Correspondence

Non-steroidal neuromuscular blocking agents to re-establish paralysis after reversal of rocuronium-induced neuromuscular block with sugammadex

To the Editor:

We read the excellent editorial by Dr. Donati[1] with great interest. In his analysis of sugammadex-rocuronium dosing, he stated the importance of using the smallest possible dose of sugammadex to avoid limiting options should reintubation of the trachea or repeat surgery be needed shortly after the end of the case. We offer two possibilities for such scenarios; either re-establish block with rocuronium, as suggested by Donati, or use a non-steroidal blocking agent such as cisatracurium or mivacurium. We herein consider the results of rocuronium dose calculations for the first possibility, and the consequences for sugammadex dosing if a "second reversal" should become necessary.

In a study examining the pharmacodynamics of sugammadex in Rhesus monkeys, a model was developed that is consistent with the equilibrium scheme presented by Dr. Donati.[2] In this model the equilibrium constant is described in the common volume of distribution of rocuronium and sugammadex. Concentrations are then transformed to dosages (concentration = dose/volume) and free and bound rocuronium doses are established. Assuming that for humans 600 $\mu g \cdot kg^{-1}$ rocuronium is available as free molecule, the depth of block will be sufficient for tracheal intubation. If the addition of sugammadex results in only 75 $\mu g \cdot kg^{-1}$ (or less) free rocuronium, the block is fully reversed. The equilibrium constant for the complex formation of rocuronium and sugammadex in humans then follows; for example, the data of Gijsenbergh demonstrate that sugammadex 6 $mg \cdot kg^{-1}$ provides optimal reversal of rocuronium 600 $\mu g \cdot kg^{-1}$.[3] From this equilibrium constant the free rocuronium can be calculated at any dose combination of rocuronium and sugammadex.

The results of these calculations are depicted in the Figure (panels A and B). As Dr. Donati suggests, it can be inferred from these data that re-establishment of muscle relaxation is possible, after reversal by sugammadex, by raising the total rocuronium present in the body (one should estimate how much drug remains at any time (t) after the initial dose) to 750 or 1500 $\mu g \cdot kg^{-1}$, respectively (corresponding to reversal using sugammadex 1–4 $mg \cdot kg^{-1}$; Figure, Panel A). It also follows that a second reversal is possible using sugammadex at high doses between 8 and 20 $mg \cdot kg^{-1}$ (Figure, Panel B). Consistent with Dr. Donati's warning, initial reversal by sugammadex 8 $mg \cdot kg^{-1}$ would require a very high dose of rocuronium for re-establishment of neuromuscular block, and would exclude a second reversal attempt. The margins of error for these calculations are mostly dependent on the variance of individual pharmacokinetics and pharmacodynamics of rocuronium. Additional contributions to these errors, resulting from formation of the rocuronium-sugammadex complex, are estimated to be small, because of the almost pure physico-chemical character of the complex itself.

Another study performed in Rhesus monkeys showed that sugammadex had no effects on neuromuscular blockade induced by the non-steroidal neuromuscular blocking drugs atracurium and miva-

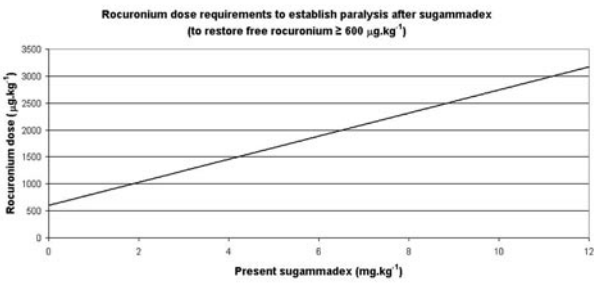

FIGURE (Panel A) Rocuronium dose required to re-establish neuromuscular block (to restore free rocuronium concentration to 600 $\mu g \cdot kg^{-1}$) as a function of the amount of sugammadex in the body (expressed as $mg \cdot kg^{-1}$). If re-establishment occurs immediately after reversal with sugammadex 4 $mg \cdot kg^{-1}$, almost 1500 $\mu g \cdot kg^{-1}$ is required. This amount includes the rocuronium remaining in the body so, if the initial block was established with 600 $\mu g \cdot kg^{-1}$, based on the elapsed time and the half-life of rocuronium, an approximate residual amount of rocuronium can be estimated and subtracted. However, if reversal was performed with sugammadex 8 $mg \cdot kg^{-1}$, the required rocuronium dose would be approximately 2250 $\mu g \cdot kg^{-1}$ to provide for adequate blockade.

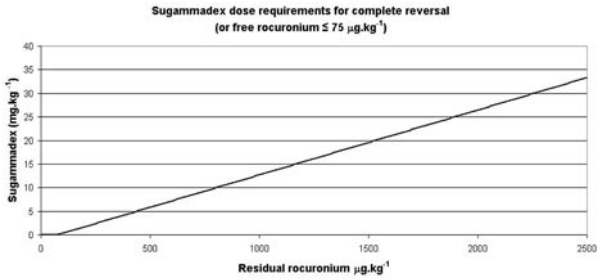

FIGURE (Panel B) Sugammadex dose requirements for reversal of rocuronium block, as a function of the amount of rocuronium in the body (expressed as $\mu g \cdot kg^{-1}$). If re-establishment was performed by increasing the total amount of rocuronium in the body to 1500 $mg \cdot kg^{-1}$ (see also the legend of panel A), reversal would be feasible with a sugammadex dose of about 20 $mg \cdot kg^{-1}$. As the elimination half-life of sugammadex is approximately 100 min, most of the sugammadex from the first reversal will be still available, and a dose of 6 $mg \cdot kg^{-1}$ would suffice (if the first reversal took place by administration of sugammadex 4 $mg \cdot kg^{-1}$).

curium.[4] These results confirm that the size of the sugammadex cavity is too small to accommodate the bulky molecules of mivacurium and atracurium, and emphasize the relative selectivity of sugammadex in binding rocuronium. This means that, if muscle relaxation is needed for reintubation of the trachea or repeat surgery, non-steroidal neuromuscular blocking drugs can be used to obtain an adequate level of neuromuscular block for this indication. It should be realized; however, that re-establishment of neuromuscular block by atracurium or mivacurium excludes the use of sugammadex for reversal of a second blockade. In this case, reversal with neostigmine is indicated after the twitch count and train-of-four response have recovered to acceptable levels once again.

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Reply:

The simulations presented by de Boer et al. are interesting and bring quantitative data to back up qualitative predictions made in my editorial.[1] The required dose of rocuronium is perhaps less than I would have anticipated; even after sugammadex 4 $mg \cdot kg^{-1}$, rocuronium 1.3 $mg \cdot kg^{-1}$ is expected to produce blockade that is similar to rocuronium 0.6 $mg \cdot kg^{-1}$ without previous sugammadex administration. Larger sugammadex doses would need more rocuronium, and such large doses are beyond the recommended doses for rocuronium. In addition, reversal of a second dose requires very large doses of sugammadex, which may well be beyond the recommended doses for that product when it reaches market. Studies are needed to demonstrate whether the simulations presented by de Boer et al. turn out to be accurate.

The possibility of this reintubation scenario shows that there will be a niche for neuromuscular blocking agents other than rocuronium and for reversal drugs other than sugammadex, when the latter becomes available. Succinylcholine might be the drug of choice for reintubation after sugammadex, and mivacurium is probably the best non-depolarizing alternative to succinylcholine in this case. Unfortunately, mivacurium is no longer available in North America. Cisatracurium appears as the best maintenance drug. For both mivacurium and cisatracurium, sugammadex is ineffective and conventional reversal agents must be used. For this reason and others (hypersensitivity reactions in some patients, renal failure – sugammadex is excreted by the kidney -, cost considerations, etc…), it would be unwise to recommend

the withdrawal of any neuromuscular blocking agents or reversal agents, even after sugammadex becomes available.

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Reference

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Appraising the evidence in managing fibroproliferative acute respiratory distress syndrome

To The Editor:

I write further to the appraisal of the "Best Evidence in Critical Care Medicine" article written by Drs. Ewanchuk and Jacka in the September 2007 issue of the *Journal*.[1] They correctly identify that routine use of methylprednisolone in patients with established acute respiratory distress syndrome (ARDS) does not improve outcome. However, they also reiterate the original article's conclusion that commencing the use of methylprednisolone more than 13 days after onset of acute respiratory distress syndrome "*had a significantly higher case fatality rate*".[2] A more detailed examination of the data may lead to a different conclusion.

The primary outcome of the study was 60-day mortality. In the placebo group the mortality rate was 28.6% [95% confidence interval (CI) 20.3 to 38.6%], and in the methylprednisolone group the mortality rate was 29.2 % (95% CI 20.8 to 39.4%). These mortality rates are similar to those reported in other studies of patients with ARDS.[3] In patients who were randomized between 14 and 28 days after onset of ARDS, the 60-day mortality rate in the methylprednisolone group (n = 23) was 35% (95% CI 15.3 to 54.2%), and in the placebo group (n = 25) it was 8% (95% CI 0 to 18.6%). While there was a statistically significant difference in the event rate between these two groups of patients, this outcome is due to a lower than would be expected mortality rate in the placebo group, as opposed to methylprednisolone directly increasing risk.

The mortality rate in the small group of patients who received placebo more than 13 days after the onset of ARDS, was far lower than that observed in other studies evaluating similar patients. It is difficult to reconcile that administration of a placebo more than 13 days after the onset of ARDS would in itself lead to a reduction of the expected mortality rate in this patient population. This is an example of problems that can arise from random error. In the trial published in the New England Journal of Medicine (NEJM), it appears that the low 60-day mortality rate observed in the placebo group was due to an effect of chance. Small samples increase the likelihood of misleading results through random error. It is surprising that this issue was not identified during peer review by the NEJM. This example serves as a gentle reminder for the readers to scrutinize the data when critically appraising an article. Guidance on this aspect of critical appraisal has been published.[4]

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Reply:

We thank Dr. Daniel for his interest in our critical appraisal and in the role of steroids for the treatment of fibroproliferative acute respiratory distress syndrome (ARDS).[1]Dr. Daniel is correct in confirming that the central finding of the National Institute of Health (NIH) trial was that a statistically significant differ-