Reviewer's report

Title: Efficacy of N,N'bis-(2-mercaptoethyl)isophthalamide on mercury intoxication: A randomized controlled trial

Version: 1 Date: 03 Dec 2017

Reviewer: Erik Jørs

Reviewer's report:

Dear Authors!

I have read your article with your corrections and find it much more suitable for publication after the corrections made. However I still have some suggestions for improvement, and a major revision needed before I can recommend the article to be published.

The article is part of a validation of a new drug called NBMI (N,N'bis-(2-mercaptoethyl)isophthalamide thought to be able to lower the amount of mercury in the human body. The study was financed by the medical company EmeraMed Ltd. who is producing this new drug.

The study involves 36 miners from Ecuador with urine values of mercury >15mygram/L urine, and fullfilling other selection criterias. The miners were randomly divided into three groups and treated with a daily dosis of NBMI or placebo - one group got 300 mg NBMI/day, another 100 mg/day and a third group got placebo. The treatment took place during 14 days. Serum and urine levels of mercury were evaluated at day 0, day 15 and day 45. Moreover symptoms of intoxication were evaluated in 1. an aggregated in a medical intoxication score, 2. a physical fatigue score, 3. a mental fatigue score, 4. a neuromotoric test battery (CATSYS tests) and 5. finger to nose test.

Minor revision: on page 10 line 200-201 and line 210-212 you are repeating the same information.

Results were compared using non-parametric statistics and ANCOVA.

The trial showed a significant lower amount of mercury in urine (μg/L) after treatment in the group given 300 mg NBMI for 14 days compared to the placebo group. But this significance was not seen when comparing mercury in urine after adjusting for creatinine (μg/g creatinine).
Of the other tests relying on symptoms and motoric performance only the physical fatigue score showed a significant drop in fatigue score but in all three groups although most pronounced in the group treated with 300 mg NBMI. No adverse effects of the treatment were seen.

The authors conclude that "NBMI was successfully tested for therapeutic effects in the treatment for mercury intoxication. But further studies are needed with greater sample size, longer follow up, higher NBMI doses and repetitive treatment periods.

Major revision:

The conclusion of a succesfull test is not correct in my opinion, if you wanted to look at the ability of NBMI to lower the body burden of mercury. If you only look at the feasability of the study and unwanted side effects of the study then you might say that the test was successfull. Please revise this conclusion that seems still to be too optimistic regarding the ability of NBMI to lower the body burden of mercury.

The ability to mobilize mercury in the body and lower the body burden by an accelerated excretion of mercury was in my opinion not really evaluated or shown by this study. No lowering of mercury in plasma was seen, no higher excretion of mercury through urine or faeces was shown and the lowering of symptoms of intoxication was only shown in one of the tests, were all three groups including the placebo group had fewer symptoms at follow up, although it was most pronounced in the most intensive threated group.

As you the authors correctly discusses much can be improved in a future study including 1. a bigger sample size to improve the statistical analysis with relevant control for confounders, 2. a better control with eventual mercury exposure during the trial as it seems that some of the miners could have been affected by on going use of mercury in mining, 3. a closer/maybe daily measurement of mercury in urine (µg/g creatinine) or mercury in 24 hours urine sampling, 4. a continous measurement of mercury excretion in faeces as this according to the authors are the most common route of mercury excretion when using NBMI, and 5. measuremnt of mercury on whole blood among others.

I hope you will be able to go on with a more comprehensive study as better drugs and access to drugs de-toxification of mercury in mining areas in developing countries are needed.

Best regards
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