Author’s response to reviews

Title: Sex steroids do not affect shigatoxin cytotoxicity on human renal tubular or glomerular cells

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Dear Editor

Please find enclosed the revised manuscript entitled "Sex steroids do not affect shigatoxin cytotoxicity on human renal tubular or glomerular cells" by Hughes et al (MS# 6888744672290368). The following revisions have been made in response to the reviewers' comments. We hope that these changes have now made the manuscript acceptable for publication.

Response to Dr. Obrig's review:

Compulsory revisions:
1. The data have now all been changed in the tables to show percent survival rather than a percentage of a percentage. In addition, the baseline survival with Stx-1 alone is also shown in the tables to facilitate comparison with the effects of sex steroids.
2. The time of exposure to Stx-1 is now stated in the legend to Figure 1.
3. The results of 1 and 7 days of exposure to sex steroids are now included in the legend to Figure 2.
4. The results have a paragraph devoted to the Gb3 data

Discretionary revisions
1. We have determined that the sex steroids are biologically active. This was done using assays available in the Division of Endocrinology at the University of Utah and are described at the end of the Results section.
2. We have included two references (at the end of the Discussion section) indicating the known effects of sex steroids on the cell types employed.

Response to Prof. Mathieson's review:

Compulsory revisions:
1. The errors in the text of Tables 1 and 2 where the abbreviations for endothelial and epithelial cells had been transposed have now been corrected.

Discretionary revisions:
1. The statement was made that the peak incidence of HUS is in very young children hence sex steroids cannot explain this phenomenon. We agree that sex steroids do not explain the peak incidence of HUS in children 1-2 years of age, however we have cited literature indicating that HUS does occur significantly until about age 11. This leads us to believe that several factors are involved in HUS
occurrence and that sex steroids might have been involved in the later decline in HUS incidence that occurs in adolescents and adults. This is discussed in the beginning to the Discussion and Background sections. We also discuss alternative explanations for the age-related incidence of HUS in the Discussion section.

2. The choice of physiologic concentrations of sex steroids is now justified by referring to reference values in humans from a respected clinical laboratory reference.

3. The reviewer requested that we change the tables to figures or to text. We believe this is not best. We would need at least 6 figures to show the data and even then the data looks very crowded on the figures. Text would have to be quite extensive to cover all the data unless we simply state that sex steroids had no effect - this does not do the data justice, in our opinion. Rather, by now showing the basal effect of Stx-1 on cell survival and changing the data to show cell survival, we feel the data are now displayed in the best possible format.

Thank you for consideration of this revision. We appreciate the reviewers' and editor's suggestions.

Sincerely,

Donald E. Kohan