Determining the potency of neuromuscular blockers

Editor—Kopman and colleagues assert, and I agree, that ED_{50} is a robust parameter, that is, different analysis techniques are likely to yield similar results. They also note differences in the estimate of ED_{95} when different analysis approaches [linear regression (LRA) of logit-transformed data vs non-linear regression (NLR) of non-transformed data] are applied and conclude that LRA is ‘fundamentally flawed’. Despite this flaw, the authors advocate that LRA should be considered acceptable because NLR might require the researcher to ‘seek statistical help’ and the resulting error—which they estimate to average 15%—is acceptable.

Their suggestion that a flawed method should be applied in order to avoid seeking statistical help is misguided. If I chose to use a flawed drug assay rather than seek assistance from a bench scientist who could perform a better assay, surely I would be criticized. More importantly, they assume that the error will always be in an acceptable range. However, it is possible that the error in ED_{95}, estimated with LRA, would be far more than 15%. In that the analyst does not know the magnitude of the error a priori, it seems foolhardy to select a flawed method when better methods are available.

Another major issue regards the authors’ handling of 0% and 100% response data. They note that ‘responses of 0% and 100% can be plotted, but this is not allowed with probit or logit data transformation’. They applied an arbitrary value (‘complete twitch depression was plotted as an effect of 99.5%’)—this is flawed because it assumes that peak twitch responses of 99.51% and 99.99% could result from the same dose. They also omitted extreme data for cisatracurium; this is frowned upon because omission of extreme data may bias results. Finally, they claim to have used ‘log dose’ in their LRA analyses, but an equation that they display [10^{(\log ED_{50})}] indicates that the data were actually not in the log domain.

Methods papers (ones in which the authors attempt to establish standards for future investigations) require special scrutiny. Kopman and colleagues establish that logit approaches are flawed, yet, their conclusion that these anti-quated techniques are still appropriate is misguided.

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Editor—Dr Fisher makes several valid points. Upon analysing raw data from our files for an additional four drugs, it is clear that ED_{95} values calculated by traditional probit or logit linear regression methods may differ by as much as 20% from the values for the same data calculated by NLR (Table 1). This difference is larger than the value of 15% we put forward in our paper. While it would be nice to have these differences validated by a clinical study, and the average difference in the ED_{95} for the eight drugs we studied was only <13%, a potential error of 20% is too large to ignore. As we point out in our paper, a problem with data transformation methods is that they cause some assumptions of linear regression to be violated, particularly at the extreme ends of the dose–response relationship. Thus, we agree that the investigator wishing to define the ED_{95} is best served by using nonlinear regression (NLR) analysis. We also agree that the clinician unfamiliar with this method of analysis should seek experienced help.

With regard to 100% responses, when plotting values using linear regression analysis, we relied on recommendations from the good clinical practices in neuromuscular research consensus paper. The recommendation in that paper for handling 100% responses when using logit or probit analysis was as follows: ‘These undefined values

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th># with 100% block</th>
<th>ED_{50}, log dose-logit (mg kg^{-1})</th>
<th>ED_{95}, non-linear regression (mg kg^{-1})*</th>
<th>% ΔED_{95}, logit vs NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>40</td>
<td>4</td>
<td>0.0550</td>
<td>0.0662</td>
<td>−20.3</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>50</td>
<td>2</td>
<td>0.273</td>
<td>0.323</td>
<td>−18.3</td>
</tr>
<tr>
<td>Rapacuronium</td>
<td>48</td>
<td>2</td>
<td>0.733</td>
<td>0.854</td>
<td>−16.5</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>41</td>
<td>0</td>
<td>0.325</td>
<td>0.367</td>
<td>−12.9</td>
</tr>
<tr>
<td>Cisatracurium†</td>
<td>40</td>
<td>0</td>
<td>0.0404</td>
<td>0.0447</td>
<td>−10.6</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>50</td>
<td>6</td>
<td>0.0403</td>
<td>0.0445</td>
<td>−10.4</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>45</td>
<td>0</td>
<td>0.0447</td>
<td>0.0413</td>
<td>+9.2</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>32</td>
<td>2</td>
<td>0.0485</td>
<td>0.0513</td>
<td>−5.8</td>
</tr>
<tr>
<td>Atracurium</td>
<td>45</td>
<td>0</td>
<td>0.2560</td>
<td>0.2680</td>
<td>−4.7</td>
</tr>
</tbody>
</table>

* Same group as below but the 10 patients who received cisatracurium 0.05 mg kg^{-1} were excluded from analysis.
should be adjusted by half the assumed resolution of the measuring method’. Since the resolution of the Datex neuromuscular monitor was 1%, we defined 100% block as 99.5%. However, as Dr Fisher notes this is an arbitrary value. Plotting these values as 99.99% would have resulted in a significant change in the slope of the best-fit line of regression. Thus, when using linear regression analysis, these data points should be kept to a minimum. Values of 0% and 100% are best handled using NLR. It is for this reason that we think that protocols which pre-select the doses to be administered are not ideal. We prefer an adaptive or flexible approach to dosing which allows administered doses to be modified as additional data are obtained. Regarding our cisatracurium data, we omitted the 0.05 mg kg\(^{-1}\) group from our analyses because six of 10 individuals developed 100% block. However, and this may have been a lucky accident, the ED\(_{95}\) values calculated by both linear regression analysis (0.0411 and 0.0410 mg kg\(^{-1}\)) and NLR (0.0448 and 0.0446 mg kg\(^{-1}\)) for \(n=40\) vs 50 were virtually identical!

The major point we tried to make in our paper was that ED\(_{50}\) values calculated by either regression method are inter-changeable. Traditional logit or probit methods of data transformation are perfectly adequate for determining this value. It is the ED\(_{50}\) that should be used when comparing the potencies of different neuromuscular blockers. We also emphasized that because of its wide 95% confidence limits, the ED\(_{95}\) is best thought of as an approximation. We stand by these conclusions.

**Conflict of interest**

None declared.

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1 Kopman AF, Lien CA, Naguib M. Determining the potency of neuromuscular blockers: are traditional methods flawed? Br J Anaesth 2010; 104: 705–10

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**Lung recruitment and positive airway pressure before extubation: one may not be enough**

**Editor**—The elegant study of lung recruitment and positive airway pressure before extubation needs a few comments and questions to be answered.\(^1\) The cohort was enrolled more than 3 yr and is populated by relatively lean patients compared with studies evaluating the effect of atelectasis on oxygenation, possibly affecting the differences between the groups in terms of efficacy of the treatment (may have affected your power analysis). The treatment proposed is controversial, considering that other authors have proposed a longer period of recruitment, repeated recruitment during the surgery, and valuing the effects of a continuous pressure if applied and sustained after extubation. We do not have any information on the type of elective surgery that the patients underwent or the specific anaesthetic and analgesic techniques. What neuromuscular blocking agent was used and were the patients antagonized? All this information may be of relevance to the recovery in post-anaesthesia care unit and possibly to the ventilation effort, thus contributing to confound the results presented. On the basis of the anaesthetic protocol, an intraoperative management of ventilatory support varying from 7 to 10 ml kg\(^{-1}\) body weight was used—surely this is not a negligible variance? The choice to maintain an \(F_{\text{IO2}}\) of 100% at the time of extubation, besides justified in the hypothesis, isn’t a source of major confounding possible blunting the effect of the experimental therapeutic strategy. Although it is an interesting working idea in non-bariatric elective general anaesthesia cases, reaching the conclusion that a recruiting manoeuvre followed by a pre-extubation continuous positive airway pressure (CPAP) is not effective seems to be a non-sustainable finding. The conclusion may be that a non-effective, uncontrolled, variable, single attempt of recruitment without knowing the relaxation status in patients oversedated followed by CPAP with high oxygen concentration at extubation is ineffective.

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Editor—We thank Dr Cattano for his kind comments regarding our study.\(^2\) The population of Leeds will be pleased to be described as lean, despite officially being overweight with an average BMI of around 28. It is true that we did not specifically select obese patients—this was a pragmatic study of all patients presenting for major surgery, although the possibility that our interventions may be more efficacious in obese patients would undoubtedly make an interesting next stage for our work.

We cannot agree that the treatment proposed is controversial as all the components of our intervention have been shown to be effective when used individually. More importantly, our interventions were chosen to be safe in clinical practice. For example, a recruitment manoeuvre lasting longer than 15 s, as suggested by Dr Cattano and used in the early studies of recruitment manoeuvres, may be associated with greater cardiovascular depression with no further recruitment of atelectasis.\(^2\) There was insufficient space in our paper to list the individual operations for all 44 patients, but a summary was provided in Table 1 of the manuscript. Other factors that may also affect the amount of atelectasis.