Reviewer’s report

Title: A review of the experimental evidence on the toxicokinetics of carbon monoxide: The potential role of pathophysiology among susceptible groups

Version: 0 Date: 14 Nov 2017

Reviewer: Simon Clarke

Reviewer's report:

Thank you for asking me to review this interesting and well-written paper. I have a number of questions and comments for the authors to consider:

Background

1. I would suggest that the case history is superfluous - it raised the clinical question that motivated the authors to review the literature but the details of case series do not add to the paper. It might be useful as a separate paper to highlight the limitations of COHb as a biomarker.

2. Page 7: the authors report that people with COPD have reduced elimination of CO. They also have increased endogenous CO production due to secondary polycythaemia and increased exposure from smoking.

Methods

3. Page 8: why did the authors not search Embase? It is supposed to include more toxicology and non-American articles than Medline. Also why did they not include Cochrane in their search strategy?

Results

4. Page 9: the authors state that they did not identify articles published after 2008 yet they include studies published after that date in the discussion (references 73-78)

5. Page 10 is largely devoted to a description of the limitations of the Coburn-Forster-Kane equation as a model of CO uptake. Although interesting this does not directly answer the study aims (the evidence for the effect of the specified co-morbidities on CO uptake, distribution and elimination and clinical outcome.
6. Page 12 (1st paragraph): although it is interesting to compare the changes in baseline COHb between the different groups, the small numbers and the inability to take into account the potential for smoking to act as a confounder means that the authors should not make any conclusion about whether there is a genuine difference between the groups.

7. Page 12 (last 3 lines): the authors state that the relationship between higher COHb levels and outcomes were investigated but only quote levels not any outcomes.

Discussion

8. Page 14 (1st 2 lines): I do not think that the authors can justify their assertion that higher levels may be expected in some groups; as stated in comment 6 above, the evidence is not robust enough. However I do agree with their statement in the last line of that paragraph that more evidence is needed.

Overall this is a well conducted and written study; it is important clinical question for which there is insufficient evidence to draw any conclusions. The authors highlight the need for further research and discuss the logistical and ethical difficulties in undertaking clinical research in this subject so they look at alternative strategies such as modeling and epidemiological work.

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