Reviewer's report

Title: Pharmacokinetics of quinacrine in the treatment of prion disease

Version: 1 Date: 14 October 2004

Reviewer: Mario Salmona

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Following the epidemic of bovine spongiform encephalopathy and the appearance of a new variant of Creutzfeldt-Jakob disease, apparently causally linked, it has become increasingly urgent to develop drugs to treat the condition. In the last ten years many research groups have concentrated on identifying substances that could be therapeutic for neurodegenerative disorders associated with protein misfolding. Particular attention has been paid to compounds that cross the blood-brain barrier and are already used in humans since they may be immediate candidates for the treatment of prion-related encephalopathies.

Quinacrine is an old anti-parasitic drug that was withdrawn from the market because of toxicity. Its kinetics have been extensively studied and its main kinetic parameters are known. Based on in vitro data several US and UK groups have recently proposed to test quinacrine in patients suffering from prion diseases and a formal clinical trial in CJD patients is now ongoing. Although the outcome of the first studies in man is equivocal this reviewer feels more information is still needed on the kinetics of this drug in the brain.

The paper by Yung et al. reports new data on the blood-brain barrier passage and brain accumulation of quinacrine in mice and unveils a still not totally clarified feature of this drug. Therefore the paper is worth publishing since it gives fresh information that may help improve the treatment schedule of quinacrine in prion diseases.

Specific comments are:
1. The text could be more concise and focus only on the brain kinetics of quinacrine. Its accumulation in liver and spleen is already known;
2. Animal models. Page 6. The authors state that two strains of mice were used, but only report the data on FBV strain (See also Figures 4-6). This point should be clarified.
3. Analysis of quinacrine. The authors should explain why, at variance with liver samples, brain and spleen samples were “soaked” in methanol at 4°C for two weeks. Does this mean that the drug is tightly bound to proteins in brain and spleen, ruling out (or minimizing) its ability to interfere with the conversion? A comment on this point should be added. A quantitative evaluation of the stability of quinacrine in brain and spleen after the long extraction procedure should also be given.
4. Methods. It is not clear how any animals were used in each experiment.
5. Results. The levels of quinacrine rose almost linearly with the dose in plasma and brain, but not liver and spleen. A comment on this point should be added also considering previous (very old) studies.
6. Figures. The captions are missing.
7. Metabolism data. Although the study of metabolites was beyond the scope of this paper, since the authors determined their presence they should comment the importance of this finding. The metabolism of quinacrine is well known and the structure of its main metabolites has been clarified as well. Do the authors have any information to establish whether the biotransformation of quinacrine influences its anti-prion activity. This is important since in vitro tests quinacrine is poorly metabolized, if at all.

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What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

NONE