Reviewer's report

Title: Stampidine Prevents Mortality In An Experimental Mouse Model Of Viral Hemorrhagic Fever Caused By Lassa Virus

Version: 2 Date: 25 September 2003

Reviewer: Daniel Bausch

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General: Although the research has scientific merit, there are significant problems in the presentation of the methods and results as well as in the writing of the manuscript which need to be addressed before this manuscript should be published.

Discretionary Revisions (which the author can choose to ignore):

1) Various sections of the Background and Discussion contain rather long descriptions of extraneous data, usually referencing the authors' previous research on stampidine and other viruses. In most cases, a much more brief mention and simple citation would suffice.

Minor Compulsory Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

1) There are significant factual/grammatical/spelling errors or omissions in the background and discussion sections regarding Lassa and the arenaviruses:

Page 3:
- The term “Argentine” hemorrhagic fever is preferred over “Argentinian.”
- The "Josiah" strain of Lassa virus is repeatedly misspelled as "Josiach"
- There are quite a few spelling mistakes in the References section.
- There are not presently sound data to support the assertion that Lassa fever is “found in every country of West Africa from Nigeria to Senegal.”
- In discussing countries outside of Africa where cases of LF have been exported, the authors fail to mention the United States, a significant omission given the likely readership (Holmes et al., Lassa fever in the United States. Investigation of a case and new guidelines for management. NEJM 1990 Oct 18;323(16):1139-41).

Page 4:
- The authors’ state that Lassa fever “shows evidence of persistent infection, is tremendously contagious, and has a high mortality rate” and that it is “transmitted by the respiratory route.” Although many of the terms used are relative, there is debate in the literature, and in some cases published data, to bring many of these statements into question. The authors should make their points more clearly and give specific references to support them.
- The authors write repeatedly of the “unique ability of Lassa virus to spread from person to person.” A great number of viruses show person-to-person spread. These statements should be omitted.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached):

1) There are many unclear aspects regarding the Methods and Results which unfortunately render the data virtually uninterpretable:
-It is unclear what the challenge dose of Lassa virus was. It is first stated on page 6 under “Animal infection” that “1*LD50, 10*LD50 and 100*LD50 doses were used for inoculation.” Immediately below, however, under “Lassa virus model,” it states that mice were infected with “10-100 LD50.” Finally, on page 5 under “Results” it is stated that mice were inoculated with “1000 PFU dose level,” which appears to indicate that all mice were given the same dose. Based on previous literature, 1000 PFU would probably correspond to an LD100.

-What was the delivery schedule of the drug or vehicle and corresponding results? Although it is stated repetitively that the mice were treated “24 hours prior to, 1 hour prior to, and 24 hours, 48 hours, 72 hours, and 96 hours after virus inoculation,” the results make no mention of outcomes based on treatment timing. Was the stated schedule followed? If so, how many animals were in each treatment group, considering that there were only 10 total animals to be divided between six different schedules? Does the statement in the Discussion section on page 8 that stampidine exhibits “a potent prophylactic effect” imply that only the pre-challenge administration of drug was carried out or successful?

-There are many discrepancies between data as presented in the “Results” section and the Table. In the results it states that the 18-vehicle-treated mice developed decreased mobility and scruffy fur between days 6-9. The table shows the scruffy fur to be between days 6-10, however. The results state 16 of 18 control mice to develop seizures but the table shows only 14. The results state 13 mice to have developed 5-10% weight loss, but the table again shows only 4 mice with this degree of weight loss. The results state that all 9 of the remaining mice which received the 50 mg/Kg dose remained healthy, but the table shows a few of them to have had decreased mobility and scruffy fur. The median survival for the control mice is stated to be 9 days, but the it appears from the table to, in fact, be 10. While these discrepancies would probably not amount ultimately to drastically different conclusions, they do bring into question the validity of the experimentation and results.

-The authors make no mention as to whether some of the subjected measurements, such as decreased mobility and scruffy fur, were made in a blinded fashion.

2) Lastly, although the laboratory work was done in Belarus under Biosafety Level 3 conditions, it should perhaps be noted that Lassa virus in the United States is considered a Biosafety Level 4 pathogen for the benefit of American readers who might be interested in repeating such experiments.

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: A paper whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Declaration of competing interests: None