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Review

Maximal Dosage of Local Anesthetics in Regional Anesthesia Techniques: narrative review and experts' advice

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Abstract

Local anesthetics (LAs) are the cornerstone of regional anesthesia (RA), offering targeted nerve blockade with a favorable safety profile when used within recommended dosages. However, determining the maximal recommended dose remains a critical concern, as exceeding this limit may result in local anesthetic systemic toxicity (LAST). This article provides an overview of the factors determining maximal dosages of LAs in RA, the inherent limitations and relativity of the published maximal dosages, the clinical implications of these dosages, and strategies to mitigate associated risks. Further research and refined guidelines are encouraged to enhance patient safety in this evolving field.
We discuss guidelines and clinical insights from recent literature, with the goal of supporting clinicians in optimizing both efficacy and safety.

Key words: **Anesthesia, Regional, Nerve block, Anesthetics, Local, Drug Toxicity, Adverse effects.**

Key Recommendations for Safe Use of Local Anesthetics in Regional Anesthesia

1. Maximum recommended doses of local anesthetics should be regarded as **approximate** guidance, not absolute safety thresholds.
2. Local anesthetic dosing must be individualized, considering the injection **site, vascularity**, block **technique**, and **patient-specific factors** (age, pregnancy, organ dysfunction).
3. When calculating doses, **ideal body weight** should be used in obese patients to reduce the risk of systemic toxicity.
4. The **lowest effective dose** of the **least cardiotoxic local anesthetic** should be selected to achieve the desired block characteristics.
5. Injection site matters: **highly vascular or plane blocks** require dose reduction compared with low-vascularity sites.
6. **Incremental injection with frequent aspiration** should be systematically used to reduce the risk of inadvertent intravascular administration.
7. **Ultrasound guidance** should be employed to improve accuracy, reduce required volumes, and enhance safety.
8. The **combination of multiple amide local anesthetics** should be avoided due to unpredictable pharmacokinetics and increased toxicity risk.
9. **Continuous infusions and repeated dosing** require dose reduction and enhanced vigilance, particularly in patients with impaired clearance.
10. Any unexpected neurological or cardiovascular sign after local anesthetic administration should raise immediate suspicion of **local anesthetic systemic toxicity** (LAST), with lipid emulsion therapy immediately available."

Practical Clinical Summary: Safe Use of Local Anesthetics in Regional Anesthesia

The safe administration of local anesthetics in regional anesthesia requires an individualized,

systematic approach that goes beyond adherence to fixed "maximum recommended doses." These doses should be regarded as approximate reference values rather than absolute safety limits, as systemic toxicity is influenced by multiple patient-, drug-, and technique-related factors.

Dose selection should be individualized for each patient and procedure. When calculating doses, ideal body weight should be used in obese patients to avoid excessive systemic exposure. Dose reduction should be considered in neonates, elderly patients, pregnant patients, and those with hepatic, cardiac, or renal dysfunction, particularly when repeated dosing or continuous infusions are planned. The lowest effective dose of the least cardiotoxic agent capable of providing the desired block density and duration should always be selected.

Injection site and technique play a critical role in determining systemic absorption. Highly vascular areas and plane blocks are associated with faster uptake and higher peak plasma concentrations, requiring lower total doses than low-vascularity sites. Ultrasound guidance should be used whenever possible, as it improves accuracy of local anesthetic deposition, reduces required volumes, and enhances safety margins. Continuous communication with the patient during block performance, when feasible, allows early detection of neurological symptoms suggestive of systemic toxicity.

Incremental injection is a key safety measure. Local anesthetics should be administered in small, fractionated aliquots (typically 3–5 mL), with deliberate pauses between injections and frequent gentle aspiration. This approach limits peak plasma concentrations and allows early cessation of injection should symptoms of toxicity occur. The use of epinephrine as a pharmacologic marker may assist in detecting inadvertent intravascular injection and modestly reduce systemic absorption.

Monitoring and environment are essential components of safety. Standard ASA monitoring should be applied during and after local anesthetic administration. Regional anesthesia should only be performed in settings equipped for immediate resuscitation, with personnel trained in the recognition and management of local anesthetic systemic toxicity (LAST). Any unexpected neurological (e.g., tinnitus, perioral numbness, confusion, seizures) or cardiovascular sign (e.g., arrhythmias, hypotension, cardiac arrest) following LA administration should immediately raise suspicion of LAST.

Drug selection and combinations require caution. Mixing multiple amide local anesthetics should be avoided, as it offers no proven clinical benefit and introduces unpredictable pharmacokinetic interactions that may increase toxicity risk. Continuous infusions and repeated boluses require vigilance, as accumulation may occur despite apparently acceptable total doses, especially in patients with impaired clearance.

Preparedness for LAST is mandatory. Intravenous lipid emulsion therapy must be immediately available wherever regional anesthesia is performed, and institutional protocols for LAST management should be clearly established and rehearsed.

In summary, safe use of local anesthetics depends not on rigid numeric dose limits but on a comprehensive strategy integrating individualized dosing, careful technique, appropriate monitoring, and constant vigilance. No local anesthetic should be considered inherently "safe," and prevention of intravascular injection remains the single most effective measure to reduce the risk of severe systemic toxicity.

Introduction

RA has established itself as a fundamental component of contemporary multimodal antinociceptive strategies, providing superior perioperative analgesia while significantly reducing the reliance on systemic opioids and their associated adverse effects. The cornerstone of these techniques is the administration of LAs, whose efficacy must be judiciously balanced against their potential for systemic toxicity. A precise understanding of maximal safe dosages, calculated according to actual, ideal, or adjusted body weight, is imperative to mitigate the risk of LAST, an infrequent yet potentially life-threatening complication.

Despite the clinical significance of appropriate dosing, inconsistencies and misconceptions regarding optimal dosage regimens remain prevalent in practice, leading to unnecessary patient exposure to the risk of LAST. This underscores an urgent need to standardize clinical protocols, grounded in current evidence and safety principles, to promote the rational and individualized use of LAs within the perioperative setting.

Several variables influence the determination of maximal LA dosages, including the physicochemical properties and pharmacokinetics of the specific agent, patient-specific characteristics (such as age, weight, and comorbid conditions), and the concurrent use of adjuvant medications. Although multiple practice advisories and consensus guidelines exist, heterogeneity persists in their application across clinical environments.

This article aims to synthesize the existing literature on maximum recommended dosages

of commonly used local anesthetics in regional anesthesia, delineate the key factors that modulate their clinical applicability, and propose pragmatic, evidence-informed strategies to optimize patient safety while preserving the analgesic benefits of regional techniques within contemporary perioperative care. Throughout this manuscript, the term "maximum recommended dose" refers to a regulatory or reference value intended to provide general dosing guidance under standard conditions; it should not be interpreted as an absolute safety threshold, as it does not account for patient-specific factors, procedural characteristics, injection site, or technical aspects that critically influence the risk of local anesthetic systemic toxicity.

Defining the classically accepted maximum recommended dosages of LAs: historical and clinical foundations

Maximum recommended doses of local anesthetics serve as practical guidance in clinical practice; however, it is essential to recognize that their scientific basis is limited and that these values are inherently relative rather than absolute safety thresholds. Controlled clinical trials designed to define toxic dose limits are neither feasible nor ethical[1]. Consequently, current recommendations are derived from a heterogeneous body of evidence, including experimental models, case reports, registries, observational studies, and regulatory decisions.

Historically, concerns regarding systemic toxicity have accompanied the clinical use of local anesthetics for over a century. Early reports, such as those published by the American Medical Association in 1928, documented fatal outcomes related to cocaine use and prompted the development of less toxic agents[2]. Initial clinical experience with lidocaine in the mid-20th century demonstrated wide variability in tolerated doses, highlighting early on the difficulty of defining universally recommended dose limits[3]. Regulatory dose limits were ultimately set conservatively, often independent of maximal doses reported in early clinical practice.

Following the publication of Albright's editorial highlighting severe cardiotoxicity associated with bupivacaine[4-6], greater clinical vigilance and regulatory restrictions contributed to a reduction in reported catastrophic events, particularly through limitations on high-concentration formulations. Nevertheless, these historical developments further illustrate that so-called "safe maximum doses" emerged from precautionary regulatory decisions rather than robust dose–response evidence.

Experimental models used to study local anesthetic systemic toxicity are highly heterogeneous, which substantially limits their translational applicability. Variability in animal species, dosing regimens (bolus vs continuous), route of administration, physiological conditions, blood sampling techniques, and toxicity endpoints results in widely divergent toxicity thresholds[7-10]. Therefore, no single experimental model reliably defines a universally applicable recommended dose for humans.

As emphasized by Rosenberg et al., maximum recommended doses published in textbooks or product labeling are not evidence based and should be regarded as crude approximations of safety[11]. This is illustrated by international discrepancies in recommended lidocaine doses and unsupported assumptions regarding the protective effect of epinephrine on systemic absorption[11]. Once adopted by regulatory agencies, such dose limits are difficult to revise, even when subsequent experimental or clinical data challenge their validity[12].

Importantly, a "maximum recommended dose" applies only to systemic absorption following correct extravascular injection and does not protect against accidental intravascular administration, which remains the principal mechanism underlying severe LAST[13]. Indeed, even a fraction of a conventionally accepted dose may provoke life-threatening toxicity if injected intravascularly[9].

Finally, experimental work has demonstrated that the ratio between doses producing cardiovascular collapse and central nervous system toxicity (CC/CNS ratio) differs markedly between agents, with bupivacaine exhibiting a much narrower safety margin than lidocaine[14]. This pharmacodynamic characteristic further reinforces the inadequacy of uniform dose limits across different local anesthetics[14].

Current evidence: ester-type LAs[15,16]

Ester-type LAs represent an older but pharmacologically distinct class within RA, characterized by their unique metabolic pathway, shorter duration of action, and differing toxicity profiles compared to amide counterparts. Unlike amino-amide LAs, which undergo hepatic metabolism via cytochrome P450 enzymes, ester LAs such as procaine, chloroprocaine, tetracaine, and benzocaine are hydrolyzed rapidly in plasma by nonspecific pseudocholinesterases (butyrylcholinesterase). This enzymatic degradation, occurring predominantly in the intravascular compartment, results in significantly shorter systemic half-lives and limited tissue accumulation, making ester LAs theoretically

safer in terms of systemic toxicity, particularly in patients with hepatic dysfunction. However, their metabolic by-product, para-aminobenzoic acid (PABA), is a well-documented allergen, responsible for a higher incidence of true allergic reactions compared to amide LAs. Clinically, ester LAs are favored in specific contexts where rapid onset and brief duration are desired, such as in minor surgical procedures or spinal anesthesia (notably chloroprocaine), and they are often used in topical formulations (e.g., benzocaine in mucosal anesthesia) due to their high surface activity. Tetracaine, despite its high potency and lipid solubility, is associated with greater systemic toxicity when used in high doses, particularly via spinal or ocular routes, necessitating caution and strict dose limitation. Ester LAs possess a higher pKa than many amides, which results in a lower percentage of non-ionized molecules at physiological pH, theoretically contributing to slower membrane penetration and potentially slower onset. However, onset is also significantly influenced by lipophilicity, concentration and dose. A structural characteristic of most ester local anesthetics is the absence of stereogenic centers, meaning they do not exhibit enantiomer-specific pharmacodynamic differences, unlike certain chiral amide local anesthetics like bupivacaine. However, their instability in solution and susceptibility to hydrolysis limit shelf-life and complicate formulation. In patients with atypical plasma cholinesterase deficiency, whether congenital or acquired (e.g., due to liver disease, pregnancy, or chronic illness), ester LA clearance may be impaired, increasing the risk of toxicity. Furthermore, their hydrolysis is pH-dependent, and acidic environments (as found in infected tissues) may reduce efficacy. Given these characteristics, the clinical use of ester LAs is now largely limited to niche indications or when amide LAs are contraindicated due to allergy, although they retain historical and educational importance in understanding LA pharmacodynamics and systemic safety[11].

Current evidence: amino-amide LAs

Several factors determine the maximal safe dosage of LAs:

1. *Type of local anesthetic:*

   The choice of LA plays a critical role in determining the risk of systemic toxicity, due to significant differences in their chemical structure, lipid solubility, protein binding, stereochemistry, and pharmacodynamic behavior. Lidocaine, bupivacaine, and ropivacaine, commonly used amino amide-type LAs, exemplify these variations.

   Lidocaine, with moderate lipid solubility and a relatively short elimination half-life, exhibits the most favorable safety profile among the three. It has lower potency and weaker binding to voltage-gated sodium channels, and its rapid hepatic metabolism contributes to a reduced risk of systemic accumulation and cardiotoxicity[11].

   Bupivacaine, by contrast, is highly lipophilic and exhibits strong, stereoselective binding to cardiac sodium channels, particularly in their inactivated state. This affinity, coupled with slow dissociation kinetics, leads to a higher risk of conduction block and malignant arrhythmias, especially following intravascular injection. Its high degree of plasma protein binding (primarily to α1-acid glycoprotein) and long half-life further increase systemic exposure and toxicity potential. The agent is used as a racemic mixture, but it is primarily the R(+)-enantiomer that is implicated in severe cardiotoxicity due to its higher affinity for myocardial ion channels,

   Levobupivacaine is the pure S(-)-enantiomer of bupivacaine, developed as a safer alternative, maintaining similar anesthetic potency and duration of action while demonstrating a significantly reduced risk of cardiotoxicity owing to its lower affinity for cardiac sodium channels and more favorable pharmacokinetic profile.

   Ropivacaine, a mono-isomeric S(-)-enantiomer and structural homolog of bupivacaine, was specifically developed to reduce cardiotoxic risk. Its lower lipid solubility, reduced intrinsic potency, and faster unbinding kinetics from sodium channels contribute to a significantly safer cardiovascular profile. Although it is slightly less potent in motor blockade, it provides effective sensory anesthesia, making it a preferable option in many regional techniques. The stereoselectivity of ion channel interaction, combined with favorable pharmacokinetics and reduced lipophilicity, accounts for its improved safety margin.

   A detailed understanding of these chemical and pharmacological properties is essential to guide the safe selection, dosing, and monitoring of LAs in clinical practice, particularly in high-risk populations or procedures where systemic absorption may be increased.

2. *Patient characteristics:*

   Patient-specific physiological and pathological characteristics profoundly influence the pharmacokinetics, protein binding, and ultimately the toxicity risk of LAs.

As amino-amide LAs, such as lidocaine, bupivacaine, ropivacaine, levobupivacaine, are primarily metabolized hepatically via cytochrome P450 isoenzymes (notably CYP1A2 and CYP3A4), hepatic dysfunction represents a critical determinant of systemic accumulation and prolonged half-life. In patients with liver failure or cirrhosis, reduced hepatic perfusion and impaired enzymatic activity can substantially decrease LA clearance, heightening the risk of systemic toxicity even at standard dosages. Similarly, while LAs are not predominantly excreted renally in their active form, chronic renal dysfunction can still alter LA pharmacokinetics indirectly, through fluid and electrolyte disturbances, acid–base imbalances, or accumulation of LA metabolites with potential neurotoxic effects (e.g., MEGX (monoethylglycinexylidide) from lidocaine).

Heart failure reduces organ perfusion, which can in turn decrease the hepatic elimination of local anesthetics, particularly amide-type LAs. It can also alter the volume of distribution. Furthermore, any additional hypotensive effects from local anesthetics may exacerbate the heart failure state.

Age extremes further complicate LA pharmacology. Neonates possess immature hepatic enzyme systems, reduced plasma protein concentrations (especially α_1-acid glycoprotein, AAG), and a larger extracellular water compartment, all of which reduce protein binding and increase the free (active) fraction of LA, leading to heightened CNS and CV toxicity. Conversely, elderly patients may exhibit reduced hepatic blood flow, altered body composition (e.g., increased fat-to-lean mass ratio), and diminished organ reserve, prolonging LA half-life and reducing tolerance to systemic exposure. As an illustration, in a 90-year-old, 70 kg patient undergoing a fascia iliaca block, 40 mL of ropivacaine 0.375% (150 mg) may be preferred over 0.5% (200 mg) to account for reduced physiological reserve while maintaining block efficacy.

Pregnancy introduces unique challenges: increased cardiac output and plasma volume dilute circulating AAG levels, decreasing the protein-bound fraction and thereby increasing the free fraction of LAs. Progesterone-mediated changes may sensitize neuronal membranes to LAs, enhancing both efficacy and toxicity potential.

Under normal obstetric regional anesthesia practice, the risk of LAST in the newborn is negligible, but maternal toxicity or large doses given immediately before delivery can result in transient neonatal depression due to placental transfer of local anesthetics.

Obese patients often exhibit altered volumes of distribution due to excess adipose tissue, which disproportionately affects lipophilic local anesthetics, such as bupivacaine. Consequently, dosing strategies based solely on total body weight may lead to an overestimation of dose requirements and an increased risk of systemic toxicity[17,18]. In the absence of robust pharmacokinetic evidence supporting alternative strategies, a conservative IBW-based approach is therefore justified as a safety-oriented standard.

Accordingly, as a standard safety principle, and considering the limited, heterogeneous, and inconclusive evidence regarding plasma local anesthetic concentrations in obese patients, we recommend that local anesthetic dosing should be calculated based on IBW. Dosing based on actual or adjusted body weight is discouraged, as it may overestimate requirements without providing proven clinical benefit and may increase toxicity risk.

This framework aligns with the overarching principle of administering the lowest effective dose and has been clarified in the revised manuscript to provide readers with a pragmatic and safety-focused reference for clinical practice. For example, in a 170 cm, 135 kg patient undergoing a fascial plane block, ropivacaine dosing may be calculated using ideal body weight (e.g., 3 mg/kg IBW) rather than total body weight, avoiding dose overestimation in a highly perfused plane block.

α_1-Acid Glycoprotein (AAG), the principal plasma binding protein for basic drugs including most LAs, plays a central role in modulating free drug concentration and systemic toxicity[19]. Its levels vary significantly in response to acute phase reactions, chronic illness, and physiological states. Elevated AAG (e.g., in cancer, trauma, or inflammation) can buffer free LA concentrations and offer transient protection against toxicity, whereas decreased AAG, as seen in neonates, pregnancy, or liver failure, significantly increases the unbound, pharmacologically active LA fraction[20]. Failure to account for dynamic changes in AAG can thus lead to substantial underestimation of toxicity risk, particularly in vulnerable populations[21].

Beyond enzyme activity, LAs differ in whether their hepatic clearance is ‘flow-limited’ or ‘capacity-limited’. Lidocaine is a high-extraction-ratio drug (extraction ratio >

0.7), meaning its clearance is largely dependent on hepatic blood flow: any reduction in liver perfusion (e.g., heart failure, hypovolemia) markedly decreases clearance and increases toxicity risk. In contrast, bupivacaine and levobupivacaine are low-extraction-ratio agents (extraction ratio ≈ 0.2–0.3); their clearance relies primarily on hepatic metabolic capacity (CYP-mediated biotransformation). Thus, factors that impair enzyme function, such as cirrhosis, drug–drug interactions, or genetic polymorphisms, more profoundly affect their elimination. Ropivacaine occupies an intermediate position but is closer to capacity-limited clearance, so both flow and enzyme activity can modulate its pharmacokinetics. Recognizing these distinctions is essential for anticipating how changes in hepatic blood flow versus metabolic function will differentially impact LA accumulation and toxicity, and for tailoring dosing strategies in patients with altered hepatic physiology[22].

3. *Injection site and vascularity:*

The rate and extent of systemic uptake of LAs are profoundly influenced by the vascular architecture and perfusion characteristics at the injection site. Regions with dense capillary networks and high blood flow, such as the intercostal muscles, scalp, bronchial mucosa, and pleural surfaces, facilitate rapid LA diffusion into the systemic circulation, elevating peak plasma concentrations and the attendant risk of toxicity. By contrast, subcutaneous tissues and peripheral nerve sheaths, with their relatively sparse microvascular beds and lower perfusion rates, exhibit slower absorption kinetics and a wider safety margin. Anatomically, blocks performed in proximity to large-caliber vessels (e.g., interscalene or stellate ganglion approaches near the vertebral and subclavian arteries) carry an additional hazard of inadvertent intravascular injection, which can precipitate abrupt, high-concentration plasma spikes.

From a pharmacological standpoint, the speed of LA uptake is governed by Fick's law of diffusion, driven by surface area, concentration gradient, and capillary permeability, and modulated by the agent's physicochemical properties (lipid solubility, pKa, and protein binding). Highly lipophilic agents (e.g., bupivacaine) partition more readily into vascular endothelium-rich tissues, whereas less lipophilic drugs (e.g., lidocaine) exhibit relatively slower transcapillary movement. Physiologically, organ blood flow, influenced by sympathetic tone, local autoregulatory mechanisms, and patient factors (e.g., hypovolemia or vasopressor use), further alters absorption dynamics. Compounding these effects, virtually all LAs induce local vasodilation, which accelerates systemic uptake and shortens block duration; ropivacaine is unique in possessing intrinsic vasoconstrictive properties, thereby slowing absorption and prolonging its clinical effect23. Clinicians must therefore adjust dosing regimens not only for the anatomical site but also for the regional perfusion state, particularly when performing fascial plane blocks where large volumes are commonly injected. In such settings (e.g., transversus abdominis plane, erector spinae, fascia iliaca blocks), high tissue perfusion and extensive surface area may result in rapid systemic absorption, warranting dose reduction and increased vigilance. For example, reducing total dose in intercostal or plane blocks, where perfusion rates can exceed 200 mL/min per 100 g tissue, versus higher permissible doses in subcutaneous infiltration where perfusion may be less than 10 mL/min per 100 g. The accepted hierarchy of site-related systemic absorption, and thus toxicity risk, remains: subcutaneous < brachial plexus < sciatic/femoral < epidural < caudal < intercostal/plane blocks[24].

4. *Bolus versus continuous infusion*

The risk of LAST appears to be higher with continuous peripheral nerve blockade compared to single-shot techniques. Due to wide interindividual variability, a large number of subjects have total concentrations exceeding the toxic treshold. It was however reassuring to note that, because of the post-surgical rise in acute phase α_1-acid glycoprotein, the unbound ropivacaine concentration was much lower and remained well below the toxic treshold[25]. Nevertheless, continuous infusions and repeated bolus administrations require dose reduction and heightened vigilance compared with single-shot techniques, as systemic accumulation may occur over time despite apparently acceptable initial doses, particularly in patients with impaired clearance.

Recommendations of 24-hours doses of 3 LAs have been issued mainly based on experience rather than controlled evidence11. For example, in clinical practice, a lower-limb amputation managed with a continuous peripheral nerve catheter may use levobupivacaine 0.25% at 7 mL/h following an initial 10 mL bolus,

with ongoing monitoring to limit cumulative systemic exposure.

5. *Use of adjuvants*

The only excipient approved for perineural use is epinephrine, which prolongs block duration by approximately one hour through its vasoconstrictive action, thereby reducing peak plasma levels of the local anesthetic[25].

In contrast, the practice of combining multiple amide-type LAs in a single injection is pharmacologically unsound and potentially hazardous. Each LA molecule must alternately bind to the inactivated state of the voltage-gated sodium channel and then be released before undergoing hepatic biotransformation by distinct cytochrome P450 isoenzymes (primarily CYP1A2 and CYP3A4). When two agents are co-administered, they compete nonlinearly both for channel binding, prolonging blockade and heightening neurotoxicity, and for the same metabolic pathways, leading to unpredictable alterations in clearance kinetics and systemic accumulation. Empirically, mixtures do not confer faster onset or extended duration compared to single agents, yet they can magnify toxicity in ways that exceed the sum of their individual effects[14]. A frequently suggested, though unvalidated, rule is to limit combined doses to 100% of the sum of each maximum recommended dose (e.g., 45% of levobupivacaine's maximum plus up to 55% of lidocaine's), but this offers no guarantee of safety.

Discussion

As a rule, conditions (e.g., end stage pregnancy, high age in epidural or spinal block) or diseases (renal failure) that may increase the rate of the initial uptake of the local anesthetic are indications to reduce the primary bolus-dose.

On the other hand, the reduced clearance of LAs associated with renal, hepatic and cardiac diseases, is the most important reason to reduce the dose for repeated or continuous administration[11].

The maximum recommended doses appear to be useful, although they do not appear to be as effective as the steps suggested to prevent toxicity from intravascular injection[26].

Table I. — Practical considerations for local anesthetic dosing and toxicity risk in regional anesthesia.

Local anesthetic	Relative cardiotoxicity	Pharmacological features relevant to toxicity	Key factors increasing toxicity risk	Practical dose-reduction triggers
Lidocaine	Low	Moderate lipid solubility; rapid hepatic clearance; higher CC/CNS ratio	High total dose, reduced hepatic blood flow	Continuous infusion, hepatic impairment, elderly
Bupivacaine / Levobupivacaine	High (bupivacaine) / Moderate (levobupivacaine)	High lipid solubility; strong sodium channel binding; narrow safety margin (low CC/CNS ratio)	High concentrations, reduced clearance	Pregnancy, extremes of age, hepatic or cardiac dysfunction, high-vascularity or plane blocks
Ropivacaine	Lower than bupivacaine	Lower lipid solubility; intrinsic vasoconstrictive properties; wider safety margin	Large volumes, prolonged infusions, impaired clearance	Obesity (dose based on IBW), continuous catheters, elderly, renal/hepatic impairment

Table II. — Clinical contexts associated with increased risk of local anesthetic systemic toxicity and suggested safety adaptations.

Clinical context	Relative cardiotoxicity	Pharmacological features relevant to toxicity
Pregnancy	Reduced protein binding; increased free fraction	Reduce dose; incremental injection; enhanced monitoring
Neonates / Elderly	Immature or reduced clearance; altered protein binding	Lower initial dose; avoid accumulation; close vigilance
Hepatic failure	Reduced metabolism of amide LAs	Dose reduction, avoid repeated boluses
Cardiac failure	Reduced hepatic perfusion; increased sensitivity	Lower doses; careful monitoring
Renal failure	Altered physiology; metabolite accumulation	Cautious dosing; avoid prolonged infusions
Obesity	Altered volume of distribution for lipophilic LAs	Dose calculation based on ideal body weight
Plane blocks	High perfusion; large volumes	Reduce total dose; use ultrasound; incremental injection
Continuous Peripheral Nerve Blocks	Cumulative systemic exposure	Reduce infusion rate; monitor for delayed LAST

The determination of maximal safe dosages for LAs in RA stays a multifactorial process, requiring the integration of evidence-based guidelines with individualized clinical judgment. While existing recommendations provide a foundational framework derived from pharmacologic data, clinical experience and anecdotal evidence, significant variability remains in their application due to patient-specific factors, procedural demands, and institutional practices. Future research is warranted to refine these guidelines further, incorporating novel LA formulations, adjuvants, and technological innovations such as real-time plasma concentration monitoring to enhance patient safety.

A central principle in RA practice is that LA dosing should not adhere to a fixed, universal value. Recommendations for a single dose of local anesthetic that do not consider the site of injection are of little value. Instead, it should be carefully titrated based on the specific clinical scenario, with consideration given to the type of block, required volume, and patient characteristics including age, weight, comorbidities, and physiological status. For example, peripheral nerve blocks often necessitate larger volumes of LAs, warranting meticulous incremental dosing and vigilant monitoring to mitigate the risk of local anesthetic systemic toxicity (LAST). Conversely, neuraxial techniques typically require lower doses due to the proximity to target neural structures and the potential for significant cephalad spread.

The concept of a "maximum recommended dose" remains inherently imprecise, with standard recommendations offering only approximate guidance. Notably, conventional dosing based on actual body weight lacks pharmacokinetic justification, as it neither reliably correlates with achieved plasma concentrations nor accounts for crucial factors such as the injection site, tissue perfusion, and patient-specific variables including extremes of age, pregnancy, renal or hepatic dysfunction, and obesity[27].

Robust pharmacokinetic data comparing LA behavior in obese versus non-obese populations remain limited. The absence of standardized, controlled intravenous administration models complicates extrapolation, given the complex, compartmentalized, and region-specific distribution of LAs. In obese patients, alterations in adipose tissue mass, cardiac output distribution, hepatic metabolism, and plasma protein binding significantly impact both the volume of distribution and clearance of lipophilic agents such as bupivacaine and ropivacaine. Additionally, elevated levels of alpha-1-acid glycoprotein in obesity, secondary to chronic low-grade inflammation, further modulate the unbound (active) fraction of amide LAs, adding unpredictability to systemic toxicity risk profiles.

Another critical limitation lies in the inconsistent maximal dose recommendations across countries and regulatory bodies. For instance, the permitted maximum dose of ropivacaine varies from 200 mg in Europe to 300 mg in the United States and Switzerland[28], despite a lack of high-level evidence to support these thresholds. Dosing based on actual body weight risks exposing obese and pregnant patients to potentially hazardous LA concentrations.

The advent of ultrasound-guided RA has enabled enhanced precision in LA deposition, reducing required volumes and systemic absorption, and thereby improving safety margins. Nevertheless, no regional technique should be undertaken without immediate access to a fully equipped resuscitation environment and personnel trained in the recognition and management of LAST. Furthermore, an intravenous lipid emulsion (e.g., Intralipid®) must be immediately available at the bedside as a critical intervention for severe systemic toxicity.

Recommendations

Knowing that in most cases, there is no scientific justification for presenting exact milligram doses or mg/kg doses as maximum recommendations and only clinically adequate and recommended doses (ranges) are justified, we should take into consideration the site of local anesthetic injection and patient-related factors such as age, organ dysfunction, and pregnancy, which may influence the effect and the pharmacokinetics of the local anesthetic. So, the dose of the drug should be individualized as clinically indicated [11].

Nevertheless, it is reasonable to use some standard as a starting point for deciding on a dose. In using these standards, for safety reasons (primum non nocere), this maximum dose of LAs should be calculated based on ideal body weight[24].

And knowing that the majority of these toxicities seen in humans occur with the unintentional intravascular injection of LAs, the central fact remains that we need to avoid intravascular injection if we are to avoid serious toxicity.

To mitigate the risk of LAST, several safety measures are recommended:

- Use standard American Society of Anesthesiologists (ASA) monitoring.
- Safety is promoted by use of the least toxic drug consistent with achieving the desired outcomes of density and duration of the nerve block.
- Use the lowest possible dose of this local anesthetic necessary to achieve the desired extent and duration of block.

- Adjust the dose according to patient characteristics. Consider dose reduction in neonates, elderly, pregnant patients, and those with heart, liver, or kidney impairment. Use ideal body weight (IBW) when dosing obese patients.
- Consider the site of injection
- Consider using a pharmacologic marker (epinephrine).
- Incremental Injection: LAs should be administered in small, fractionated doses (typically 3–5 mL aliquots separated by 15 to 20 seconds) to reduce the blood drug concentration, but mainly to be able to cease drug administration with less of the dose having been given at the onset of toxic symptoms or signs, with frequent and deliberate gentle aspiration before each injection to minimize the risk of inadvertent intravascular delivery
- For the same reason continual communication with the patient during the procedure where feasible is useful.
- Use of Ultrasound Guidance: The use of real-time ultrasound not only improves anatomical accuracy and block efficacy but also allows for lower volumes of local anesthetic, reducing systemic absorption and the likelihood of toxicity.
- Availability of Lipid Emulsion Therapy: Lipid rescue is a critical intervention in the event of systemic toxicity and should be readily available in any setting where RA is performed. The detailed management of LAST, including lipid emulsion therapy, is beyond the scope of this review, and readers are referred to established American Society of Regional Anesthesia guidelines for treatment algorithms.
- Adherence to Guidelines: Following practice advisories such as the 2012 ASRA guidelines[22] is essential to ensure dosing safety
- Avoidance of High-Risk Practices: The use of large, unmonitored boluses, mixing of multiple LAs, and performing blocks in inadequately equipped settings should be strictly avoided.
- Constant vigilance: any unusual cardiovascular or neurological sign, including outright cardiac arrest, after LA administration should raise suspicion of LAST.

None of the LAs should truly be regarded as 'safe'.

A formal consensus methodology, such as a Delphi process, was not applied; therefore, the recommendations presented reflect expert agreement rather than a structured consensus.

Conclusion

Determining the optimal dose of LAs in RA remains a complex process, influenced by pharmacokinetics, procedural factors, and patient-specific variables. Safe and effective practice demands an individualized, evidence-based approach, incorporating ultrasound guidance, vigilant monitoring, and readiness to manage complications such as local anesthetic systemic toxicity (LAST). Rational dosing strategies should use the lowest possible dose of the least toxic LA necessary to achieve the desired extent and duration of block and should avoid unvalidated LA combinations and off-label adjuvants lacking proven benefit. As RA advances within multimodal analgesia frameworks, continuous research, clinician education, and institutional support are essential to optimize patient safety and care quality.

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