

## EDITORIAL VIEWS

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### *Is Ropivacaine Less Potent than Bupivacaine?*

IN this issue of ANESTHESIOLOGY appears the first clinical trial comparing the relative analgesic potency of epidural ropivacaine to epidural bupivacaine.<sup>1</sup> Both drugs are amide local anesthetics and similar in structure; however, ropivacaine is marketed as the L-isomer, whereas bupivacaine is marketed as a racemic mixture. Because bupivacaine produces motor block and can cause cardiac arrest when large volumes are accidentally administered intravenously, ropivacaine has been investigated as a possible replacement. Indeed, evidence suggests that ropivacaine may be less cardiotoxic<sup>2</sup> and produces less motor block<sup>3</sup> than bupivacaine. Until now, these differences were attributed to the chemical properties of the local anesthetics rather than to differences in potency because it was assumed that ropivacaine and bupivacaine were equipotent. These findings, however, would be subject to reassessment if ropivacaine were 40% less potent than bupivacaine, as Polley *et al.*<sup>1</sup> suggest. This result would imply that both local anesthetics might produce similar side effects at equipotent concentrations. All too often, comparison trials are completed without full knowledge of the relative potencies or the respective dose-response curves for any two drugs; most likely because traditional dose-response studies are tedious, time consuming, and costly. Nevertheless, only when these variables are known can adequate comparison trials be designed. Even now that Polley *et al.*<sup>1</sup> estimate the effective dose in 50% of a population (ED<sub>50</sub>) for ropivacaine and bupivacaine, the full dose-response curves, with respect to labor analgesia, for each remain unknown. Until the slope and shape of these dose-response curves are known, are isolated

ED<sub>50</sub> values meaningful? Let us discuss the technique used by Polley *et al.*<sup>1</sup> to estimate the ED<sub>50</sub> values for ropivacaine and bupivacaine and the implications of differences in potency between these two local anesthetics.

Polley *et al.*<sup>1</sup> estimate the relative potencies of epidural ropivacaine and bupivacaine by using an up-down sequential allocation study design, as first described for the study of epidural/spinal agents by Columb.<sup>4</sup> This is an elegant, yet simple, study design that estimates the minimum local analgesic concentration (MLAC) or ED<sub>50</sub> of any local anesthetic using a small number of patients (usually < 25/group). Up-down studies are open label, with each subsequent patient's dose varied according to the previous patient's response. Dosing intervals are usually set at equal intervals on a log scale. This design is much more efficient at estimating the ED<sub>50</sub> than traditional dose-response designs because it focuses all the sampling doses in the immediate vicinity of the ED<sub>50</sub>. However, shortcomings exist (although not all apply to the article in question). The high statistical efficiency of up-down studies are dependent on the choice of the initial drug dose and the sequential spacing between dose levels, which are somewhat arbitrarily selected by the investigators. If the initial dose tested does not approximate the ED<sub>50</sub>, initial trials are wasted in finding the vicinity of the ED<sub>50</sub> value; and, if the spacing of incremental doses does not approximate the standard deviation of the ED<sub>50</sub>, the 95% confidence limits become biased. Unfortunately, neither good estimates of the ED<sub>50</sub> nor its standard deviation may be available when designing a study. Additionally, up-down studies cannot replace traditional dose-response studies. The ED<sub>50</sub> estimated in an up-down study does not provide information regarding the slope or the shape of the dose-response curve or ED<sub>95</sub>, among others. For example, although the ED<sub>50</sub> values for two drugs may vary, it is possible the dose-response curves overlap at higher concentrations. In fact, this may explain why ropivacaine appears to be 40% less potent than bupivacaine at ED<sub>50</sub> concentrations but equipotent at higher concentrations. Finally, because only a few patients are enrolled in up-down studies, it is difficult to control for confounding variables. Although six studies to date

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**Table 1. ED<sub>50</sub> Estimations of Bupivacaine and Ropivacaine Using an Up-Down Design**

Drug	ED <sub>50</sub> (% wt/vol)	Cerv Dil (cm)	Nulliparous (%)
Bupivacaine	0.065 (0.045–0.085) <sup>4</sup>	4.5	87
Bupivacaine	0.069 (0.057–0.080) <sup>6</sup>	3.0	68
Bupivacaine	0.104 (0.090–0.117) <sup>5</sup>	4.2	19
Bupivacaine	0.048 (0.037–0.058) <sup>7</sup>	2.0	?
Bupivacaine	0.141 (0.132–0.150) <sup>7</sup>	5.0	?
Bupivacaine	0.093 (0.076–0.110) <sup>8</sup>	?	?
Bupivacaine	0.067 (0.052–0.082) <sup>1</sup>	4.4	15
Ropivacaine	0.111 (0.100–0.122) <sup>1</sup>	4.6	18

ED<sub>50</sub> values are means (95% confidence intervals).

? = not reported.

using nearly identical up-down designs have estimated the ED<sub>50</sub> of epidural bupivacaine,<sup>1,4–8</sup> the estimated ED<sub>50</sub> values vary considerably (table 1). In fact, three of seven estimated ED<sub>50</sub> values for bupivacaine are similar to the estimated ED<sub>50</sub> for ropivacaine by Polley *et al.*<sup>1</sup> The differences in ED<sub>50</sub> values for bupivacaine may reflect variations in patient populations or, potentially, uncontrolled variables. For example, parity was not controlled in any of these six labor pain studies. Because the duration<sup>9</sup> and pain intensity<sup>10</sup> of labor varies with parity, this variable may have contributed to this discrepancy. In fact, we recently confirmed this observation, to our chagrin, when data from 40 patients in an up-down study at our institution estimating the ED<sub>50</sub> of spinal sufentanil had to be discarded when significant differences in visual analog scale scores were observed between nulliparous and parous women (unpublished findings, 1996–1997). We now only enroll nulliparous women in our up-down studies.

Although Polley *et al.*<sup>1</sup> suggest that epidural ropivacaine is 40% less potent than epidural bupivacaine, clinical experience in treating the pain of labor at our institution does not support such a large difference in potency between ropivacaine and bupivacaine. We recently compared 0.125% ropivacaine to 0.125% bupivacaine with and without fentanyl, 2 µg/ml, using patient-controlled epidural analgesia (6 ml basal infusion, 5 ml on-demand bolus, 10 min lockout, 30 ml hourly dose limit) for precise titration.<sup>11,12</sup> Patients self-administered the same doses of ropivacaine and bupivacaine to produce clinically indistinguishable analgesia and patient satisfaction. These studies were adequately powered to have observed a 40% difference in potency between drugs at such clinically rel-

evant concentrations, if it exists. Likewise, numerous studies comparing 0.2–1.0% ropivacaine to 0.2–0.5% bupivacaine describe equipotent analgesia between local anesthetics. However, as Polley *et al.*<sup>1</sup> suggest, the concentrated solutions used in these studies may have masked any differences in potency or may reflect overlapping at the higher end of the dose-response curves.

Despite the limitations of up-down studies, the ED<sub>50</sub> values estimated by Polley *et al.*<sup>1</sup> are meaningful and may have clinical implications. By suggesting that ropivacaine is less potent than bupivacaine at the ED<sub>50</sub>, the possibility exists that differences in potency between local anesthetics also exist at other points of the dose-response curves. Indeed, differences in potency could have accounted for differences in side effects and toxicity observed in all previous studies. Until traditional dose-response studies thoroughly evaluate the potency of epidural ropivacaine and bupivacaine, investigators must now at least consider the potency of ropivacaine when designing comparative trials.

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