Author’s response to reviews

Title: A Phase II Clinical Trial to assess the safety of Clonidine in Acute Organophosphate Poisoning

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Author’s response to reviews: see over
Editors Comments:

The paper still suffers from statistical overkill and sometimes what I view as misguided analysis. For example, the first sentence in the data analysis section says that the analysis was performed on all randomized patients "based upon intention to treat". I think what the authors mean is that everyone randomized was in the analysis; however, the analysis broke the randomization because all placebo patients were put into one group even though randomization was by dose cohort. The relevance here is that as Table 1 and the text point out, the distribution of pesticide use differed by dose cohort. A rigorous analysis would reflect that process of randomization. I am not arguing for this analysis, but if there is going to be formal analysis, then it should reflect the actual randomization.

-We agree that what we meant by “intention to treat” was that all post randomisation outcomes were in the analysis whether or not the assigned treatment was given per protocol. We think this is the conventional and correct meaning of the phrase. No change seems required to the wording if that is the case.

We have as you note already acknowledged several times the deficiencies in the staged randomization in terms of balancing baseline variables between groups. Is the request to simply remove all statistical analysis of outcomes?? We are willing to oblige if you insist but our analysis is very conservative in the sense no remarkable conclusions are being drawn and the statistics are largely highlighting deficiencies in the randomisation (such as the baseline imbalance) and the power (such that most clinical outcomes are not significantly different).

If not please advise further what you are actually requesting us to do.

Some specific comments:

Page 7 says, "It was deliberately underpowered...". I would not write the sentence like this. The first sentence in the paragraph describes the purpose of the study. This next sentence should say something like, "Therefore, it had low power to detect..." But then, why was the pre specified primary outcome "ventilation or death"? My interpretation of this trial is that its purpose was to look at safety of clonidine.

Good advice in terms of the wording and we have corrected as advised. The pre-specified primary outcome was largely chosen with respect to safety – ventilation would be the most important adverse clinical outcome from the sedating effect of clonidine. It is also quite likely to be a primary outcome in subsequent efficacy trials.

Page 8, last sentence. I would say, "therefore, the trial was stopped before proceeding to the cohort at the highest planned dose (0.6mg bolus)."

-Corrected as advised

Page 12, the paragraph on limitations. Why is the small size a limitation?
The purpose was to guide choice of dose - the size was adequate for that choice.

There was no formal sample size done in this study. Phase II trials are designed such that they are underpowered to detect any difference in outcomes. Our well-founded belief is that most of the people treating poisonings might not be aware of this (while in contrast being very aware of the magnitude of the problem). Many studies as small or smaller than this have been put forward as providing sufficient evidence to change management (e.g. Lin JL, et al Crit Care Med. 2006 Feb;34(2):368-73 – n=23).

We think it is worth emphasising that this study provides information about tolerable doses of clonidine but was too small to examine realistic changes in clinical outcomes related to possible efficacy of clonidine.

Table 1 - Given the seasonal change in use of pesticide, I would like to see the distribution of pesticide use in the 4 placebo patients randomized at Level 3.
- The flow chart has been modified to indicate the types of pesticides at each dose level. Two versions are provided – one provides all the details - the second simpler one simply highlights the big shift from chlorpyrifos to dimethoate in the third cohort. We would be happy with either version.

Table 3 - These should be n’s along with the %’s and CI - that will remind the reader than many of these numbers that look big represent only 1 or 2 patients. In particular, the line for death is scary until you realize that it represents 1 and 3 deaths. And the paper doesn’t give insight into whether the higher deaths in Level 3 were due to the dimethoate or to the high dose of clonidine.

- We have changed table 3 to include N.

The high death rates in level 3 and its relationship to dimethoate was already covered in the 2nd paragraph of the discussion on level 3 which talks of the high mortality and rate of dimethoate ingestions, higher incidence of hypotension and lower use of pralidoxime. We have made this potential explanation more explicit by adding a further phrase in this paragraph. (This is obviously not a large enough study to look at sub-groups such as dimethoate ingestions.)

Table 2 - if hypotension is a known effect of clonidine, why bother with statistical testing?

In the setting of excessive acetylcholine, atropine and pralidoxime (all of which have significant effects on vascular function and therefore blood pressure regulation) we really were not sure whether clonidine would have a significant hypotensive effect and at what doses. Further in some circumstances you can get an initial pressor (hypertensive) effect with clonidine.

Graphs - I have no idea what the p-values mean here - how many degrees of freedom? what are they testing?"
P values, df, are now explained in a footnote.