dose should be individualized as outlined earlier. This is the practice also in modern general anesthesia, as well as in other fields of medicine. Doses of local anesthetics should be block specific and site specific, and in comparison with doses suitable or applicable in healthy young adults, doses need to be modified (reduced) according to age- and disease-related influences on the pharmacodynamics and pharmacokinetics of local anesthetics.

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