Elevation of Clozapine Serum Concentrations: Probable Interaction with Omeprazole

F. Traccis[1], A. Deidda[1], M.E. Stochino[2], V. Martinelli[3], A. Squassina[1], D. Congiu[1], A. Bocchetta[1,3]

[1]Dept. of Biomedical Sciences, University of Cagliari, Italy
[2]Sardinian Regional Center of Pharmacovigilance, Cagliari, Italy
[3]Unit of Clinical Pharmacology, Azienda Ospedaliero-Universitaria, Cagliari, Italy

Clozapine is an atypical antipsychotic belonging to the chemical family oftricyclic dibenzodiazepine derivatives. Clozapine has low affinity for dopamine-type-2 receptors and is not usually associated with extrapyramidal side effects. However, clozapine is a second-line drug for the treatment of schizophrenic disorders, principally due to the risk of agranulocytosis. Its therapeutic use is currently limited to patients who are non-responsive to other antipsychotic drugs.
Despite its long and widespread use, pharmacokinetic proprieties of clozapine are not completely elucidated. According to*in vitro*studies, clozapine is mainly metabolized by CYP1A2 even if CYP3A4 and CYP2C19 may also been involved (Sirot et al., 2009).
Specific environmental conditions, such as smoking and caffeine intake, and genetic factors, including polymorphism of hepatic cytochromes isoforms, determine a wide interindividual concentration variability. Moreover, as schizophrenia is often treated with olypharmacotherapy, interactions are on the agenda.
We report and discuss an emblematic case of an interaction between clozapine and omeprazole in a Sardinian middle aged-woman.
A 58-year-old woman affected by schizoaffective disorder had been treated with various psychotropic drugs since the age of 40. In 2004 she was started with a combined treatment of clozapine, valproic acid, and lithium. Clozapine serum concentration was 709 ng/ml. Clozapine dose was reduced from 150 mg/daily to 100 mg/daily and serum concentrations were maintained within the therapeutic range (350-450 ng/ml). Low-dose haloperidol was added to manage emerging psychotic symptoms. In November 2014 she complained dyspepsia and was prescribed omeprazole 20 mg/daily. Clozapine serum concentrations were found progressively increased over the next few months from an initial 321 ng/ml (November 2014) to 532 ng/ml (February 2015) and up to 865 ng/ml (March 2015).
An adverse reaction form was sent to the Sardinian Regional Center of pharmacovigilance. According to the Adverse Drug Reaction Probability Scale (Naranjo Algorithm), a clozapine/omeprazole interaction was probable, as no other known variations were identified (the patient does not smoke and her other medications had been continued at the same doses). The only noteworthy event (administration of the antispasmodic phlorogucinol 80 mg daily for epigastric pain) regarded the week preceding the peak clozapine serum concentration.
Omeprazole was discontinued and clozapine reduced to 50 mg/daily. Gastrointestinal symptoms subsided in a few days. Clozapine serum concentrations were lowered to 220 ng/ml (April 2015). However, the patient experienced mild psychotic symptoms and clozapine dose was brought back to 100 mg/daily, resulting in a serum concentration of 350 ng/ml (April 2015).
Nor-clozapine serum concentrations paralleled clozapine concentrations, the ratio remaining approximately 1/3 throughout the study.
To our knowledge, there is no report of clozapine interactions with the antispasmodic phlorogucinol, which might have played a role in the highest clozapine concentration. On the other hand, omeprazole has been reported to either increase (Coulter, 2002) or decrease (Frick et al., 2003) clozapine concentrations. We also suspect that this patient may be a poor clozapine metabolizer, given the relatively low clozapine dose/concentration ratio. However, environmental variables cannot be ruled out. With regard to other potential interactions, it is noteworthy that valproic acid has been reported to either increase or decrease clozapine metabolism (Diaz et al., 2014).
In conclusion, metabolism of clozapine can still be considered problematic, and new or unexpected interactions are still being observed many decades after its introduction.

Sirot et al. (2009). J Clin Psycopharmacol 29, 319-326.
Coulter (2002). Prescriber Update 23, 39.
Frick et al. (2003). Pharmacopsychiatry 36, 121-123
Diaz et al. (2014). Pharmacopsychiatry 47, 89-96.