

Comparison of 3 guideline lipid emulsion regimens for local anesthetic systemic toxicity: an in silico study of bolus duration, total dose, and treatment delay in intravenous bupivacaine overdose

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Purpose: Lipid emulsion is the only specific antidote for local anesthetic systemic toxicity, but no dose-finding study has been conducted. We compared 3 published regimens and alternative schedules that deliver the same dose in different ways using a human model of intravenous bupivacaine overdose.

Methods: A 14-compartment human bupivacaine model was independently reimplemented without fitted parameters, replacing first-order lipid elimination with a saturable term. Toxicity was modeled as 112.5 mg administered intravenously over 3 minutes. Benefit was defined as the predicted maximum decrease in myocardial bupivacaine within 30 minutes, and harm as the predicted relative lipid load, indexed by peak plasma triglyceride concentration. Neither measure is a validated surrogate.

Results: The 3 guidelines specify the same doses but different bolus durations: 1 minute versus 2–3 minutes. At a matched dose of 12 mL/kg, myocardial bupivacaine decreased by 30.5% with the 1-minute bolus and 24.9% with the 2.5-minute bolus, with the same lipid load. The completed American Society of Regional Anesthesia and Pain Medicine regimen (7.64 mL/kg) achieved a 24.6% decrease versus 24.9% with 12 mL/kg; thus, complete regimens differ in schedule as well as dose. Repeating the 1-minute bolus twice, for a total of 4.5 mL/kg, achieved a 31.9% decrease with 62% less emulsion. Start time had the greatest effect: the best regimen achieved a 41.8% decrease when started at the end of the injection, but only 9.6% when started at 10 minutes.

Conclusion: In this bupivacaine model, bolus duration distinguished the regimens more than dose did, and delay had a greater effect than either, eliminating most of the benefit without changing the lipid load. Treatment should begin at the first signs of toxicity, and 20% lipid emulsion should be immediately available wherever local anesthetics are used.

Keywords: Local anesthetics; Bupivacaine; Intravenous fat emulsions; Biological models; Practice guidelines as topic

Introduction

Local anesthetics block voltage-gated sodium channels; when sufficient drug enters the systemic circulation, they also block these channels in the heart. Bupivacaine dissociates slowly from cardiac channels, producing toxicity characterized by conduction block, refractory ventricular arrhythmia, and cardiac arrest [1]. Lipid emulsion is the only specific antidote, and all major societies recommend it as first-line treatment [2-5]. The setting of risk is shifting away from the operating room: since the 2010 advisories, the proportion of reported deaths occurring there has decreased from 47% to 15% [6]. The regimen, however, has not changed. The American Society of Regional Anesthesia and Pain Medicine (ASRA) in 2018, the Association of Anaesthetists (AoA) in 2023, and the European Resuscitation Council (ERC) in 2025 all specify the same dose: a 1.5 mL/kg bolus of 20% emulsion, an infusion at 0.25 mL/kg/min, doubling of the infusion rate if circulation does not recover, and a maximum cumulative dose of 12 mL/kg [2-5]. They differ in bolus duration and the permitted frequency of repeat boluses.

An international workgroup appraised the evidence in 2016 and reported that “the maximum safe dose of [intravenous lipid emulsion] is unknown,” that “no studies have assessed varying doses and infusion rates or their combinations in humans,” and that “dose-finding studies are much needed [7].” None has been performed in the intervening decade. The most recent resuscitation guideline describes its recommendation as based on “very low-certainty evidence ... but without documented harm” and specifies a 12 mL/kg maximum “to avoid fat overload [5].” This maximum is precautionary: it was intended to prevent fat overload, was not derived from observed dose-limiting toxicity, and has never been tested.

A randomized trial cannot provide the required scale of evidence. Local anesthetic systemic toxicity (LAST) occurs in about 1 per 1,000 peripheral nerve blocks [8,9]; consent cannot be obtained after cardiac arrest, and no investigator would administer placebo in that situation. An alternative is to calculate the effects of a schedule using a physiological model, as has been done for drug concentrations produced by resuscitation and antidote guidelines [10,11]. A human physiologically based pharmacokinetic model of bupivacaine has been available since 2013 [12]. It represents one proposed antidotal mechanism: drug

moves from tissues into lipid droplets circulating in plasma and can no longer reach the heart. The same process has been modeled for liposomes [13].

Those models evaluated whether lipid uptake is effective [12-14], rather than how the antidote should be dosed. Each used the guideline regimen as an input and varied only the total dose. One group also modeled the lipid load produced by the very large volumes used off-label for poisoning with orally ingested lipid-soluble drugs and proposed a maintenance rate well below guideline rates [15]. That model could quantify the lipid produced by a schedule but not the drug removed from the heart; its authors explicitly stated that their focus was not LAST.

Other investigators have proposed that an optimal regimen should exist. Work in isolated rat hearts concluded that “an optimal concentration should exist [16].” A subsequent study in the same preparation compared lipid with epinephrine and concluded that “the optimal dosing regimen of lipids combined with epinephrine ... needs further study [17].” A volunteer crossover study suggested that lipid administration while anesthetic concentrations are still increasing should attenuate the peak [18]. None of these studies examined dose and schedule jointly or assessed benefit and lipid load on the same axes.

We compared the 3 published regimens with one another and with 2 schedules that deliver the same total dose differently. Each regimen was encoded from its primary source document and evaluated using an independently reimplemented model.

Methods

Ethics statement

This study used only previously published data and involved no human participants, human material, or animals. Institutional review board approval and informed consent were therefore not required.

The model

The model of Kuo and Akpa [12] was reimplemented in Python (NumPy, SciPy) from the published equations. This 14-compartment human physiologically based pharmacokinetic model of bupivacaine

includes 12 perfusion-limited organ compartments, with elimination occurring only in the liver. Drug in blood is partitioned in rapid equilibrium among 4 subcompartments: unbound drug in plasma water, drug bound to plasma protein at 2 saturable sites, drug taken up by erythrocytes, and drug bound to circulating lipid droplets. The capacity of the lipid-droplet subcompartment is proportional to the plasma lipid volume fraction [19], which is tracked by an additional state variable.

Parameters

The model contains no fitted parameters. Plasma protein binding was represented using the 2-site constants from Table 1 of the 1984 human serum study [20] cited by Kuo and Akpa [12]. Tissue-to-plasma partition coefficients were taken, as published, from Table S3 of the 2010 human model they cited [13]; these values had themselves been predicted using a mechanistic tissue-composition model [21]. Organ volumes and perfusion rates were standard reference values (Table S1) [22] for the 72 kg adult male used as the reference subject by Kuo and Akpa [12]; this weight was used throughout [20]. Cardiac output was therefore set to the resting value of 6.09 L/min. Because both the drug and emulsion are carried by this flow, lower cardiac output was examined separately. The source leaves 2 quantities unspecified: hematocrit and the interpretation of the unbound blood fraction. Both were recovered from values reported in the source (Supplementary S4 and S5, Table S2). Reproduction of the source results is presented in Table S5 and Fig. S1, systemic pharmacokinetics in Table S4, validation against an independent human study in Table S6, and code in S11.

Lipid elimination

Kuo and Akpa modeled plasma lipid removal as a first-order process without specifying its rate. Fettiplace et al. [23] reported a triglyceride half-life of 14 minutes, consistent with an intravenous fat-tolerance test in which 12 normolipidemic men received a 0.5 mL/kg bolus of 20% emulsion and had a triglyceride half-life of 13.7 ± 5.2 minutes [24]. However, that test dose is 1/3 of the 1.5 mL/kg guideline bolus and 1/24 of the permitted 12 mL/kg maximum. The half-life measured at that dose cannot be assumed to apply at antidotal doses.

Lipid removal was therefore modeled as saturable, increasing with triglyceride concentration until reaching a maximum. This maximum was set to $0.21 \text{ g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, as measured in healthy adults receiving lipid emulsion [25,26] and supported by a population analysis in patients [27]. The Michaelis constant, the concentration at which removal occurs at half the maximum rate, was set to 210 mg/dL based on an animal study [28]; no human value has been published. The saturable form is not new. Since 1980, the same emulsion has been described as exhibiting “zero order kinetics for removal at high substrate concentrations and first order kinetics for removal at lower substrate concentrations” at doses reaching 0.2 g fat/kg [29]. The guideline bolus alone delivers 0.3 g/kg, and the 12 mL/kg maximum, equivalent to 2.4 g/kg of lipid, delivers 12 times that threshold. The maximal clearance capacity reported in that work, $110 \mu\text{mol}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$ in normal subjects, converts to $0.25 \text{ g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, close to the value used here.

The substitution was tested against a human infusion study that had not contributed to model development [30]. The saturable form reproduced the measured concentration and half-life within 1 standard deviation (Table S7, Fig. S2).

Scenario and endpoints

Toxicity was modeled as 112.5 mg of bupivacaine administered intravenously over 3 minutes to a 72 kg adult. This dose was reported in a case of accidental intravascular injection during a brachial plexus block that Kuo and Akpa [12] also used for their overdose simulation [31]. At that dose, the patient reported dryness in the throat and eyes. The injection was immediately stopped and the needle removed, followed immediately by generalized convulsions.

Lipid emulsion administration began 2.5 minutes after the injection ended. This interval was derived from the reported sequence: thiopental stopped the convulsions within 60 seconds, after which narrow-complex tachycardia broadened and slowed to asystole over a further 90 seconds; emulsion administration began just before asystole [31].

During inadvertent intravascular injection, symptoms prompt injection cessation, so the end of injection coincides with the first signs of toxicity. The modeled injection was stopped for that reason [31], and delay was measured from its end. The zero-delay condition represents the earliest physically possible start, rather

than an achievable target. This correspondence does not apply after infiltration or catheter infusion, when absorption continues for hours.

Benefit was measured as the largest reduction in myocardial bupivacaine concentration within 30 minutes after lipid administration began, relative to the untreated simulation at the same time point. The reduction in cumulative myocardial exposure over that window was also recorded. This endpoint takes the largest relative difference between simultaneous points on the 2 curves; it does not measure a reduction in peak concentration. The untreated peak occurs 4.2 minutes after injection begins, before lipid administration, and cannot be lowered by a regimen started afterward. This ordering reflects the clinical problem: lipid is administered in response to toxicity that has already developed.

Harm was measured as the predicted relative lipid load, indexed by peak plasma triglyceride concentration, the quantity that the 12 mL/kg maximum is intended to limit. Neither measure is a validated surrogate: no myocardial concentration has been shown to predict survival, and no plasma triglyceride concentration has been established as safe after antidotal dosing. Because the model also retains all delivered lipid in plasma, its reported concentrations are upper bounds (Supplementary S10). The 2 measures therefore rank schedules within the model and do not estimate absolute clinical risk.

Comparators and sensitivity analyses

The 3 regimens were encoded from their primary documents [2-5] (Table 1, Fig. 1). ASRA [2] and its 2020 checklist [3] recommend a repeat bolus but specify neither the number nor the interval. That regimen was therefore simulated in 2 forms: without a repeat bolus and with 2 repeat boluses, each given over the same 2–3 minutes as the initial bolus and at the 5-minute intervals specified by AoA and ERC [4,5]. Two additional test schedules were constructed. The first repeats the ERC bolus [5] at 2.5-minute intervals to a total dose of 4.5 mL/kg; the second delivers the entire 12 mL/kg dose in 1 minute to define the upper limit.

Three comparisons were performed: a 1-minute versus a 2.5-minute bolus, both delivering 12 mL/kg; the completed ASRA regimen versus the AoA regimen; and the 3-bolus test schedule versus the full ERC regimen.

All 3 comparisons were repeated across the model settings and reduced cardiac outputs listed in [Table 2](#). Every organ flow was scaled together, hepatic intrinsic clearance was left unchanged, and the time to the first drop of emulsion was varied from 0 to 60 minutes ([Table 3](#)).

Results

The ASRA advisory [2], AoA handbook [4], and ERC guideline [5] specify identical doses ([Table 1](#)). ERC specifies a 1-minute bolus, whereas ASRA and AoA specify 2 to 3 minutes. AoA and ERC also quantify repeat dosing: at 5 and 10 minutes, or a maximum of 2 additional boluses at 5-minute intervals. ASRA states only “consider rebolus.”

At a matched total dose of 12 mL/kg, myocardial bupivacaine decreased by 30.5% with the ERC regimen and 24.9% with the AoA regimen. The corresponding peak plasma triglyceride concentrations were 56.9 and 56.6 mmol/L ([Fig. 2](#)).

The ASRA regimen, completed with 2 repeat boluses, delivered 7.64 mL/kg and reduced myocardial bupivacaine by 24.6%, with a peak plasma triglyceride concentration of 35.7 mmol/L.

The first test schedule delivered 1.5 mL/kg over 1 minute, repeated at 2.5-minute intervals, for a total of 4.5 mL/kg, and was completed by 6 minutes. It reduced myocardial bupivacaine by 31.9%, with a peak triglyceride concentration of 21.5 mmol/L and a maximum delivery rate of 108 mL/min. Cumulative myocardial exposure decreased by 15.1%, compared with 16.0% for the ERC regimen. The second schedule delivered the entire 12 mL/kg dose in 1 minute at 864 mL/min and reduced myocardial bupivacaine by 58.8%.

When started at the end of the local anesthetic injection, the ERC regimen reduced myocardial bupivacaine by 41.8% ([Table 3](#)). The reduction was 30.5% at the base-case delay of 2.5 minutes, 9.6% at 10 minutes, and 3.9% at 60 minutes. Peak plasma triglyceride concentration remained 56.9 mmol/L at every start time.

Across all settings, the 1-minute bolus produced a greater reduction than the 2.5-minute bolus, and increasing the dose changed the reduction less than accelerating the bolus did. At reduced cardiac output,

every regimen produced a greater reduction in myocardial bupivacaine than at resting output. The 1-minute bolus produced 1.23 times the reduction of the 2.5-minute bolus at resting output and 1.06 times the reduction at 35% of resting output. The 3-bolus test schedule produced the same reduction as the full ERC regimen at resting cardiac output. Its reduction was 3.4% points lower than the ERC regimen at 65% of resting output, 10.7 points lower at 35%, and 0.9 points lower with the back-calculated partition coefficients.

Discussion

This study compared 3 guideline lipid emulsion regimens for LAST. In the model, bolus duration distinguished the regimens more than total dose did. ERC specifies an initial bolus over 1 minute, whereas ASRA and AoA specify 2 to 3 minutes; the faster bolus produced a larger modeled reduction in myocardial bupivacaine. At a fixed total dose of 12 mL/kg, the predicted reduction was 30.5% with the 1-minute bolus and 24.9% with the 2.5-minute bolus. Because the AoA and ERC regimens are otherwise identical, bolus duration is their only differing variable and accounts for the difference. In a hypothetical schedule of three 1.5 mL/kg boluses, totaling 4.5 mL/kg within 6 minutes, the reduction in myocardial burden matched that of the full ERC regimen at resting cardiac output, with a much lower lipid load. Treatment delay had a greater effect than either duration or dose: the reduction decreased from 41.8% when emulsion was started immediately after the local anesthetic injection to 9.6% when it was started 10 minutes later, without changing peak triglyceride concentration.

Lipid emulsion is thought to act through 3 mechanisms: sequestration of lipophilic local anesthetic into the lipid phase, increased cardiac contractility, and expansion of circulating volume [14,32]. Only sequestration is represented here. Parameters for the other 2 mechanisms are available only for rats, and the investigators who fitted them could identify only 2 of 6 [14]. The model can therefore indicate that a schedule reduces myocardial drug exposure, but not that it improves survival. This limitation does not invalidate the argument: an effect on contractility appears only after myocardial concentration has fallen enough for the heart to respond, so faster drug removal enables that effect.

The model fails to reproduce 1 measurement from the only volunteer crossover trial [33]. During lipid infusion in that trial, total plasma bupivacaine decreased to 0.74 and 0.79 of control at 20 and 30 minutes after emulsion initiation, respectively; the model instead predicts increases to 1.29 and 1.39 (Table S6). This discrepancy is structural rather than parameter-dependent, because drug sequestered by circulating droplets remains in plasma, whereas the trial authors attributed the decrease to accelerated tissue distribution. The model does reproduce the unbound concentration, which determines the effect. The trial used 0.5 mg/kg, a dose well below toxicity (Supplementary S8), whereas an in vitro study at a toxic concentration found greater extraction than the binding capacity used here permits [34]. No human data are available at antidotal doses, precluding model validation at those doses. This is why the study reports relative rankings of schedules rather than absolute predictions.

Since 2010, the AoA handbook has revised its lipid dosing once, extending the initial bolus from 1 minute to 2 or 3. Thus, the only change to date has been in the opposite direction to that favored by this model, without an explanation. A plausible concern is that half of the volunteers in one study reported arm pain when 1.5 mL/kg was administered over about a minute [35]. In the model, the longer bolus reduces predicted protection by 5.6% points. The ASRA checklist states that administration order, bolus or infusion, is “not critical” [3], allowing the infusion to begin first, although the modeled decrease in myocardial bupivacaine was produced by the bolus.

One clinical observation directly distinguishes infusion rate from dose. A patient developed ropivacaine toxicity during anesthesia maintained with propofol, itself a 10% lipid emulsion. The 98 mL of propofol administered over 90 minutes did not prevent toxicity, whereas a 100 mL bolus of 20% emulsion over 10 minutes resolved it within 5 minutes. The lipid loads were similar, but delivery rates differed 18-fold [36]. In addition, repeating the 1.5 mL/kg bolus at 2.5-minute intervals instead of switching to infusion produced the same maximum reduction as the best published regimen, with 62% less lipemia than the two 12 mL/kg regimens, whose lipid loads were equal.

Although the test schedule consists only of boluses, infusion remains relevant. In the modeled case, cardiotoxicity recurred 40 minutes after infusion ended; the authors attributed relapse to a decreasing serum lipid concentration, and no additional lipid was available [31]. This is consistent with sequestration, which can operate only while droplets remain present. Front-loading determines the peak effect, whereas

continued infusion determines its duration. Lipid must be present in plasma when toxicity occurs, so administration in advance does not help. A pilot study of 1,621 arthroplasty patients given lipid before the anesthetic found no reduction in severe toxicity [37], because infiltration-related toxicity appears hours later.

No plasma triglyceride concentration has been established as safe after antidotal dosing, and the model reports an upper bound rather than a concentration expected to be measured in a patient. The modeled loads are therefore compared with one another, not with a clinical threshold (Supplementary S10). The maximum rate of the 3-bolus schedule is 108 mL/min in a 72 kg adult, matching the rate specified by ERC for its bolus. The 12 mL/kg bolus at 864 mL/min cannot be delivered in practice.

The model does not fully resolve the decrease in cardiac output accompanying local anesthetic-induced cardiac arrest. Lower output slows drug removal, allowing continued emulsion administration to remain useful for longer. The simulations reflect this: the test schedule produced reductions 3.4% points below the ERC regimen at 65% of resting cardiac output and 10.7 points below it at 35%. Resting output represents treatment at the first signs of toxicity, as directed by the American advisory, which recommends emulsion “at the first signs of LAST” and “on the early side of administration” [2]. Reduced output represents treatment after circulatory failure, the setting for which the European document specifies dosing under “during cardiac arrest” [5]. The 3-bolus schedule therefore fits the recommended treatment timing but loses its advantage when treatment is delayed. In the modeled case, emulsion was administered as circulation was failing [31], so resting-output results represent the optimistic end of the range for that patient.

Delaying emulsion initiation from the end of injection to 10 minutes later reduced benefit by nearly 6 times the entire difference between the fastest and slowest published regimens. By 1 hour, little benefit remained, while peak triglyceride concentration was unchanged at all start times.

All 11 cases submitted to an online registry between 2014 and 2016 received emulsion within 5 minutes, whereas nearly 40% of cases in the series accompanying the same advisory received it at 10 minutes or later [2]. Approximately 55% of published pediatric cases received emulsion within 10 minutes [38]. In a 10-year poison-center cohort, 12.6% of 143 patients received it, at a median of 63 minutes after symptom onset [39]. This distribution reflects the care setting rather than severity. The longest delays occurred in the poison-center cohort, in which 59.4% of exposures followed local infiltration and the authors identified delayed treatment access as a substantial barrier [39].

The call for dose-finding studies has remained unanswered for a decade, with the perceived obstacle that such studies would require exposing participants to a toxic dose. A study of dosing schedules need not do so: antidote pharmacokinetics can be measured in volunteers receiving different schedules, and the clinical endpoint can be derived through a validated model. This design was used to establish repeat dosing for naloxone [11].

Kuo and Akpa [12] developed the reimplemented model to test whether sequestration can work, rather than to select a dose; here, it is applied at concentrations beyond those studied in humans. The model supports relative ranking of schedules at a fixed physiology for intravenously administered bupivacaine. It does not support absolute reduction estimates, survival claims, a weight-based dosing rule, or extrapolation to infiltration-related toxicity. Varying the only rat-derived parameter, the Michaelis constant for lipid removal, by more than 12-fold changed each comparison by no more than 0.1 percentage points (Table 2). The advantage of the 3-bolus schedule is the finding most dependent on physiology and holds only at resting cardiac output.

Limitations

The largest uncertainty concerns the drug-binding capacity of the lipid phase. Halving or doubling this capacity changed the predicted reductions across a range of 14.8% to 45.2%, a larger effect than that of any other tested parameter (Table 2).

No identified human study of lipid rescue measured plasma triglyceride concentration, so the harm measure relies on nutritional and case-report data. Clinical harm itself is not hypothetical: 2 of the 18 patients receiving emulsion in the poison-center cohort developed acute respiratory distress syndrome or fat overload syndrome [39]. Only one comparison holds total dose constant; the others also vary repeat dosing and infusion patterns, preventing isolation of the effect of total dose. Cardiac output remains fixed within each simulation, so deterioration during severe toxicity is not represented. The reduced-output scenarios are static approximations of that state rather than a time course. Finally, the analysis addresses acute intravascular bupivacaine overdose, not infiltration, in which absorption continues for hours, or other local anesthetics, for which no equivalent human model has been published.

Conclusion

The 3 published regimens specify the same doses but differ in initial bolus duration and the permitted frequency of repeat boluses. In this model of intravenous bupivacaine overdose, at a fixed total dose of 12 mL/kg, administering the bolus over 1 minute rather than 2.5 changed the predicted reduction in myocardial bupivacaine by 5.6% points. Delaying emulsion initiation had a greater effect than any difference between regimens. A guideline could therefore specify the administration rate and schedule as well as total dose. Treatment should begin at the first signs of potentially serious toxicity, and 20% lipid emulsion in quantities sufficient for repeat dosing must be immediately available wherever local anesthetics are used.

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Authors' contribution

Conceptualization: SC. Data curation: SC. Formal analysis: SC. Investigation: SC. Methodology: SC. Validation: SL, SC. Visualization: SL, EC. Software: SL, SC. Writing—original draft: SL, SC, EC. Writing—review & editing: SC. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

The reimplementation, regimen definitions, analysis scripts, and parameter files are openly available on Zenodo at <https://doi.org/10.5281/zenodo.22792763>.

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Supplementary materials

None.

Ahead of print

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Table 1. Comparison of 3 published regimens

	ASRA 2018, checklist 2020 [2,3]	AoA 2023 [4]	ERC 2025 [5]
Formulation	20% lipid emulsion	20% Intralipid	20% lipid emulsion
Initial bolus	100 mL if >70 kg; 1.5 mL/kg if <70 kg	1.5 mL/kg (about 100 mL for 70 kg)	1.5 mL/kg
Bolus duration	Over 2–3 min	Over 2–3 min	Over 1 min
Infusion	200–250 mL over 15–20 min if >70 kg; 0.25 mL/kg/min if <70 kg	15 mL/kg/hr (=0.25 mL/kg/min)	0.25 mL/kg/min
Infusion-rate escalation	Increase to 0.5 mL/kg/min if stability is not achieved	Double to 30 mL/kg/hr at any time after 5 min	Double at 5 min if no ROSC
Repeat bolus	“Consider rebolus”; number and interval not specified	Same dose at 5 min and 10 min	Maximum of 2 further boluses at 5-min intervals
Maximum cumulative dose	About 12 mL/kg (“upper limit for initial dosing”)	12 mL/kg (70 kg: 840 mL)	12 mL/kg (“to avoid fat overload”)
Weight basis	Fixed volume if >70 kg; ideal body weight if <70 kg	mL/kg throughout	mL/kg throughout
Propofol	“Not a substitute for lipid emulsion”	“Propofol is not a suitable substitute”	-
Strength/certainty of evidence	Lipid emulsion I; B · 12 mL/kg limit IIb; B · propofol III; B	Not graded	“Very low-certainty evidence ... but without documented harm”
Total delivered, 72 kg adult ^{a)}	4.86 mL/kg	12.0 mL/kg	12.0 mL/kg
Predicted peak plasma triglyceride concentration, 72 kg	22.2 mmol/L	56.6 mmol/L	56.9 mmol/L
Predicted maximum reduction in myocardial bupivacaine concentration, 72 kg	21.1%	24.9%	30.5%

All 3 documents specify identical doses and differ only in initial bolus duration and whether repeat dosing is quantified. Strength and certainty gradings are those of the source documents.

ASRA, American Society of Regional Anesthesia and Pain Medicine; AoA, Association of Anaesthetists; ERC, European Resuscitation Council; ROSC, return of spontaneous circulation.

^{a)}ASRA as written, without a repeat bolus because neither the number nor the interval is specified; with 2 repeat boluses, it delivers 7.64 mL/kg and produces a 24.6% reduction. Above 70 kg, ASRA uses a fixed volume, so the dose in mL/kg decreases as weight increases: 4.86 at 72 kg, 3.89 at 90 kg, and 3.18 at 110 kg, equivalent to 27% of the stated maximum. Infusion ends according to circulatory stability rather than a fixed duration (“continue for at least 10 min after circulatory stability is attained” in the 2018 advisory [2] and “≥15 minutes once hemodynamically stable” in the 2020 checklist [3]). The total is therefore open-ended: 5.88 mL/kg at 17.5 minutes and 9.00 mL/kg at 30 minutes.

Table 2. Sensitivity of the 3 comparisons to parameter choices

Setting	1-min bolus (%)	2.5-min bolus (%)	Ratio	ASRA 7.64 mL/kg (%)	AoA 12 mL/kg (%)	Difference (% points)	Three boluses 4.5 mL/kg (%)	ERC 12 mL/kg (%)	Difference (% points)
Base case ^{a)}	30.5	24.9	1.23	24.6	24.9	-0.3	31.9	30.5	+1.4
Partition coefficients									
Scaled from a rodent set	30.8	25.3	1.22	24.9	25.3	-0.4	32.0	30.8	+1.2
Back-calculated from the source's exposure table	30.7	26.0	1.18	24.7	26.0	-1.3	29.8	30.7	-0.9
Lipid elimination									
First-order, 14 min (source assumption)	28.6	23.1	1.23	22.9	23.1	-0.2	30.0	28.6	+1.4
First-order, 7.8 min	26.9	21.6	1.24	21.4	21.6	-0.2	28.3	26.9	+1.4
First-order, 22 min	29.4	23.9	1.23	23.6	23.9	-0.3	30.8	29.4	+1.4
V _{max} 0.12 g·kg ⁻¹ ·h ⁻¹	30.7	25.1	1.22	24.7	25.1	-0.3	32.1	30.7	+1.4
V _{max} 0.24 g·kg ⁻¹ ·h ⁻¹	30.5	24.8	1.23	24.5	24.8	-0.3	31.9	30.5	+1.4
K _m 48 mg/dL	30.4	24.8	1.23	24.4	24.8	-0.3	31.8	30.4	+1.4
K _m 588 mg/dL	30.6	25.0	1.22	24.7	25.0	-0.3	32.0	30.6	+1.4
Lipid binding capacity									
× 0.5	19.3	15.2	1.27	14.8	15.2	-0.3	20.1	19.3	+0.9
× 2	43.6	36.8	1.18	36.4	36.8	-0.4	45.2	43.6	+1.7
Cardiac output									
65% of resting	46.3	40.4	1.15	39.1	40.4	-1.3	42.9	46.3	-3.4
35% of resting	64.8	61.0	1.06	57.5	61.0	-3.5	54.1	64.8	-10.7
Lipid dose per kg, same physiology ^{b)}									
55 kg	25.8	20.7	1.24	22.0	20.7	+1.4	27.0	25.8	+1.2
90 kg	34.7	28.6	1.21	24.6	28.6	-4.1	36.2	34.7	+1.5

Values are predicted maximum reductions in myocardial bupivacaine concentration, expressed as percentages, in a 72 kg adult unless otherwise stated. Comparison 1 contrasts the ERC regimen with a 1-minute bolus against the same regimen with the 2.5-minute bolus modeled for the other 2 documents, at a matched dose of 12 mL/kg. Comparison 2 contrasts the completed ASRA regimen, delivering 7.64 mL/kg, with the AoA regimen, delivering 12 mL/kg. Comparison 3 contrasts three 1.5 mL/kg boluses at 2.5-minute intervals, totaling 4.5 mL/kg, with the full ERC regimen.

ASRA, American Society of Regional Anesthesia and Pain Medicine; AoA, Association of Anaesthetists; ERC, European Resuscitation Council; V_{max}, maximum rate of triglyceride removal from plasma; K_m, Michaelis constant, the plasma triglyceride concentration at which removal occurs at half its maximum rate.

^{a)}Independently reimplemented 14-compartment model using the binding constants from the cited 1984 study [20], the partition coefficients from the cited 2010 model as published [13], hematocrit recovered from the source's reported concentrations, saturable lipid elimination with a V_{max} measured in humans [25-27], and a K_m measured in rats [28]. No parameters were fitted. ^{b)}Every row uses the organ volumes, perfusion rates, plasma volume, and bupivacaine dose of the 72 kg reference subject. These 2 rows vary only the weight used to convert regimens into milliliters, testing dose per kilogram rather than allometric scaling.

Table 3. Effect of the time from injection to the start of lipid emulsion

Delay to first emulsion administration (min)	ERC 12 mL/kg (1-min bolus) (%)	AoA 12 mL/kg (2.5-min bolus) (%)	ASRA 7.64 mL/kg (%)	Three boluses 4.5 mL/kg (%)	Peak triglyceride concentration (mmol/L) ^{a)}
0	41.8	35.8	35.0	42.4	56.9
1	37.3	31.4	30.8	38.3	56.9
2.5 (base case)	30.5	24.9	24.6	31.9	56.9
5	20.0	15.4	15.2	21.4	56.9
10	9.6	7.2	7.3	8.8	56.9
20	5.1	4.3	3.9	4.9	56.9
30	4.8	4.0	3.1	4.0	56.9
45	4.2	3.7	3.0	3.8	56.9
60	3.9	3.5	3.0	3.8	56.9

Predicted maximum reductions in myocardial bupivacaine concentration, expressed as percentages, in a 72 kg adult, with emulsion started at progressively longer intervals after the end of the 3-minute injection. The benefit window shifts with start time, so each row compares a regimen with the untreated simulation over the same 30-minute interval occupied by that regimen. The 2.5-minute row is the base case, corresponding to the interval in the modeled clinical case. The zero-delay row represents the earliest physically possible start in this scenario, rather than an achievable target. Peak plasma triglyceride concentration is independent of start time.

ERC, European Resuscitation Council; AoA, Association of Anaesthetists; ASRA, American Society of Regional Anesthesia and Pain Medicine.

^{a)}The peak triglyceride concentration shown is for the 12 mL/kg regimens, which deliver the most emulsion. Lower-dose regimens reach lower peaks: 35.7 mmol/L for ASRA 7.64 mL/kg and 21.5 mmol/L for the 3-bolus schedule. None of these values varies with start time.

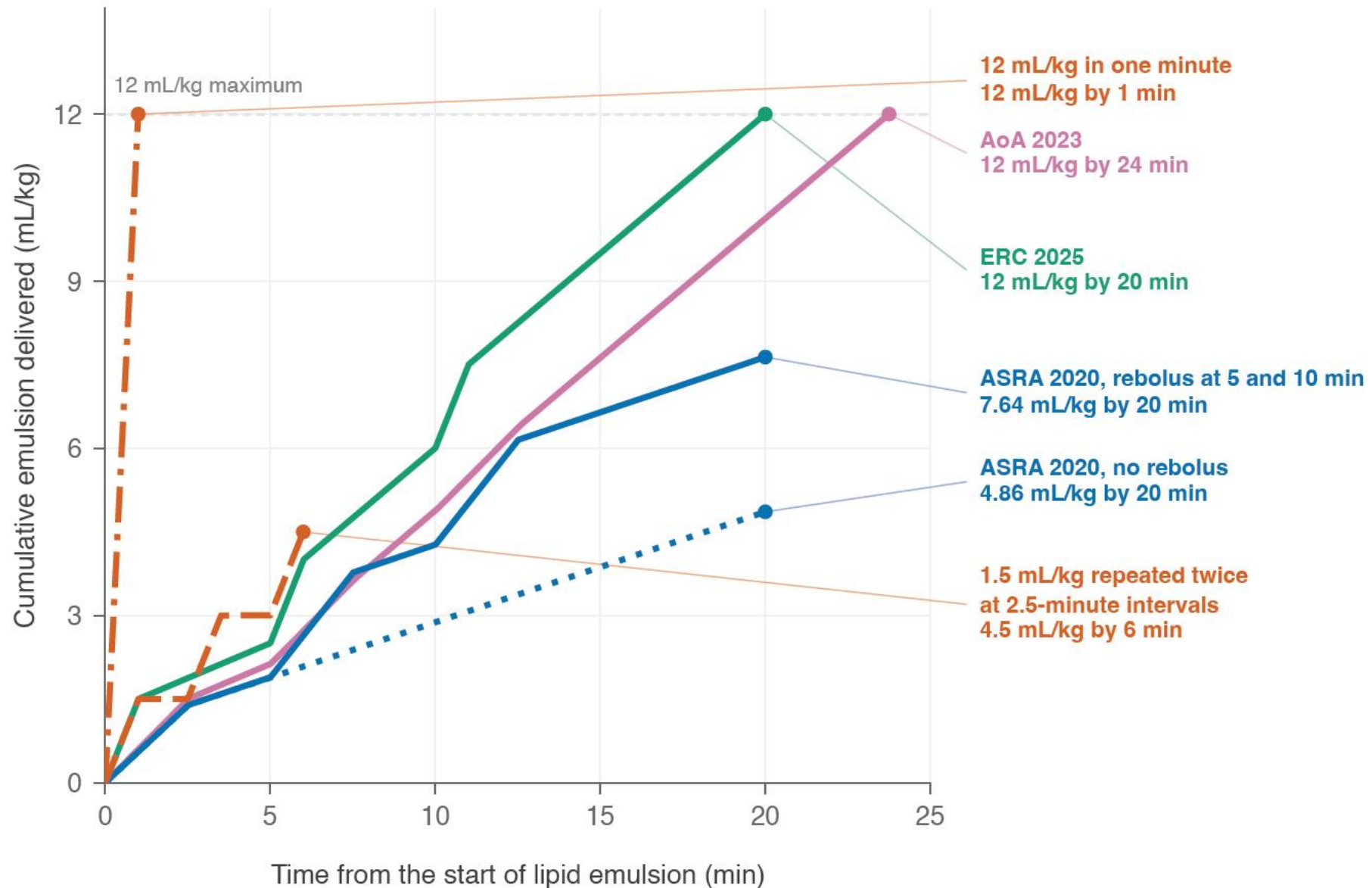
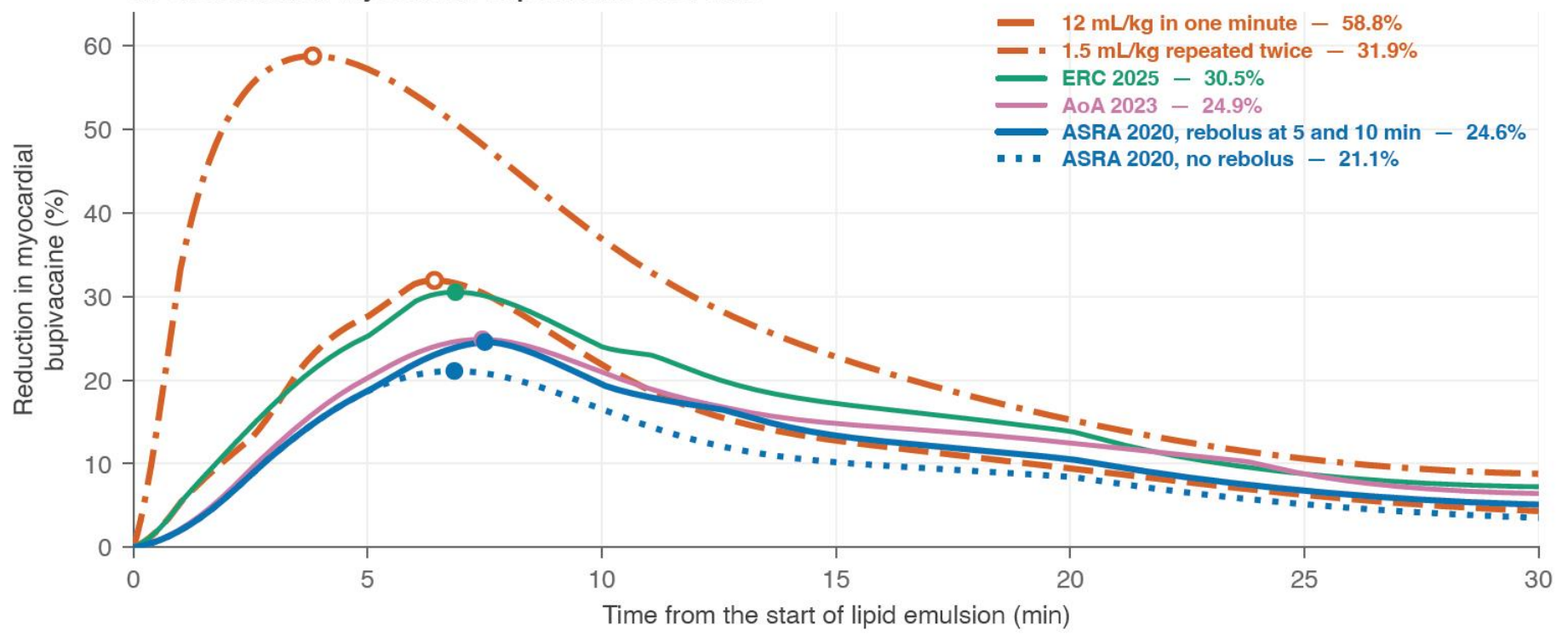


Fig. 1. Cumulative lipid emulsion volume delivered by each regimen. The curves show the cumulative volume of 20% emulsion delivered to a 72 kg adult; their slopes represent delivery rates, with steeper curves indicating greater front-loading. Solid lines represent published regimens. The American Society of Regional Anesthesia and Pain Medicine (ASRA) regimen is shown with and without repeat boluses, which its wording recommends but does not quantify; its doses follow the 2018 advisory and are repeated unchanged in the 2020 checklist. Broken lines represent the 2 constructed test schedules. All 3 documents specify identical doses but differ in how quickly the first 1.5 mL/kg is delivered and how much follows. AoA, Association of Anaesthetists; ERC, European Resuscitation Council.

A Reduction in myocardial bupivacaine over time



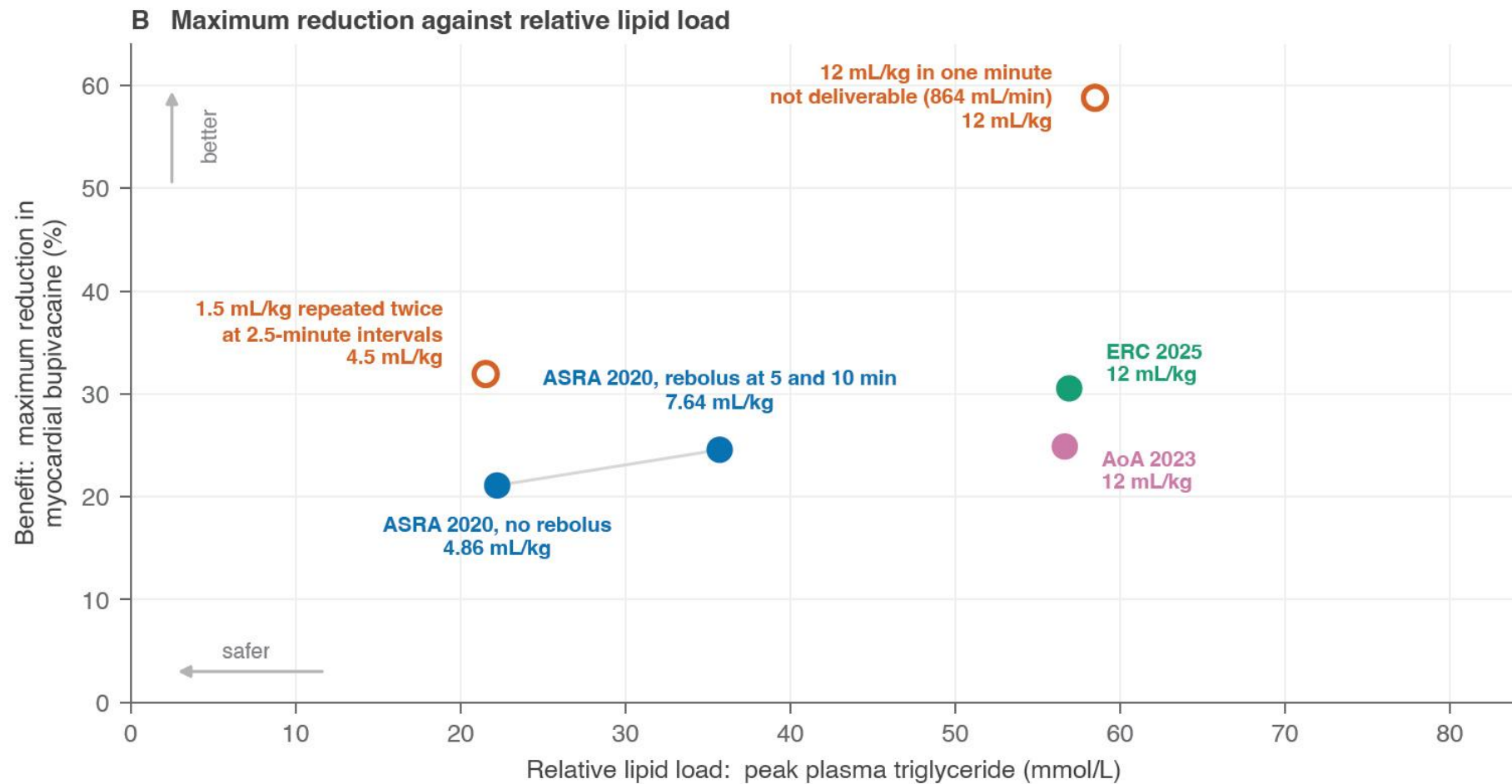


Fig. 2. Predicted benefit and lipid load of each regimen. (A) Myocardial bupivacaine over time, expressed as the percentage reduction in concentration relative to no treatment. The marker identifies each curve's peak, which is the benefit plotted in (B). The curves explain why rapid and prolonged schedules can rank differently: 3 boluses completed by 6 minutes produce a deeper reduction that then diminishes, whereas infusion continued for 20 minutes sustains the reduction longer. (B) Each peak reduction plotted against the corresponding predicted lipid load, indexed by peak plasma triglyceride concentration. Filled markers represent published regimens, open markers represent the 2 constructed test schedules, and the gray line connects the 2 American Society of Regional Anesthesia and Pain Medicine (ASRA) implementations. Greater lipid load produces little additional height on the plot: Association of Anaesthetists (AoA) and European Resuscitation Council (ERC) both deliver 12 mL/kg and reach the same triglyceride concentration but differ by 5.6 % points, while the 3-bolus schedule lies above both at one-third of the lipid load. The 12 mL/kg dose delivered in 1 minute illustrates the upper limit of the dose's potential effect; it is not a practically deliverable schedule.