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A therapeutic interaction between cimetidine and clozapine: case study and review of the literature

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Case description

JF, a 53-year-old male smoker of Caribbean descent was transferred from prison to a medium-security hospital unit because of concerns regarding his mental health. He had been previously diagnosed with paranoid schizophrenia, complicated by substance misuse. He was treated with a combination of olanzapine 20 mg daily and aripiprazole 20 mg daily but this was ineffective and therefore stopped. Clozapine was initiated and titrated up to a dose of 900 mg/day over a period of 4 months. As a result of doubts about compliance, JF was switched between liquid and tablet formulation several times. He was carefully observed after dose administration. During the period of titration and afterwards his plasma clozapine concentrations never exceeded 0.29 mg/l and plasma norclozapine concentrations never exceeded 0.21 mg/l (see Table 1 and Figure 1). He had shown no improvement in his mental state since starting clozapine. However, he did complain of adverse effects: he presented with mild tachycardia 3 months into the treatment (successfully treated with atenolol 25 mg daily), as well as indigestion, which resolved with lansoprazole 15 mg in the morning.

Having observed persistently low clozapine plasma levels, a decision was made to 'augment' clozapine with fluoxetine (an inhibitor of clozapine metabolism) 10 mg daily, further increased to 20 mg daily. Fluoxetine was subsequently replaced with fluvoxamine 50 mg daily (fluvoxamine is a more potent inhibitor of clozapine metabolism via CYP1A2). The introduction of fluvoxamine was preceded by a reduction in clozapine dosage to 600 mg/day. Two days after the first fluvoxamine administration JF developed a rash which only resolved once the drug was stopped.

Following this apparent allergic reaction, clozapine was titrated back to 900 mg/day and the histamine,

H2 antagonist cimetidine (a moderately potent multi-enzyme inhibitor) was initiated at a dose of 800 mg/day. Five days after first cimetidine dose his clozapine plasma concentration was 0.47 mg/l and norclozapine 0.31 mg/l. This increase in plasma concentration was accompanied by a substantial clinical improvement which was sustained while the patient remained on both drugs and resulted in a transfer to a low-security hospital unit. At each stage of treatment the patient was kept fully informed of the reasons for prescribing enzyme inhibitors.

Clozapine metabolism

Unambiguously, clozapine has been demonstrated to be the most effective choice of treatment for refractory schizophrenia, acting against both positive and negative symptoms of the psychiatric disorder [Kane *et al.* 1988; Lewis *et al.* 2006; McEvoy *et al.* 2006].

Clozapine undergoes extensive hepatic first-pass metabolism via the CYP450 system, which results in the formation of two major metabolites, clozapine-N-oxide and N-desmethylozapine (norclozapine), as well as three hydroxylated polar metabolites and protein-reactive derivatives [Pirmohamed *et al.* 1995]. The active N-desmethyl derivative, similarly to clozapine, exhibits very elaborate psychopharmacological binding properties but it is also more toxic to stem cells than its parent compound.

Both *in vitro* and *in vivo* studies have demonstrated that CYP1A2 plays the most significant role in clozapine disposition as it is the main catalyst in its oxidation and therefore the formation of norclozapine. Nonetheless, other CYP isoenzymes such as 3A4, 2D6, 2C9, 2C19, 2E1 have also been implicated in the drug's metabolism,

Table 1. Clozapine and norclozapine levels during various stages of therapy.

Treatment regime	Day	Clozapine level (mg/l)	Norclozapine level (mg/l)
clozapine 600 mg tablets	0	0.21	0.18
Clozapine 800 mg tablets	31	0.26	0.22
Clozapine 800 mg liquid	44	0.27	0.23
Clozapine 900 mg tablets	65	0.21	0.17
Clozapine 900 mg liquid	79	0.29	0.18
Clozapine 900 mg liquid + fluoxetine 10 mg	141	0.26	0.21
Clozapine 900 mg liquid + fluoxetine 20 mg	172	0.36	0.19
Clozapine 600 mg liquid + fluvoxamine 50 mg	209	1.00	0.32
Clozapine 600 mg liquid	221	0.15	0.12
Clozapine 900 mg liquid + cimetidine 800 mg	230	0.47	0.31
Clozapine 900 mg liquid + cimetidine 800 mg	253	0.61	0.37

Figure 1. Clozapine and norclozapine levels at different points of treatment.

but to a lesser and arguable extent [Doude van Troostwijk *et al.* 2003; Fang *et al.* 1998; Ozdemir *et al.* 2001; Taylor 1997; Wetzels *et al.* 1998]. *In vitro* data suggest that other CYPs which are also involved in the formation of norclozapine are 2C19 and 3A4, with the latter also being the main enzyme mediating the formation of clozapine N-oxide [Eiermann *et al.* 1997; Olesen and Linnet 2001]. The importance of 2D6 has been questioned by many as no difference in clozapine's metabolite generation has been seen in 2D6 ultra-rapid metabolizers compared with slow metabolizers [Dahl *et al.* 1994]. The role of CYP 1A2 is confirmed by the observation that smoking (an inducer of CYP1A2) is associated with more rapid clozapine metabolism [Haring *et al.* 1989]

Manipulation of plasma concentration

The correlation between clozapine plasma levels and response is well established. Levels above

0.35 mg/l are linked to a better response rate [Taylor *et al.* 2012]. Therefore, therapeutic plasma blood level monitoring when prescribing clozapine is considered beneficial.

Drug-level manipulation can be achieved by co-administering a substance which induces or inhibits enzyme(s) responsible for the metabolism of a drug. Fluvoxamine, a potent CYP1A2 inhibitor is sometimes added to clozapine treatment as a way of boosting its plasma concentration. This drug is useful in patients in whom CYP1A2 is induced by environmental factors (e.g. smoking) or where it is naturally expressed at constitutively high levels. It has been shown that adding fluvoxamine to clozapine treatment leads to a 5- to 12-fold increase in serum clozapine concentration [Chetty and Murray 2007; Heeringa *et al.* 1999]. Although usually beneficial, this interaction is potentially fatal given the magnitude of the clozapine plasma level elevation.

The patient described in this case had an allergic reaction to fluvoxamine. As a result of this, a different and less-potent CYP1A2 inhibitor, cimetidine, was introduced. This histamine H₂ antagonist is known to inhibit CYP1A2 [Martinez *et al.* 1999] as well as other isoenzymes such as 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 [Burton *et al.* 2006; Preissner *et al.* 2010]. In this case, the addition of cimetidine to clozapine treatment led to an average of 1.9-fold increase in the clozapine level. There have been two previous reports of the concomitant use of cimetidine and clozapine [Sandson *et al.* 2007; Szymanski *et al.* 1991], but none for therapeutic purposes. In both cases clozapine level increased as a result of starting cimetidine.

An alternative to metabolic inhibition is to increase the dose of clozapine above the 900 mg daily maximum. This method is preferred by some because it allows slow titration against plasma levels. However, this unlicensed prescribing places the legal responsibility for adverse consequences on the prescriber. Moreover, it is an unusual practice and so might not be considered a prescribing practice likely to be undertaken by a competent practitioner, thus placing the prescriber in further legal peril.

This pharmacokinetic interaction between cimetidine and clozapine can be valuable for patients who are not suitable for treatment with an antidepressant or where adding a potent CYP1A2 inhibitor such as fluvoxamine would carry too much risk. Cimetidine might also be a useful treatment for the gastroesophageal reflux often seen with clozapine [Van Veggel *et al.* 2013].

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Burton, M., Shaw, L., Schentag, J. and Evans, W. (2006) *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring*. Baltimore, MD: Lippincott, Williams and Wilkins.

Chetty, M. and Murray, M. (2007) CYP-mediated clozapine interactions: how predictable are they? *Curr Drug Metab* 8: 307–313.

Dahl, M., Llerena, A., Bondesson, U., Lindstrom, L. and Bertilsson, L. (1994) Disposition of clozapine in man: lack of association with debrisoquine and S-mephenytoin hydroxylation polymorphisms. *Br J Clin Pharmacol* 37: 71–74.

Doude van Troostwijk, L., Koopmans, R., Vermeulen, H. and Guchelaar, H. (2003) CYP1A2 activity is an important determinant of clozapine dosage in schizophrenic patients. *Eur J Pharm Sci* 20: 451–457.

Eiermann, B., Engel, G., Johansson, I., Zanger, U. and Bertilsson, L. (1997) The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. *Br J Clin Pharmacol* 44: 439–446.

Fang, J., Coutts, R., McKenna, K. and Baker, G. (1998) Elucidation of individual cytochrome P450 enzymes involved in the metabolism of clozapine. *Naunyn Schmiedebergs Arch Pharmacol* 358: 592–599.

Haring, C., Meise, U., Humpel, C., Saria, A., Fleischhacker, W. and Hinterhuber, H. (1989) Dose-related plasma levels of clozapine: influence of smoking behaviour, sex and age. *Psychopharmacology* 99(Suppl.): S38–S40.

Heeringa, M., Beurskens, R., Schouten, W. and Verduijn, M. (1999) Elevated plasma levels of clozapine after concomitant use of fluvoxamine. *Pharm World Sci* 21: 243–244.

Kane, J., Honigfeld, G., Singer, J. and Meltzer, H. (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45: 789–796.

Lewis, S., Barnes, T., Davies, L., Murray, R., Dunn, G., Hayhurst, K. *et al.* (2006) Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 32: 715–723.

Martinez, C., Albet, C., Agundez, J., Herrero, E., Carrillo, J., Marquez, M. *et al.* (1999) Comparative *in vitro* and *in vivo* inhibition of cytochrome P450 CYP1A2, CYP2D6, and CYP3A by H₂-receptor antagonists. *Clin Pharmacol Ther* 65: 369–376.

McEvoy, J., Lieberman, J., Stroup, T., Davis, S., Meltzer, H., Rosenheck, R. *et al.* (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 163: 600–610.

Olesen, O. and Linnet, K. (2001) Contributions of five human cytochrome P450 isoforms to the

- N-demethylation of clozapine *in vitro* at low and high concentrations. *J Clin Pharmacol* 41: 823–832.
- Ozdemir, V., Kalow, W., Posner, P., Collins, E., Kennedy, J., Tang, B. *et al.* (2001) CYP1A2 activity as measured by a caffeine test predicts clozapine and active metabolite steady-state concentration in patients with schizophrenia. *J Clin Psychopharmacol* 21: 398–407.
- Pirmohamed, M., Williams, D., Madden, S., Templeton, E. and Park, B. (1995) Metabolism and bioactivation of clozapine by human liver *in vitro*. *J Pharmacol Exp Ther* 272: 984–990.
- Preissner, S., Kroll, K., Dunkel, M., Senger, C., Goldsobel, G., Kuzman, D. *et al.* (2010) SuperCYP: a comprehensive database on cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. *Nucleic Acids Res* 38: D237–D243.
- Sandson, N., Cozza, K., Armstrong, S., Eckermann, G., Fischer, B. and Phillips, B. (2007) Clozapine case series. *Psychosomatics* 48: 170–175.
- Szymanski, S., Lieberman, J., Picou, D., Masiar, S. and Cooper, T. (1991) A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 52: 21–22.
- Taylor, D. (1997) Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 171: 109–112.
- Taylor, D., Paton, C. and Kapur, S. (2012) *Maudsley Prescribing Guidelines in Psychiatry*, 11th edn. Oxford: Wiley-Blackwell.
- Van Veggel, M., Olofinjana, O., Davies, G. and Taylor, D. (2013) Clozapine and gastro-oesophageal reflux disease (GORD) - an investigation of temporal association. *Acta Psychiatr Scand* 127: 69–77.
- Wetzel, H., Anghelescu, I., Szegedi, A., Wiesner, J., Weigmann, H., Harter, S. *et al.* (1998) Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 18: 2–9.

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