The sensitivity of sheep to vecuronium: an example of the limitations of extrapolation

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To the Editor,

In the absence of species-specific data and despite the obvious pitfalls, it is common practice for investigators to extrapolate pharmacokinetic and pharmacodynamic information between species. Although sheep are used frequently as a model for research projects, there is a paucity of pharmacological information for many drugs in this species. Our empiric observations suggest that the potency of vecuronium in sheep may be much greater than that in humans. This study measures the potency of vecuronium in sheep under general anesthesia.

Following Cornell University Institutional Animal Care and Use Committee approval, fifteen healthy adult female sheep (52–69 kg) were anesthetized for experimental stifle surgery, the results of which are to be published elsewhere. After sedation with intravenous midazolam and morphine, anesthesia was induced with propofol and maintained with isoflurane in oxygen. Neuromuscular monitoring was carried out with acceleromyography (TOF-Watch SX, Organon, Dublin, Ireland), similarly to a previous description in the dog.¹ Train-of-four stimulation was applied to the ulnar nerve every 15 sec (60 mA, 0.2 msec), with the acceleration-sensitive crystal taped to the manus. After baseline stabilization and calibration, a dose of vecuronium (4, 6, or 8 $\mu\text{g}\cdot\text{kg}^{-1}$, randomly allocated) was administered and T1 depression was measured. The averages of three consecutive values at baseline and at maximal depression were used for analysis. The effective doses for 50% and 95% T1 depression (ED_{50} and ED_{95}) were

calculated by the log-dose/logit method as described previously.²

The mean ED_{50} (standard deviation [SD]) and mean ED_{95} (SD) were 3.5 (1.2) $\mu\text{g}\cdot\text{kg}^{-1}$ and 13.2 (3.8) $\mu\text{g}\cdot\text{kg}^{-1}$, respectively. The slope of the log-dose/logit linear regression was 2.22. Twitch depression after vecuronium and onset times are presented in the [Table](#).

Considering that the ED_{50} and ED_{95} of vecuronium in humans are approximately 30 and 45 $\mu\text{g}\cdot\text{kg}^{-1}$, respectively,³ sheep are substantially more sensitive than humans. Although morphological differences between muscles have been identified to account for unequal responses to vecuronium within a species,⁴ further study is needed amongst species to identify the mechanisms responsible for the differences in sensitivity to a given neuromuscular blocking agent (NMBA).

There are limitations to this study. First, the study involved a modest number of animals. A recent investigation suggests that at least 24 subjects should be recruited.⁵ Second, vecuronium 6 $\mu\text{g}\cdot\text{kg}^{-1}$ and 8 $\mu\text{g}\cdot\text{kg}^{-1}$ had similar effects ([Table](#)). This could be explained by direct muscle stimulation in the presence of complete neuromuscular block; however, this is unlikely considering the pulse duration used (0.2 msec). Furthermore, in pilot studies using this preparation, larger doses ($> 12 \mu\text{g}\cdot\text{kg}^{-1}$) abolished twitch height completely. It is also possible that the normal variation between subjects combined with a small sample size resulted in the effects of these two doses being indistinguishable.

Of importance, the slope for the log-dose/logit relation in these sheep was only 2.22. In humans, the slopes for the log-dose/logit curves of a number of NMBAs approximate 4.5.² It is not known whether this is a real difference between species or an artifact created by the small sample size. This question could be answered by collecting data

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Table Maximum depression of T1 as a percentage of baseline and time to reach those values after vecuronium was administered to sheep under isoflurane anesthesia

	Maximum T1 depression (%)	Time to maximum effect (min)
4 $\mu\text{g}\cdot\text{kg}^{-1}$ ($n = 5$)	52 (35–71)	6 (2.5–6.5)
6 $\mu\text{g}\cdot\text{kg}^{-1}$ ($n = 5$)	88 (79–92)	5.5 (5.0–7.75)
8 $\mu\text{g}\cdot\text{kg}^{-1}$ ($n = 5$)	88 (46–91)	5.75 (4.75–6.75)

Values are expressed as median (range)

from a larger number of subjects. The use of a *post hoc* calculation using a slope value of 4.5 gives values for ED_{50} and ED_{95} of 4.5 and 8.6 $\mu\text{g}\cdot\text{kg}^{-1}$, respectively, substantially less than in humans.

In conclusion, the sensitivity of sheep to the neuromuscular effects of vecuronium is several times greater than that of humans, dogs or cats.⁶ Extrapolating vecuronium doses from data obtained in other species can result in overdosing, which increases the risk of prolonged neuromuscular block and postoperative residual curarization.

Conflict of interest None declared.

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