Reviewer’s report

Title: Systematic review and stratified meta-analysis of the efficacy of RhoA and Rho kinase inhibitors in animal models of ischaemic stroke.

Version: 2 Date: 14 February 2013

Reviewer: David Howells

Reviewer’s report:

This is an interesting study of the data supporting targeting the Rho system far ischemic stroke. However there are some problems particularly with the discussion which need to be addressed.

Major Compulsory Revisions:

The discussion suggests that Rho GTPase Kinase is a potential target for treatment of stroke. However no attempt is made to rank this against other candidate approaches. Is there any reason to think the data is stronger for example than that for NXY-059 which failed in clinical trial?

A clinical trial of fasudil is alluded to but requires detailed discussion of its outcome in relation to the data presented here. Why was fasudil singled out for more detailed study wouldn't ibuprofen make more sense as it is probably used coincidentally by many patients when they have their stroke, is there data on this? If so it should be discussed.

The study finds greater effect in models were reperfusion is possible but does not discuss this in any detail. Surely this is a critical point if the mechanism of action is vasodilation of collaterals?

The authors must define what they mean by anesthetic agents with intrinsic neuroprotection and discuss why such properties might confound interpretation of the data presented.

The authors make much of the apparent publication bias but need to discuss whether the data sets are large enough to support this interpretation.

Minor Essential Revisions:

The authors state that the behavioural data has essentially no heterogeneity. This needs to be discussed. For example, is it because the same outcome is measured in all studies, or is the behavioural data all from one group?

In describing the timing of intervention, medians don't seem to be very useful here. The proportion initiated at the most common times might be better?

What is meant by nested and pre-nested?

Figure 1 needs to have the stages of analysis clearly aligned with the flow chart.
elements.
In Figure 4, lumping of times between 120 and 2880 minutes post stroke is unhelpful and requires some subdivision.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have published with the senior authors of this manuscript