

Review Article

Drug interactions affecting clozapine levels

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Abstract

Clozapine is used in combination with psychotropic medication and a wide variety of non-psychotropic medications. This article reviews the literature on clozapine drug interactions and the effect these have on serum level changes in clozapine. A total of 54 articles with a total of 109 individual case reports were obtained by manual and computerised literature search from January 1970 to May 2013. Psychotropic medications most likely to increase clozapine levels include: fluvoxamine, lamotrigine, aripiprazole and the discontinuation of levomepromazine and carbamazepine. Non-psychotropic medications associated with increase in clozapine levels include: erythromycin, ciprofloxacin, omeprazole, cimetidine, OCP containing ethinylestradiol, amiodarone, aluminum hydroxide and isoniazid. Rifampin and St John's wort resulted in low clozapine levels. Smoking cessation also increased clozapine levels. The role of routine clozapine monitoring in clinical practice requires further clarification. In the absence of recommendations for routine clozapine level monitoring, clinical judgment should always be used in addition to diagnostic testing. Clinicians must maintain increased clinical vigilance for adverse side effects when clozapine is combined with other medications.

Keywords

Clozapine; plasma level; interactions

INTRODUCTION

Clozapine is an atypical antipsychotic primarily indicated for the management of treatment resistant schizophrenia and reduction in the risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder (Lehman et al. 2010). However, a subset of patients fail to respond or have only a partial response to clozapine, leading clinicians to search for potential augmentation

strategies to improve outcomes. Psychotropic medications used in combination with clozapine include antidepressants, antipsychotics and mood stabilisers (Calabrese & Gajwani, 2000; Fuchs, 1994; Chan & Sweeting, 2007). Non-psychotropic medications are also added for management of associated medical conditions. Smoking and smoking cessation have also been reported to affect clozapine levels (Sandson et al. 2007).

It is proposed that the therapeutic efficacy of clozapine is mediated through antagonism of the dopamine type 2 (D₂) and serotonin type 2A (5-HT_{2A}) receptors (Lieberman & Safferman, 1992). In addition, clozapine acts as an antagonist

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at alpha-adrenergic, histamine H1 and cholinergic which accounts for its side effects (Lieberman & Safferman, 1992). Studies using PET and a variety of ligands show less than 50% dopamine receptor occupancy at normal therapeutic levels of clozapine (Farde et al. 1992). Positron emission tomography imaging studies found that clozapine, at doses known to be effective in routine clinical settings, showed a D₂ occupancy clearly lower (16%–68%) than that of other atypical antipsychotics (Kapur et al. 1999). The use of this finding in routine clinical practice is not known. Clozapine is 97% bound to plasma proteins and has a mean half-life of about 12 hours (range 6–33 hours). It is metabolised in the liver by CYP1A2 and CYP3A4 to the relatively inactive compounds norclozapine and clozapine-N-oxide (Bertilsson et al. 1994; Brøsen, 1993). There are variety of analytical methods to assay clozapine and its metabolite including high performance liquid chromatography, gas chromatography, gas chromatography/mass spectrometry and radio-immunoassay (Cooper, 1996). Medications interfering with the activity of these cytochrome enzymes results in changes in plasma clozapine levels. The therapeutic drug monitoring (TDM) of clozapine, and of its principal plasma metabolite N-desmethyl clozapine (norclozapine), has been shown to assist management by: identifying or confirming suspected non-adherence; assessing whether clozapine is being used at a therapeutic dose; and minimising the risk of dose-related toxicity (Couchman et al. 2013). Plasma clozapine concentrations in the range of 0.35–0.60 mg l⁻¹ are associated with a good antipsychotic response in many adult patients, although the upper limit remains a subject of debate (Hiemke et al. 2004; Khan & Preskorn 2005; Taylor et al. 2009). The threshold for therapeutic response may be lower once a degree of symptom control has been achieved (Yusufi et al. 2007). Results for both clozapine and norclozapine below the tenth percentile are taken to suggest recent poor adherence, although rapid metabolism (notably in young, male, smokers) cannot always be excluded (Couchman et al. 2013). Norclozapine has a longer plasma half-life than clozapine in patients who have been taking the drug chronically, hence plasma norclozapine shows less day-to-day variation than plasma clozapine

(Couchman et al. 2013). The clozapine:norclozapine ratio has practical significance; for example, a ratio of <0.5 suggests either poor adherence within the last 24 hours or that alterations in dose schedule might be beneficial; and a ratio >3 suggests that either absorption of clozapine from the last dose may not have been completed at the time the sample was obtained, or that clozapine metabolism is saturated either because of the dose prescribed or because of inhibition of clozapine metabolism by a coadministered drug (Yusufi et al. 2007). Besides medications, other demographic variables can also affect clozapine levels including gender, race, age, smoking behaviour and weight. The gender-associated differences can be a function of hormonal balance, body composition, and/or activity of certain enzymes (Rowland & Tozer, 1995). The age-related differences can be a function of drug absorption, distribution, delay in gastric emptying, and/or changes in renal and/or hepatic elimination (Haring et al. 1989). Changes in body water spaces, muscle mass, organ blood flow, and organ function are related to body weight and can effect volume of distribution and clearance (Rowland & Tozer, 1995).

In this paper we will review the case report literature on clozapine drug interactions and the effect of these interactions on serum level changes in clozapine.

METHODS

We reviewed the literature by manual and computerised database search from January 1970 to May 2013 (Medline, Ovid database, PsycARTICLES, PsychINFO and PsychiatryOnline). The following terms were cross-referenced with clozapine in the search: high level, interactions, case report, selective serotonin reuptake inhibitors (SSRI), fluvoxamine, fluoxetine, lamotrigine, valproate, neuroleptic, antipsychotics, antidepressants, proton pump inhibitors (PPIs), antibiotics, infection, smoking and caffeine. The initial process of cross referencing was restricted to antidepressants but cross-referencing of published bibliographies yielded additional reports. Our search was therefore broadened to other classes of psychotropic and non-psychotropic medications, but our

selection was not all inclusive. Individual case reports were reviewed for patient's age, sex, clozapine dose, dose of interacting drug, plasma clozapine level pre and post interaction, and the clinical status post interaction. We narrowed our search to case reports since these papers, unlike other studies, reported clozapine levels both pre and post drug–drug interactions. In vitro studies data, post marketing studies or trial data were not included.

RESULTS

A total of 54 articles with a total of 109 individual case reports were found. The results were further divided based on drug interactions with clozapine levels and associated changes in adverse events or psychopathology. We found 27 reports of drug interactions with clozapine levels >1000 ng ml⁻¹ with adverse events (Table 1), 12 reports with clozapine levels <1000 ng ml⁻¹ with adverse events (Table 2), 14 reports with clozapine levels >1000 ng ml⁻¹ with no adverse events (Hiemke et al. 1994; Jerling et al. 1994; Dequardo & Roberts, 1996; DuMortier et al. 1996; Pinninti & de Leon, 1997; Carrillo et al. 1998; Raaska K 2002; Haack et al. 2003; Sandson et al. 2007; Bugamelli et al. 2007; Sambhi et al. 2007; Stevens et al. 2008) and 13 reports with clozapine levels <1000 ng ml⁻¹ with no adverse events (Raitasuo et al. 1993; Finley & Warner, 1994; Tyson et al. 1995; Nebel et al. 1999; Conca et al. 2000; Frick et al. 2003; Bugamelli et al. 2007; Avari et al. 2011). A total of 41 case reports found no association of drug interactions with changes in clozapine levels (Taylor et al. 1998; Spina et al. 2000; Bergemann et al. 2005; Khan & Preskorn, 2005; Abu-Tair et al. 2006). We also reviewed the changes in norclozapine levels with drug interactions and found 16 studies (Table 3). These results were further compared for norclozapine levels pre and post interactions, and clozapine dose to norclozapine level ratios following drug interactions (Table 3). We present these results by drug class.

Antidepressants

There are 41 reports on interactions of antidepressants with clozapine (Hiemke et al. 1994;

Jerling et al. 1994; Dequardo & Roberts, 1996; DuMortier et al. 1996; Koponen et al. 1996; Armstrong & Stephans, 1997; Chong et al. 1997; Pinninti & de Leon, 1997; Kuo et al. 1998; Taylor et al. 1998; Heeringa et al. 1999; Spina et al. 2000; Khan & Preskorn, 2005; Sandson et al. 2007). Among selective serotonin reuptake inhibitors (SSRIs), fluvoxamine resulted in marked increased in plasma clozapine level (Hiemke et al. 1994; Jerling et al. 1994; Dequardo & Roberts, 1996; DuMortier et al. 1996; Armstrong & Stephans, 1997; Chong et al. 1997; Kuo et al. 1998; Heeringa et al. 1999; Koponen et al. 1996). Clozapine is metabolised by cytochrome P450 3A3/4 and 1A2 (Brøsen, 1993; Bertilsson et al. 1994), and fluvoxamine inhibits both 3A3/4 and 1A2.

There is one case report for fluoxetine (Sandson et al. 2007), where a fivefold rise in clozapine levels was observed. Ferslew et al. (1998) reported a case of fatal drug interaction with fluoxetine resulting in death from pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis and eosinophilia.

Kahn & Preskorn (2005) reported that paroxetine use was associated with marked increase in clozapine levels. Similarly Pinninti & de Leon (1997) found high doses of sertraline (300 mg daily) was associated with marked rise in clozapine levels. Other reports on sertraline (Chong et al. 1997; Spina et al. 2000), paroxetine (Chong et al. 1997) and citalopram (Taylor et al. 1998) found no effect on clozapine levels.

No case reports were found that specifically addressed the interaction of tricyclic antidepressants with changes in plasma clozapine levels, but it has been suggested that tricyclic antidepressants with clozapine could exacerbate the adverse effects related to increased anticholinergic effect (Wetzel et al. 1998).

Anticonvulsants

There are nine reports on potential interactions of anticonvulsants with subsequent changes in clozapine levels (Raitasuo et al. 1993; Finley & Warner, 1994; Conca et al. 2000; Kossen et al. 2001; Egger et al. 2010). Among anticonvulsants,

Table 1. Drug interactions with clozapine level >1000 ng ml⁻¹

| Medication | Patient (Age; Gender) | Reference | Clozapine (mg/day) | Clozapine Levels (ng ml ⁻¹) | | Post-interaction Clinical Status (Clozapine level post intervention (ng ml ⁻¹)) |
|---------------------------------------|-----------------------|-----------------------------|--------------------|---|------------------|---|
| | | | | Pre-interaction | Post-interaction | |
| Fluvoxamine 300 mg/day | 35; F | Armstrong & Stephans (1997) | 200 | NA | 1950 | Dizziness & hypotension (175) |
| Fluvoxamine 200 mg/day | 44; M | Heeringa et al. (1999) | 400 | 407 | 4160 | Facial tics, jaw tremors and mildly elevated liver function tests (416) |
| Fluvoxamine 50 mg/day | 24; F | Chong et al. (1997) | 600 | 1146 | 2750 | Progressive worsening of psychosis (740) |
| Fluvoxamine 300 mg/day | 41; M | Dequardo & Roberts (1996) | 500 | NA | 1830 | Somnolence, slurred speech, ataxic gait and hypotension (1382) |
| Paroxetine 40 mg/day | 38; F | Khan & Preskorn (2005) | 500 | NA | 2855 | Drowsiness, sialorrhoea and partial complex seizures (335) |
| Lamotrigine 100 mg/day | 35; M | Kossen et al. (2001) | 400 | 350 | 1020 | Dizziness and sedation (450) |
| Lamotrigine 50 mg/day | 24; M | Egger et al. (2010) | 350 | 452 | 2427 | Temperature 39.2°C, disoriented, confluent rash on trunk with facial involvement (48) |
| Erythromycin 333 mg TID | 34; M | Cohen et al. (1996) | 600 | NA | 1150 | Increased somnolence, slurred mumbled speech, incontinence of stool and urine |
| Erythromycin 250 mg/day | 32; M | Funderberg et al. (1994) | 800 | NA | 1300 | Tonic clonic seizure (700) |
| Ciprofloxacin 500 mg BID | 36; M | Sandson et al. (2007) | 250 | NA | 1043 | Dizziness and somnolence (686) |
| Ciprofloxacin | 64; F | Brownlowe & Sola (2008) | NA | NA | 1498 | Confusion and irritability |
| Ciprofloxacin 400 IV/day | 58; M | Brouwers et al. (2009) | 300 | 850 | 1720 | Delirium |
| Infection (Amoxicillin) | 42; M | Darling (2011) | 300 | 493 | 1734 | Disorganisation, disorientation, confusion and difficulty expressing |
| Infection (Trimethoprim) | 50; F | Darling & Huthwaite (2011) | 300 | NA | 2598 | Sudden onset drowsiness, slurred speech, shortness of breath, urinary incontinence |
| Infection (Trimethoprim) | 45; F | Darling & Huthwaite (2011) | 700 | 361 | 4740 | Dizziness and unstable gait |
| Infection | 34; M | de Leon & Diaz (2003) | 600 | 195 | 1245 | Clozapine induced myoclonus (leg folding), sedation and difficulty walking |
| Infection (Ampicillin 3000 mg/day) | 51; F | Jecel et al. (2005) | 200 | 487 | 1066 | Short phase of aphasia and akinesia followed by incoherent speech and gait disturbance |
| Infection (source not found) | 45; M | Haack et al. (2003) | 600 | 1012 | 2400 | Somatic symptoms |
| Infection (amoxi/clav 500/125 mg/day) | 55; F | Haack et al. (2003) | 400 | NA | 1824 | Fever, somnolence and vomiting |
| Infection | 63; F | Uges et al. (2000) | 600 | 480 | 4034 | Death within 1 week |
| Esomeprazole (Dose NA) | 51; F | Wagner et al. (2011) | 300 | 312 | 1237 | No change in psychiatric status, but neutropenia |
| Cimetidine 400 mg TID | 24; M | Szymanski et al. (1991) | 900 | 1081 | 1701 | |

Table 1. Continued

| Medication | Patient (Age; Gender) | Reference | Clozapine Levels (ng ml ⁻¹) | | | Post-interaction Clinical Status (Clozapine level post intervention (ng ml ⁻¹)) |
|---------------------------------------|-----------------------|-------------------------------|---|-----------------|------------------|---|
| | | | Clozapine (mg/day) | Pre-interaction | Post-interaction | |
| Modafinil 300 mg/day | 42; M | Dequardo (2002) | 400 | 761 | 1400 | Marked diaphoresis, dizziness, vomiting, generalised weakness and slight lightheadedness on standing Dizziness, unsteady gait, and two falls Marked drowsiness, anergy and dizziness Dry mouth, muscle spasm, dizziness, blurred vision, sedation and confusion Increased agitation and confusion Hypersalivation, extreme fatigue, and daytime somnolence |
| Oral contraceptive (Ethinylestradiol) | 33; F | Sandson et al. (2007) | 500 | 448 | 1281 | |
| Smoking cessation | 28; F | Derenne & Baldessarini (2005) | 450 | 274 | 1715 | |
| Smoking cessation | 37; M | Zullino et al. (2002) | 700 | 350 | 1328 | |
| Smoking cessation | 47; F | Jain et al. (2008) | 750 | NA | 1083 | |
| | | | | | | |

Clozapine level conversion: 3.06 × ng ml⁻¹ = nmol l⁻¹; 0.003 × ng ml⁻¹ = μmol l⁻¹; NA, not available

lamotrigine (Kossen et al. 2001; Egger et al. 2010) resulted in a four- to fivefold increase in plasma clozapine levels. Clozapine and lamotrigine do not share a common cytochrome P450 pathway. The active compounds clozapine and norclozapine are further glucuronidated by uridine 5'-diphosphate glucuronosyltransferases (UGT) 1A4 (and 1A3). Lamotrigine was reported to be metabolised by UGT1A4. As both clozapine and lamotrigine use UGT1A4, the rise in clozapine and norclozapine may be due to a competitive inhibition of the conjugate (Wynn et al. 2009, pp. 423–460).

Discontinuation of carbamazepine resulted in two fold rise in clozapine levels (Raitasuo et al. 1993). A single case of neuroleptic malignant syndrome was reported by Müller et al. (1998), who concluded that combining clozapine and carbamazepine is not considered safe for risk of neutropenia and decreased seizure threshold.

Doubling of clozapine serum levels after the discontinuation of valproic acid was reported by Conca et al. (2000). Centorrino et al. (1994) reported a weak increase of clozapine serum levels (about 6%) with valproic acid in 11 patients. In contrast Longo & Salzman (1995) reported a 15% decrease in clozapine blood levels in seven patients after addition of valproic acid. The coexistence of two mechanisms of interaction (CYP 1A2 enzyme inhibition and protein binding displacement) leading to opposite changes in total clozapine concentration may explain the opposite findings (Finlay & Warner, 1994). This supports the clinical importance of therapeutic monitoring of serum clozapine.

Two cases reports indicated a worsening of psychosis after phenytoin was added for a decrease in plasma clozapine concentrations (Miller, 1981).

Antipsychotics

Since a second antipsychotic is often added as an augmentation strategy, it is important to consider the safety of these combinations. Clozapine interactions with antipsychotics have only been reported with aripiprazole and risperidone (Tyson et al. 1995; Abu-Tair et al. 2006; Avari et al. 2011). There were six reports of aripiprazole

Table 2. Drug interactions with clozapine level <math> < 1000 \text{ ng ml}^{-1}</math>

| Medication | Patient (Age; Gender) | Reference | Clozapine (mg/day) | Clozapine Levels (ng ml ⁻¹) | | Post-interaction Clinical Status (Clozapine level post intervention (ng ml ⁻¹)) |
|---------------------------------------|-----------------------|-----------------------------|--------------------|---|------------------|---|
| | | | | Pre-interaction | Post-Interaction | |
| Fluvoxamine 25 mg/day | 46; M | Kuo et al. (1998) | 600 | 686.2 | 817.9 | Sedation, hypersalivation, rigidity over orolingual area and both shoulders (686.8) |
| Fluvoxamine 150 mg/day | 42; M | Koponen et al. (1996) | 400 | 253 | 265 | Increased salivation and sedation |
| Fluvoxamine 150 mg/day | 25; M | Koponen et al. (1996) | 500 | 130 | 405 | Increased salivation, nausea and constipation |
| Sertraline 50 mg/day | 26; F | Chong et al. (1997) | 175 | 325 | 695 | Both obsessive-compulsive symptoms and psychosis worsened (460) |
| Ciprofloxacin 500 mg IV BID | 46; M | Brouwers et al. (2009) | 300 | NA | 890 | Neuroleptic malignant syndrome |
| Pneumonia (Clarithromycin 500 mg/day) | 33; F | Haack et al. (2003) | 500 | NA | 915 | Symptoms data not available. |
| Cimetidine 1500 mg divided doses | 47; M | Sandson et al. (2007) | 400 | 120 | 502 | Increased sialorrhea; medications continued and side effect tolerated |
| Aluminum hydroxide | 26; M | Allarad et al. (2008) | 200 | 391.7 | 739.3 | Increased sedation and drooling |
| Norethindrone/ethinylestradiol | 47; F | Gabbay et al. (2002) | 550 | NA | 792 | Drowsiness, weakness, and dizziness |
| Smoking (2 packs/day) | 27; M | Sandson et al. (2007) | 500 | 417 | 192 | Paranoia and hallucination, despite being compliant with clozapine |
| St John's Wort 900 mg/day | 41; F | Van Strater & Bogers (2012) | 500 | 460–570 | 160 | Signs of increased disorganisation (401) |
| INH 300 mg daily | 65; M | Angelini et al. (2009) | 400 | 397 | 756 | Excess sedation |

Table 3. *N-desmethyl clozapine (norclozapine) level changes with drug interactions*

| Medication | Reference | Norclozapine Levels (ng ml ⁻¹) | | CLZ/NCZ Ratio | Post-interaction Clinical Status |
|--|-------------------------------|--|------------------|---------------|--|
| | | Pre-interaction | Post-interaction | | |
| Fluvoxamine 150 mg/day | Koponen et al. (1996) | 68 | 101 | 4.1 | Increased salivation, nausea and constipation |
| Fluvoxamine 150 mg/day | Koponen et al. (1996) | 132 | 166 | 1.6 | Increased salivation, sedation |
| Fluvoxamine 100 mg/day | Hiemke et al. (1994) | 206 | 615 | 3.5 | Clozapine discontinued and fluvoxamine lowered to 50 mg/day |
| Fluoxetine 20 mg/day | Sandson et al. (2007) | 144 | 488 | 0.8 | Patient asymptomatic and regimen continued |
| Sertraline 300 mg/day | Pinninti & de Leon (1997) | 520 | 620 | 2.3 | Sertraline discontinued |
| Levomepromazine 200 mg/day | Bugamelli et al. (2007) | 78 | 406 | 4.7 | No improvement in psychopathology and no adverse events |
| Levomepromazine 50 mg/day | Bugamelli et al. (2007) | 107 | 287 | 3.2 | Improvement in psychopathology |
| Infection | Haack et al. (2003) | 469 | 628 | 3.8 | Medication discontinued and patient recovered |
| Infection | de Leon & Diaz (2003) | 120 | 472 | 2.7 | Sedation, difficulty walking, clozapine induced myoclonus (leg folding) |
| Infection (Ampicillin 3000 mg/day) | Jecel et al. (2005) | 154 | 379 | 2.8 | Short phase of aphasia and akinesia followed by incoherent speech and gait disturbance |
| Esomeprazole (dose NA) | Wagner et al. (2011) | 267 | 368 | 3.4 | No change in psychiatric status, but neutropenia |
| Cimetidine 1500 mg daily (divided doses) | Sandson et al. (2007) | 38 | 176 | 2.8 | Increased sialorrhea; combination was continued and side effect tolerated |
| Cimetidine 400 mg TID | Szymanski et al. (1991) | 992 | 1559 | 1.1 | Marked diaphoresis, dizziness, vomiting and generalized weakness |
| Smoking cessation | Derenne & Baldessarini (2005) | 161 | 786 | 2.2 | Dry mouth, muscle spasm, dizziness, blurred vision, sedated and confused |
| Smoking cessation | Zullino et al. (2002) | 250 | 715 | 1.9 | Increased agitation and confusion |
| INH 300 mg/day | Angelini et al. (2009) | 384 | 725 | 1 | Excess sedation noted |

CLZ/NCZ, post-interaction (clozapine dose) : (norclozapine level) ratio

and one report of risperidone interaction with clozapine. The addition of aripiprazole resulted in clozapine level reduction (Avari et al. 2011) and was associated with severe exacerbation of delusions and hallucinations in one case report (Avari et al. 2011). The other five cases (Abu-Tair et al. 2006) reported improvement in negative symptoms after combination with clozapine and no changes in clozapine levels were noted. The mechanism for this interaction is not well understood.

The addition of risperidone resulted in mild increase in plasma clozapine with transient light-headedness (Tyson et al. 1995). This may represent a pharmacokinetic interaction of competitive cytochrome P450 2D6 enzyme metabolism.

Levomopromazine discontinuation resulted in four- and tenfold rises in clozapine levels (Bugamelli et al. 2007). The most likely explanation is that levomopromazine can be an inducer of CYP2D6 isoenzymes (Hals & Dahl, 1994), which are in turn involved in the biotransformation of clozapine.

The atypical antipsychotic drug amisulpride is not known to have any drug interactions with clozapine (Bergemann et al. 2005).

Antibiotics, infections and anti-tuberculosis medications

An association of antibiotics and/or infection with the changes in plasma clozapine levels has also been reported. Both ciprofloxacin (Sandson et al. 2007; Sambhi et al. 2007; Brownlowe & Sola, 2008; Brouwers et al. 2009) and erythromycin (Funderburg et al. 1994; Cohen et al. 1996) resulted in clozapine levels $>1000 \text{ ng ml}^{-1}$, but clozapine levels prior to introduction of antibiotics were not available.

Ciprofloxacin is a potent inhibitor of CYP450 1A2 and 3A4 (Batty et al. 1995), which impairs clozapine metabolism resulting in an increase in clozapine level (Sambhi et al. 2007; Brouwers et al. 2009).

Erythromycin is a selective inhibitor of CYP 3A enzyme (Murray, 1992), resulting in decreased

metabolism of clozapine with increased serum concentration, increased somnolence, difficulty in coordination and tonic-clonic seizure (Funderburg et al. 1994; Cohen et al. 1996).

Infection (Uges et al. 2000; Raaska et al. 2002; de Leon & Diaz, 2003; Haack et al. 2003; Jecel et al. 2005; Darling & Huthwaite, 2011) was associated with an up to tenfold rise (up to 14505 nmol^{-1}) in plasma clozapine level (Darling & Huthwaite, 2011). An increase in clozapine and norclozapine levels in the early course of acute infection could be due to different infection-related, not fully understood, alterations of specific CYP 450 enzymes (Jecel et al. 2005). During the acute phase of inflammation, the cytochrome P450 enzymes, including CYP1A2, are down-regulated by up to 90% with the cytokine interleukin 6 (Siewert et al. 2000).

Isoniazid (Van Strater & Bogers, 2012) and rifampin (Nebel et al. 1999) are still the first line for treatment of tuberculosis. Rifampin is a known inducer of CYP 1A2 and 3A resulting in decreased clozapine concentrations (Nebel et al. 1999), and isoniazid inhibits CYP 1A2, responsible for a rise in clozapine levels (Van Strater & Bogers 2012). When considering the effects of antibiotics on clozapine levels, duration of treatment should also be borne in mind. For instance, ciprofloxacin and erythromycin are prescribed for 5–7 days whereas rifampin is prescribed for longer, making it necessary to monitor clozapine serum concentrations with rifampicin.

Proton pump inhibitors, antacids and histamine receptor antagonists

Omeprazole (Frick et al. 2003) resulted in a slight decrease in plasma clozapine levels, whereas the addition of esomeprazole (Wagner et al. 2011) resulted in a fourfold rise in plasma clozapine levels. Omeprazole is a mixed inducer of CYP450 1A2 and 3A4, resulting in decreased concentration of clozapine, whereas drug interaction studies with esomeprazole found no potential interaction with drugs metabolised by CYP1A2, 2A6, 2C9, 2D6, or 2E1 isoenzymes (Andersson et al. 2001). The rise of clozapine plasma levels after the substitution of omeprazole by esomeprazole may be the result of the

removal of the induction of clozapine metabolism caused by omeprazole.

The addition (Szymanski et al. 1991) and/or increase in cimetidine dose (Sandson et al. 2007) resulted in a rise in both clozapine and norclozapine levels, associated with a worsening of adverse side effects including increasing sialorrhea. Cimetidine is considered a 'pan-inhibitor' (Martínez et al. 1999) of the entire range of P450 enzymes (1A2, 2C9/19, 2D6, and 3A4), resulting in a rise of clozapine and norclozapine levels despite the constant dose of clozapine. These changes were not observed with ranitidine, which could be a better alternative (Szymanski et al. 1991).

Only one case report (Allard et al. 2008) was found suggesting the possible association of aluminum hydroxide discontinuation with a doubling of clozapine concentrations, with resultant excessive sleepiness and drooling. The mechanism of action is not known.

Others: ethinylestradiol, amiodarone, modafinil and lisinopril

The addition of oral contraceptive pills containing ethinylestradiol to clozapine resulted in a threefold increase in plasma clozapine levels with adverse events including marked drowsiness, anergy and dizziness (Gabbay et al. 2002; Sandson et al. 2007). This is a greatly under recognised drug interaction (Sandson et al. 2007). Ethinylestradiol is an inhibitor of CYP450 1A2 and 2C19 (Granfors et al. 2005), which contribute significantly to clozapine metabolism.

Amiodarone was associated with six–sevenfold rise in clozapine serum levels (Stevens et al. 2008). Although amiodarone primarily inhibits CYP 3A4, its major active metabolite desethylamiodarone, is a potent inhibitor of 1A1/2, 2B6, and 2D6 (Ohyama et al. 2000).

Modafinil resulted in a doubling of clozapine levels and the onset of dizziness and unsteady gait (Dequardo, 2002). Modafinil metabolism involves P450 1A2, 2B6, 3A4/5, 2C9, and 2C19 isoenzymes and inhibits P450 2C19 activity (Huang et al. 2002). CYP450 2C19 inhibition by modafinil interfered with clozapine clearance,

elevating serum clozapine levels and thereby producing signs of toxicity.

Lisinopril does not influence the cytochrome systems but instead causes reversible renal impairment. A case of high clozapine and norclozapine levels were reported with lisinopril, with resultant disorganised behaviour and angry outbursts (Abraham et al. 2001).

Smoking and smoking cessation

There are several reports in which patients with a nicotine based smoking history were admitted to smoke-free hospitals, with a resultant rise in plasma clozapine levels (McCarthy, 1994; Zullino et al. 2002; Derenne & Baldessarini, 2005; Sandson et al. 2007; Jain et al. 2008). Meyer (2001) found that after a no-smoking policy was implemented at a state psychiatric hospital, serum concentrations of clozapine increased by an average of 71% in 11 patients, one of whom developed aspiration pneumonia at a serum concentration of over 3 mg ml^{-1} . Smoking decreases the clozapine level by induction of CYP450 1A2, with a resultant increase in clozapine level on smoking cessation (McCarthy, 1994). Many components found in tobacco smoke belong to the polycyclic aromatic hydrocarbons, which are the classical inducers of the pathway involving the aryl hydrocarbon (Ah) receptor. The binding of inducers to the intracellular Ah receptors, together with another protein, the Ah receptor nuclear translocator, increases enzyme expression by binding to an enhancer/promoter region (Zullino et al. 2002). N-demethylation by CYP1A2 is the main metabolic pathway for clozapine metabolism. The literature search did not reveal reports of clozapine interactions with nicotine replacement therapies.

Caffeine

Two case reports (Vainer & Chouinard, 1994; Al Hadithy et al. 2012) indicated that caffeine may significantly inhibit clozapine metabolism, by competition for cytochrome P450 1A2. Carrillo et al. (1998) observed a 50% reduction of clozapine concentrations after the removal of caffeine. This signifies the importance of monitoring

consumption of coffee, cola, or other caffeinated beverages in patients treated with clozapine (Al Hadithy et al. 2012).

St John's Wort (*Hypericum perforatum*)

St John's wort (*Hypericum perforatum*) is a herbal remedy, with a favourable effect on depression (Van Strater & Bogers, 2012). Van Strater & Bogers (2012) reported a patient with schizophrenia whose psychiatric condition deteriorated after self-medication with St John's Wort began. While St John's Wort is known to induce CYP3A4, it also induces P-glycoprotein (Nebel et al. 1999) resulting in a decrease in clozapine serum concentration.

DISCUSSION

We found that psychotropic medications likely to increase clozapine levels included fluvoxamine, lamotrigine, carbamazepine, and aripiprazole. Non-psychotropic medications associated with clozapine level changes included erythromycin, ciprofloxacin, omeprazole, cimetidine, oral contraceptive pills containing ethinylestradiol, and amiodarone. Smoking cessation also increased clozapine levels.

The current literature doesn't suggest at what point in time these changes in plasma clozapine levels occur (Pr terre, 1995; Vaill au et al. 1996). Only two articles addressed the association of specific clozapine levels with clinical response and adverse side effects (Perry et al. 1998; Mitchell, 2000). VanderZwaag et al. (1996) reported the superior efficacy of the 200–300 ng ml⁻¹ and 350–450 ng ml⁻¹ serum clozapine level range over the 50–150 ng ml⁻¹ range, with no advantage for 350–450 ng ml⁻¹ over 200–300 ng ml⁻¹. According to VanderZwaag et al. (1996) giving a single dose in the evening will cause a higher elevation in plasma clozapine levels in blood drawn the next day as compared with divided dosing schedules. In contrast, Liu et al. (1996) reported an upper therapeutic limit, with clozapine plasma levels greater than 700 ng ml⁻¹ producing diminished response rates. Freeman & Oyewumi (1997) reported

that serum clozapine level above 1000 ng ml⁻¹ is linked to higher rates of adverse events.

Remington et al. (2013) discussed very limited evidence for an upper threshold related to clinical response, a 'ceiling effect', in the range 600–838 ng ml⁻¹. The upper threshold for serum clozapine levels that will consistently result in serious side effects remains unclear. Remington et al. (2013) noted that clozapine doses greater than 500–600 mg per day are associated with a higher risk of seizures, however there is no well-defined plasma threshold for seizures. Remington et al. (2013) commented that a safety-related threshold cannot be established based on increased risk of other potentially serious side effects such as cardiac and gastrointestinal side effects.

In a recent paper focusing on medical reasons that lead to termination of clozapine Nielsen et al. (2013) concluded that many potentially serious side effects (such as agranulocytosis and myocarditis) are idiosyncratic with no dose dependency, while other potentially serious side effects, such as tachycardia and seizures, appear to be related to dose. Nielsen et al. (2013) made the general statement that several pharmacokinetic interactions may change plasma levels and contribute to toxic clozapine levels but they did not elaborate on this comment.

The major metabolites of clozapine (N-desmethyl clozapine (norclozapine) and clozapine N-oxide) are the result of N-oxidation of clozapine mainly catalyzed by CYP3A4 (Eiermann et al. 1997) and demethylation by CYP3A4 and CYP1A2 (Eiermann et al. 1997) respectively. In our review, drug interactions resulted in wide variability in the increased plasma norclozapine levels from 101 to 1559 ng ml⁻¹. Most of the case reports that we reviewed with a ratio of clozapine dose to norclozapine level (CLZ/NCZ) < 2.7, were associated with either worsening side effects or discontinuation of medication (Table 3). The practical use of the clozapine:norclozapine ratio was reported by Couchman et al. (2013). A ratio of ≤ 0.5 suggests either poor adherence within the last 24 hours, or that alterations in dose schedule might be beneficial. A ratio of ≥ 3 suggests that

either absorption of clozapine from the last dose may not have been completed at the time the sample was obtained, or that clozapine metabolism is saturated either because of the dose prescribed or because of inhibition of clozapine metabolism by co-administered medications.

From our review of the literature, it appears that the preponderance of serious side effects occurs at clozapine serum levels above 1000 ng ml⁻¹ (Tables 1–3). While there are reported side effects at serum levels less than 1000 ng ml⁻¹, generally the adverse effects are not as serious as those reported above this threshold, with the exception of one case of neuroleptic malignant syndrome. While certainly not definitive, these reports suggest that a clozapine serum level above 1000 ng ml⁻¹ necessitates very close monitoring of the clinical status of the patient, and that the clinician may be well advised to take steps to lower the serum clozapine level.

CONCLUSIONS

We suggest that clozapine levels should be closely monitored in the context of potential interactions of medications with clozapine. In the absence of guidelines, it may be prudent to obtain clozapine levels at the first sign of adverse events or worsening of clinical status. Clozapine dose should probably be lowered, with plasma clozapine levels above 1000 ng ml⁻¹ or CLZ/NCZ > 2.7. Due to the difficulty in interpreting the clinical relevance of clozapine levels and absence of recommendations for routine clozapine level monitoring (Eiermann et al. 1997), clinical judgment should always be used in addition to diagnostic testing. Despite the role of checking medications and smoking status, consideration should be given to age (faster metabolism in younger patients), sex (slower metabolism in females), body weight (higher doses in heavier people) and co-morbid medical conditions as contributory factors. Future research should also focus on the role of both norclozapine and clozapine-N-oxide levels in therapeutic drug monitoring, and the relevance of specific cytochrome P450 enzymes monitoring in drug-drug interactions.

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