Reviewer's report

Title: Optimising plasma levels of clozapine during metabolic interactions: a review and case report with adjunct rifampicin treatment.

Version: 1  Date: 2 June 2014

Reviewer: Manoranjenni Chetty

Reviewer's report:

Major Compulsory Revisions

This paper presents a case study to describe the potential interaction between clozapine and rifampicin. Such case studies could be very useful to clinicians if the supporting evidence is compelling. However, in this case study the large number of variables raise questions about whether the change in clozapine concentrations can be attributed to rifampicin alone.

The paper is described as a review and a case study but what is described as a review is a very brief overview that contains some information that is both incorrect and contradictory, as explained below. In addition, recommendations have been made for clinicians but these require to be supported by scientific evidence.

1. Background

This section requires to be revised after a review of the extensive literature available in this general area. Aspects that require special attention due to inaccuracies are:

Line 118 – cigarette smoke is a known inducer of CYP1A2 (not an inhibitor as stated here – extensive evidence exists in the literature)
Line 120 – caffeine is an inhibitor of CYP1A2
Line 121 – rifampicin is NOT a POTENT inducer of CYP1A2 (in fact the reference listed by the authors state that it is a weak inducer)
Line 134 – There are many more reports of interactions between rifampicin and psychotropic medication
Line 151 – It is stated that 'changes in the bioavailability of clozapine' will be described. However, the paper does not describe changes in bioavailability – if the term is being used generically, it is unacceptable for a paper that is describing a pharmacokinetic interaction.

2. Case Study

Figure 1 contradicts the statements in lines 118 and 120

From the facts presented in this case, there is inadequate and inconclusive evidence to support the suggestion that ‘rifampicin reduced clozapine concentrations and increased concentrations were observed on stopping
Some of the factors for consideration are the following:

- The major observation for consideration is the consistently erratic plasma concentrations (Figure 2) which cannot be explained by the medication changes alone eg the very high clozapine concentration observed on stopping fluoxetine. Several questions can be raised in relation to the unpredictable and erratic concentrations of clozapine:

  - Both the drugs and the dosages were frequently changed throughout the period making it difficult to explain the change in plasma concentration on the basis of a specific drug
  - Were the timings of the plasma concentration measurements consistent eg all trough measurements?
  - Could the variability in the plasma concentrations reflect problems with absorption of the drugs due to the bowel disease?
  - Was the method of verifying compliance reliable – although nursing staff may administer the medication, mentally ill patients are known to skilfully avoid swallowing the medication
  - Some of the other medications are known to affect enzymes involved in clozapine metabolism eg isoniazid inhibits CYP2C19 and CYP3A4 and perhaps CYP1A2 – how does this contribute to the changes in clozapine concentrations?

Minor Essential Revisions

Case Study
Line 167 – ‘t’ diagnosis?
Line 196 – was this 500mg/day …… similarly in many other parts of the case presentation it is not stated whether the doses refer to daily doses
Figures require captions

**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