Author’s response to reviews

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

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Version: 6
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Title: Optimising plasma levels of clozapine during metabolic interactions: a review and case report with adjunct rifampicin treatment.

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Dear Editors,

We are very grateful to Drs. Pai, Chetty, Gramaglia and Salvi for their time in reviewing our manuscript. We have responded to their helpful comments in the following manner. We have highlighted additional amendments in response to most recent comments in **bold**.

Response to Dr. Pai:

1. (Fig 2) Abstract conclusion -‘guidance to clinicians in managing metabolic interactions between clozapine and rifampicin' could have been read as drug interactions

Lines 62 and 63 now state ‘This case report provides guidance to clinicians in managing drug interactions between clozapine and rifampicin to enable safe and effective treatment.’

2. Typological error-reference 4 (325)-It should be read as patients

This has been corrected (line 364)

3. Discretionary Revisions- Under principles be used to ensure effective and safe treatment of a psychotic illness with Clozapine when co-administering a course of TB therapy- "It may be necessary to exceed the licensed maximum dose of clozapine to attain a therapeutic plasma level." Rationale for such guideline would beneficial.

Line 320-321 have been expanded to state ‘It may be necessary to exceed the licensed maximum dose of clozapine to attain a therapeutic plasma level and practically overcome enzyme induction’

Response to Dr. Chetty:

1. Line 118 – cigarette smoke is a known inducer of CYP1A2 (not an inhibitor as stated here – extensive evidence exists in the literature)

This has been corrected to state: ‘Conversely, CYP1A2 isoforms may be induced by some antibiotics (erythyromycin) and cigarette smoke (through the effect of aromatic hydrocarbons), which will decrease clozapine plasma concentrations’, line 115-7

2. Line 120 – caffeine is an inhibitor of CYP1A2

This has been corrected to state: CYP1A2 isoforms are inhibited by some antidepressants (including fluoxetine and fluvoxamine) and caffeine, resulting in increased clozapine plasma concentrations’, line 113-4

3. 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)

This has been corrected to state: The antimycobacterial agent rifampicin is an inducer of CYP1A2 and CYP3A4’, line 117-8

4. Line 134 – There are many more reports of interactions between rifampicin and psychototropic
Three paragraphs have been added to reflect this: lines 145 -173

5. 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.

This has been altered to state: Here we discuss the changes in the plasma concentration of clozapine using an illustrative case of a patient stabilised on clozapine who commenced a course of TB treatment which included rifampicin.’, lines 178 - 181

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 rifampicin’.

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.

We have expanded on the limitations of interpretation of the plasma concentration data. Line 263 – 265 have been added to reflect this.

• Were the timings of the plasma concentration measurements consistent eg all trough measurements?

Line 246-7 now states ‘. All clozapine plasma level measurements were taken at consistent times (trough levels).’

• Could the variability in the plasma concentrations reflect problems with absorption of the drugs due to the bowel disease?

Lines 246 – 250 have been added to discuss this aspect.

• 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.

Lines 241 – 3 have been added: ‘Although confirmed compliance with medication is often difficult to assess in patients with psychosis, there were no concerns about compliance with medication at this time.’

• 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?
An extra paragraph has been added to discuss this, lines 253 - 265

Minor Essential Revisions
Case Study Line 167 – ‘t’ diagnosis? This has been corrected
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
All doses have now been stated as mg/day, see lines 217 - 233

Figures require captions
We apologise that the figures have no captions – as they are JPEG images we cannot add these, but they should be:
• Figure 1. Clozapine metabolic pathway
• Figure 2. Temporal relationship between clozapine plasma concentration, dose, and concurrent medication

Second response to Dr Chetty from comments 30th January 2015

Discretionary Revisions

• Line 328 ‘moderately rapidly’ has been rephrased to relatively rapidly.

Response to Dr. Gramaglia:

1. You may consider shortening the introduction.

Regrettably we feel unable to shorten the introduction further as requested by Dr. Gramaglia due to the requests for additional material made by other reviewers

2. Abstract: avoid saying "this case is the first to provide", since you mention also other, previously published ones.

This has been altered to state: This case report provides guidance to clinicians in managing drug interactions between clozapine and rifampicin to enable safe and effective treatment., lines 62-3

3) please check the manuscript for some typing mistakes (e.g. spaces, carribeaninstead of carribean, etc)

These have been corrected (line 193)

Response to Dr. Salvi:

Major compulsory revisions
1. The authors do not really explain what is the course of psychotic symptoms during rifampicin treatment. Being the patient that severe, it is of outmost relevance to report, with the help of rating scales, the course of psychotic symptoms with regard to suboptimal clozapine levels.

We agree with Dr. Salvi that information about the clinical presentation of the patient during the fluctuations in clozapine plasma level is essential. We also agree that this is best presented by use of
recognised rating scales. Unfortunately these were not completed at the time and so this is not possible. This is also the case for rating scales related to mood disorders. We have instead added descriptive narrative to the report regarding clinical presentation (lines 241, 227, 228).

2. The authors state that the patient was taking lamotrigine “as both a mood stabiliser and for seizure prophylaxis.” It should be noted that rifampicin alters lamotrigine pharmacokinetics by induction of the hepatic enzymes responsible for glucuronidation, leading to increased clearance and reduced half-life (Ebert et al., 2000): thus, a possible diminished efficacy of lamotrigine should be taken into account, and should be reported. Furthermore, being the patient diagnosed with schizoaffective disorder, it would be interesting to check whether there have been fluctuations in mood due to a lesser mood-stabilizing efficacy. Again, a mood disorder rating scale (such as, for instance, CGI-BP) should have been administered.

We note Dr. Salvi’s point that rifampicin may also have reduced plasma levels of lamotrigine, possibly also causing a worsening in mental state. The patient was being prescribed a slow increasing titration of lamotrigine during the time course of the rifampicin treatment. Plasma levels correspondingly increased over time. We apologise that this wasn’t made clear in the original report and have now clarified this in the discussion, and noted the interaction in the introduction (lines 167 – 173; 280 – 284).

Second Response to Dr Salvi 6th February 2015

Major Compulsory Revisions

1. I pointed out that the authors did not really explain what the course of psychotic symptoms was during rifampicin treatment. Having ascertained the interaction between clozapine and rifampicin, it would have been of outmost relevance to report more precisely, with the help of rating scales, to what extent the course of psychotic symptoms was altered by the reduction clozapine levels. The authors only stated that: “...this period coincided with Mr. X being very unwell with increased levels of psychotic symptoms” and “...the level remained sub-therapeutic and this was reflected in the clinical presentation of the patient.” The authors reported that rating scales have not been employed, making it impossible to ascertain the clinical relevance of the reduction in clozapine levels.

We have added descriptive narrative to the report regarding clinical presentation (227-236) and noted the limitations of absence of formal outcome measures in the discussion.

Minor essential revisions

In the background section (page 2, line 13) it is said that “fluoxetine and fluxoxamine, and smoking cigarettes, through the effect of aromatic hydrocarbons, is recognised to inhibit CYP1A2 or the other relative isoforms, while treatment with antibiotics such as erythromycin, and intake of caffeine induces CYP1A2 SSRIs and tobacco smoke inhibit CYP1A2, while some antibiotics and caffeine induce it.” The sentence is wrong: some SSRIs, caffeine, and some antibiotics inhibit the cytochrome, while smoking induces it. Please correct.

This has been corrected to state: ‘Clozapine undergoes complex hepatic metabolism involving multiple cytochrome P450 (CYP) isoforms, the enzyme variants that catalyse biotransformation reactions (figure 1). It is primarily metabolised by the CYP1A2 isoform, but CYP3A4 and to a lesser extent CYP2C9, CYP2C19 and CYP2D6 are also involved [15]. Consequently, clozapine is involved in significant pharmacokinetic interactions when co-administered with other drugs. CYP1A2 isoforms are inhibited by...
some antidepressants (including fluoxetine and fluvoxamine) and caffeine, resulting in increased clozapine plasma concentrations [16]. Conversely, CYP1A2 isoforms may be induced by some antibiotics (erythromycin) and cigarette smoke (through the effect of aromatic hydrocarbons), which will decrease clozapine plasma concentrations [17, 18]. The antimycobacterial agent rifampicin is an inducer of CYP1A2 and CYP3A4 [15,19]; adjunct treatment with rifampicin would be expected to decrease serum concentrations of clozapine. The consistency of CYP-mediated drug interactions with clozapine is not always easy to predict [20]. Lines 108 – 120.

Discretionary revisions

The Authors note that, after moxifloxacin and pyrazinamide were stopped, clozapine plasma levels showed a stable rise for three weeks: they conclude that “the cause for this remains uncertain”. Moxifloxacin, a 4th-generation quinolone antibiotic, is mainly excreted by glucuronide conjugation. As previously said, rifampicin induces this II-phase metabolism pathway, thus decreasing moxifloxacin plasma concentrations, although on the other hand moxifloxacin does not seem to alter rifampicin pharmacokinetics (see Ramachandran et al., 2012). Pyrazinamide also does not seem to alter other drugs pharmacokinetics (see Nishimura et al., 2004). Although it might be true that the extant knowledge on moxifloxacin/pyrazinamide pharmacokinetics does not allow explaining the observed phenomena, Authors might discuss this point more thoroughly.

We have added the follow section : ‘On stopping the pyrazinamide and moxifloxacin component of TB treatment after 2 months there was a 3 week period of raised clozapine levels. This was the only time during the total 6 months of TB treatment that levels were above the sub-therapeutic threshold. There is no literature to suggest that pyrazinamide or moxifloxacin interact with clozapine metabolism so the cause for this remains unclear. Isoniazid is a CYP1A2 inhibitor, and is therefore expected to increase clozapine plasma concentrations [42]. It is likely that this effect was counteracted, at least in part, by rifampicin in our patient. As both drugs were initiated together, it is not possible to elucidate the extent to which isoniazid may have ameliorated the effect of rifampicin on clozapine plasma levels.’ Lines 256 - 265

Yours faithfully,

Siobhan Gee (on behalf of the authors)
Mary Docherty (on behalf of the authors)