Reviewer's report

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

Version: 3 Date: 26 February 2009

Reviewer: Allan Donner

Reviewer's report:

In this exploratory dose-finding Phase II study four patients were randomized to placebo (glucose) and 12 patients to each of four increasing dose levels of clonodine in multi-stage fashion. The main purpose of the study was to determine the safety of this product when given as an antidote in adult patients presenting with signs or symptoms of acute organophosphate ingestion.

A principal conclusion as stated by the authors is that “our findings suggest that clonidine is well tolerated at the two lowest dosing levels administered”. However this statement appears too strong since it is unclear whether the trial is sufficiently powered to support it (even as a “suggestion”). That is, “absence of evidence” does not imply “evidence of absence”. As the authors acknowledge, this particularly applies to the primary outcome measure, defined as the proportion of patients in each group who either ventilated or died. (It is well-known that the statistical power for comparing binary outcomes is generally much less than that for comparing continuous outcomes). The presentation of confidence limits about the major endpoints would have made this point clearer.

In general, it is not surprising that there was no statistical difference in the primary outcomes based on intent-to-treat. Consequently a more accurate summary statement for the paper would be that the present study “presents no evidence against the conclusion that clonidine is not well tolerated at the two lowest dosing levels administered”, i.e. that the results are largely inconclusive. Similarly it is unsurprising that baseline comparisons shown in Table 1 are all non-significant.

Given the exploratory nature of the trial and the acknowledge by the authors that is underpowered, the proposed statistical analyses, involving nonparametric tests (adding further to the problem of low power), repeated measures ANOVA and Bonferroni post-hoc corrections, seems to be “overkill”.

I certainly agree with the authors that “further studies must be done to characterize ‘the efficacy profile of this product.” However from a statistical perspective I am also not convinced that questions regarding the safety profile of clonidine have been adequately addressed by this small unblinded trial.

Other comments:

1. I believe “Dunn’s test” should read “Dunnett’s test”
2. The use of multiple significance tests computed at many different time points in each of the three graphs comprising Figure 1 is wrought with problems of multiplicity and not good statistical practice. Performing fewer significance tests that focus on summary measures calculated for each patient would be much more informative.