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Predicting safe re-dosing of bupivacaine and ropivacaine in truncal catheters

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Introduction

Bupivacaine and ropivacaine are frequently used for perioperative analgesia. While re-dosing of these medications is often needed for pain control, safe re-dosing recommendations are uncertain [1]. Pragmatic re-dosing parameters exist in the published literature via practitioner reports of intermittent bolus and breakthrough doses. Conversely, pharmacokinetic data exist to describe the excretion of bupivacaine and ropivacaine, providing formulas for safe delivery from an elimination perspective. To determine safe re-dosing of bupivacaine and ropivacaine for truncal catheters, we examined pharmacokinetic elimination rates and compared them to real-world re-dosing of bupivacaine and ropivacaine in truncal catheters.

Materials and Methods

The work was determined as non-human-subject research and exempted from review by the Mass General Brigham institutional review board. For real-world re-dosing, we used a previously published dataset of paravertebral and transversus abdominis catheter infusions [2] that specifically utilized intermittent delivery or breakthrough bolus methods. For the pharmacokinetic elimination data, we identified manuscripts via a systematic search (on 5/28/2023) of Pubmed and Web of Science that examined the metabolism of bupivacaine or ropivacaine and reported terminal elimination half-life in humans. All abstracts and papers were screened and reviewed, and data was extracted by two reviewers. Adult pharmacokinetic elimination rates of bupivacaine and ropivacaine, along with the number of patients, mean age, adjuvants, and delivery location, were extracted for all delivery methods and excluded if co-administered with drugs that affect P450 enzymes or were delivered with delayed-release vehicles. We modeled elimination pharmacokinetics based on average and minimum (i.e. slowest) elimination constants. Further, we compared the data to intermittent and breakthrough bolus infusion methods from the prior dataset. We compared group data using the Mann-Whitney U-test ($p<0.05$ for significance). Curve fitting was performed with Prism 10 utilizing least squares regression without weighing for exponential plateau (Y= YM –{YM-Y0}*exp{-k*x}) and the extra-sum of squares F-test to compare the models.

Results/Case Report

For the pharmacokinetic elimination data, we identified 45 publications with a total of 69 independent groups (Table 1). Consistent with prior results, intravenous delivery was associated with a faster elimination (Figure 1) compared to

regional anesthetic delivery locations and was thus excluded from subsequent analysis. Elimination constants were similar between ropivacaine and bupivacaine for both average elimination and minimum elimination (e.g. slowest elimination). Given the similar elimination rates, ropivacaine and bupivacaine were grouped for analysis with an average elimination constant of k(Ave)=0.18 per hr (95% confidence interval: 0.054-0.47 per hr) and minimum elimination constant of k(Min)=0.10 per hr (95% confidence interval: 0.039-0.23 per hr) (Figure 2B).

The pragmatic re-dosing data consisted of 62 infusions of intermittent bolus and breakthrough infusions of bupivacaine and ropivacaine into the paravertebral or transversus abdominis spaces (Table 2). Dosing characteristics are shown in Table 3 and were similar between groups, except for a longer intermittent bolus interval in bupivacaine catheters (median 8 hrs, range 3-12 hrs) compared to ropivacaine catheters (median 6 hrs, range 1-12 hrs, p=0.03). Re-dosing of the catheters over time with bupivacaine and ropivacaine fit a shared exponential plateau curve (extra-sum-of-squared F-test: F=2.241(1,72), p=0.14) with the following equation: y(lB shared)mg/kg = 3.0mg/kg-(3.0mg/kg*exp(-1*time*0.061)) (95% confidence interval: 0.051-0.071 per hr, R^2=0.59), with weight-based dosing for a patient with 70 kg ideal body weight (Figure 2A).

Discussion

Herein, we analyzed safe re-dosing of ropivacaine and bupivacaine based respectively on real-world, truncal intermittent bolus and breakthrough infusions and pharmacokinetic elimination constants. Pragmatic re-dosing data fit to an exponential growth curve with an elimination constant of 0.061 per hr and half-life of ~12 hrs. Assuming upper limits of 2.5-3.0 mg/kg in patients, re-dosing would equate to ~0.9 mg/kg at 6 hrs (~65 mg in 70 kg patient), 1.56 mg/kg at 12 hrs (~110 mg in 70 kg patient). This is below the mean slowest clearance curve that demonstrated an elimination constant of 0.1 per hr and half-life of ~7 hrs with safe re-dosing of up to 1.35 mg/kg at 6 hrs (95 mg in 70 kg patient) and 2.1 mg/kg at 12 hrs (~150 mg in 70 kg patient). Mean clearance in the general population is even higher with an elimination constant of 0.18 per hr, half-life of 3.9 hrs, and re-dosing of ~2 mg/kg at 6 hrs (140 mg in a 70 kg patient) and a full dose at 12 hours. The lower limit data of 1 mg/kg at 6 hours comports with recent pharmacokinetic modeling that advises an upper limit of 1 mg/kg every six hours to avoid toxicity [3]. The upper limit data (full dose at 12 hours) comports with liberal dosing in healthy patients [4,5]. However, safe re-dosing can likely be accomplished with elimination constants of 0.061-0.1 per hr reflecting doses of 0.92-1.35 mg/kg every 6 hrs.

References

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Disclosures

No

Tables / Images

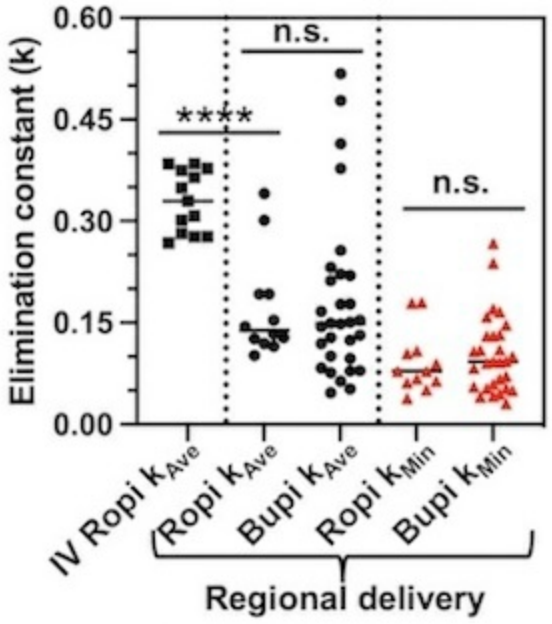

Figure 1: Comparison of elimination constants by delivery method and drug in adults.

Average elimination constants of ropivacaine delivered intravenously (mean k_{Ave}=0.33 hrs^{-1}) are statistically different compared to the ropivacaine average elimination constants determined from regional delivery, which includes peripheral and neuraxial techniques (mean k_{Ave}=0.17 hrs^{-1}). The average and minimum, i.e slowest, elimination constants for bupivacaine and ropivacaine are similar when delivered regionally (mean $k_{Ave\ Bupi}$=0.18 hrs^{-1}, mean $k_{Ave\ Ropi}$=0.17 hrs^{-1}, p=0.79; mean $k_{Min\ Bupi}$=0.10 hrs^{-1}, mean $k_{Min\ Ropi}$=0.09 hrs^{-1}; p=0.52). ****p<0.0001; n.s.=not statistically significant

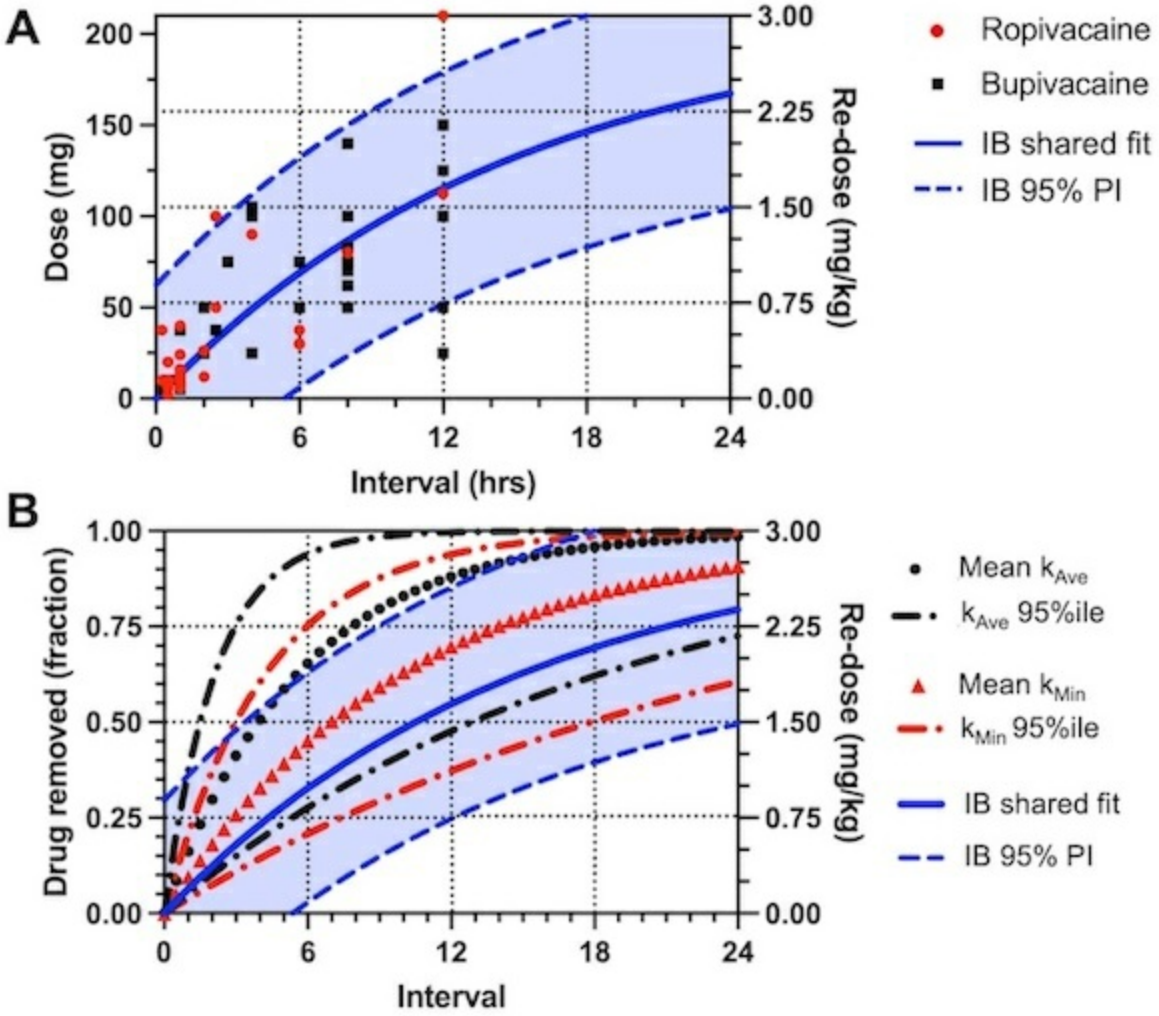

Figure 2: Re-dosing models of ropivacaine and bupivacaine based on pragmatic truncal catheter infusions and pharmacokinetic elimination constants. A) Reported re-dosing of ropivacaine and bupivacaine in transversus abdominis and paravertebral catheters (IB) in the literature with fitted exponential plateau line of $y_{drug}(mg) = 210\,mg - 210 * e^{-1*time*k}$, with the k_{shared}=0.061 hrs^{-1} for weight-based dosing in a patient with ideal body weight of 70 kg. The shared 95% prediction interval is also plotted. B) Mean and slowest bupivacaine and ropivacaine elimination co-plotted with the shared fits from part A. Bupivacaine and ropivacaine elimination constants were grouped for the average (mean k_{Ave}=0.18 hrs^{-1}, 95th percentile: 0.054 – 0.47 hrs^{-1}) and slowest values (mean k_{Min}=0.10 hrs^{-1}, 95th percentile: 0.039 – 0.23 hrs^{-1}).

Table 1. Patient and local anesthetic delivery method demographics

Truncal catheter infusion dataset				**Pharmacokinetic elimination dataset**			
		Bupi (IB)	Ropi (IB)			Bupi (PK)	Ropi (PK)
Patients**		582 (27)	1060 (35)	Patients**		528 (30)	257 (15)
Age (yrs)*; *p = 0.59*		57 [18-77]	56 [18-77]	Age (yrs)*; *p = 0.84*		35 [22-74]	34 [23-74]
Weight (kg)*; *p = 0.12*		75 [55-110]	69 [44-130]	Weight (kg)*; *p = 0.65*		73 [51-83]	73 [58-90]
*Infusion method***	Intermittent bolus	475 (21)	365 (13)	*Delivery location***	Truncal	345 (20)	134 (6)
	Breakthrough bolus	107 (6)	695 (22)		Other	183 (10)	123 (9)

*Reported as median [range]
**Reported as number of patients (number of publications)

Table 2. Publication demographics for truncal catheter infusion dataset

		Bupivacaine	Ropivacaine	Total
Number of publications (# of methods)		25 (27)	31 (35)	56 (62)
Year of publication (median [range])		2012 [1991 – 2019]	2017 [2003 – 2021]	2014 [1991 – 2021]
Country of origin	Europe	10	7	17
	North America	6	10	16
	Asia	4	9	13
Study Design	Randomized controlled trials	18	14	32
	Case report/series	2/2	5/4	13
	Retrospective cohort study	1	4	5
	Observational study	2	4	6

Table 3. Truncal catheter infusion method characteristics

		Bupivacaine	Ropivacaine	p-value
Initial bolus dose (mg)	All methods	75 [0 – 150]	75 [0 – 226.5]	0.4
	Intermittent bolus	75 [25 – 150]	112.5 [30 – 226.5]	0.53
	Breakthrough	44.6 [0 – 100]	75 [0 – 200]	0.10
Re-dosing interval (hrs)	Intermittent bolus	8 [3 – 12]	6 [1 – 12]	**0.03**
	Breakthrough	0.75 [0.2 – 4]	0.5 [0.3 – 1]	0.90
Re-dosing dose (mg)	Intermittent bolus	75 [25 – 150]	37.5 [12 – 210]	0.22
	Breakthrough	8.75 [5 – 100]	10 [2 – 40]	0.4