Reviewers report

Title: Characterization of Hypersensitivity Reactions Reported among Andrographis paniculata Users in Thailand Using Health Product Vigilance Center (HPVC) Database

Version: 4  Date: 11 June 2014

Reviewer: Matthew Bambling

Reviewers report:

Minor Essential Revisions

Page 1: results summary section is a little unclear. The authors state that only 106 case reports contained andrographis herbal product as suspected drug and reported at least one hypersensitivity reaction. The authors then go on to talk about a variety of hypersensitivity reactions greater than one. Need to clarify meaning here it looks contradictory at first reading.

Page 4: I am not sure I would call this a descriptive study, it may be more accurately described as a retrospective database study. The term retrospective is introduced in a later paragraph and should be adopted for the sake of accuracy and consistency.

Page 4:

Part of paragraph provided below, does not fit the Methods-data source heading and would be better placed in the preceding background information as it provides the context...... the text not include below is fine for the first part of the methods-data section

Intensive monitoring programmes were undertaken to promote the reporting of adverse events associated with herbal product use. After a total of five single herbal products were included in the Thai NLEM in 1999, a 2-year intensive monitoring programme of these products was launched in the year 2000. In addition, an intensive monitoring programme was initiated by the Department for Development of Thai Traditional and Alternative Medicine (which is responsible for promoting the use of herbal products in Thailand). This programme focused on four single herbal products (Cissus quadrangularis [Veld grape], Centella asiatica [Pennywort], Derris scandens [Jewel vine], Momordica charantia [Bitter melon]) that were under consideration for inclusion in the NLEM. Data collected under this programme will be crucial information used for considering whether these products are to be listed in NLEM. Since this is an aggregate analysis of spontaneous reports of adverse events submitted to HPVC, there is minimal risk of patient confidentiality breaching. As we did not obtain the consent, we present specific cases with only general demographic characteristics to ensure patient identity anonymous.

Page 5: Criteria for the selection of cases-Reports with andrographis being the only suspected cause were selected. Well worth including that only andrographis
only product cases where chosen as this is a good control.

Discretionary Revisions for clarity of content and structure of paper

The inclusion criteria should give some attention to usage of product, i.e. no restriction on length of time using the product and dosage was applied to cases. Adverse reports indicated reactions ranging from single doses to XXXX time of use.

Page 6: again I am not clear about the at least one hypersensitive report, when there are clearly more than one discussed in the data.

Page 7: first paragraph Discussion section. The authors contradict themselves by saying that they have established a link and then say they haven't made a direct causal link, which I agree with.

Bottom of page 7: while I agree that the findings are unlikely to be spurious, I am not sure that one can conclude the andrographis was the cause in all cases. In this type of report databases there may well be false positives, in that patients may have been taking other products or medications in addition to andrographis and not necessarily nominated to the person making the report. I suspect this is nearly impossible to control for in the data and it may be more reasonable to conclude that andrographis was associated with hypersensitive reactions and was the likely cause for the majority of cases.

Page 8: the authors state that andrographis containing product was the single agent. If by this they mean they only included case reports where andrographis only products were used, this is an important control and needs to be mentioned in the study design section as it adds strength to their findings.

Middle page 8: The issue of this unexpected serious adverse event associated with andrographis has been brought up during Signal Detection and Assessment Working Group and Drug Safety (pharmacovigilance) subcommittee under Thai FDA. What are the authors referring to here, it is not clear regarding what or why this is being mentioned?

Once again any proposed pharmacoepidemiology study to examine the association between hypersensitivity reactions and andrographis containing products can be complex as other ingredient in formulas my complicate findings. This should be mentioned and the authors approach seems a better way forward here.

I think the authors can conclude that retrospective studies are not designed to identify evidence of direct causation or mechanism of hypersensitivity, however, the data supports an association between andrographis and risk of hypersensitivity for modest number of individuals.

**Level of interest:** An article of importance 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 declare that I have no competing interests'