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Impact on spychiatric practice of intra-individual variability in pharmacokinetics : cas reports .

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Clozapine is an atypical antipsychotic drug which is indicated in schizophrenic patients, particularly in cases of either non-response (refractory psychosis) or intolerance to typical antipsychotics. Extensive within-patient variability due to environmental factors in clozapine plasma concentrations could lead to serious clinical effects. Two cases of adverse reactions due to the variability of clozapine levels in female schizophrenic patients are reported.

CASE REPORT 1

A 59-year old female, had been treated by clozapine for 4 consecutive years at the same dose (600mg /24h). A dosage performed in February, 2007, showed a clozapine plasma concentration of 670.6 ng/mL, whereas this level reached 3038.0 ng/ml in April, 2009. This dosage has been indicated in presence of dyspnoea, fatigue and blood oxygen saturation decreased to 89%. It is worth mentioning in particular the initiation, after the first dosage, of a treatment by Esopremazole and Oxybutinin in order to manage, respectively, gastroesophageal reflux disease and urinary incontinence. Medications prescribed during the period of interest are listed in Table 1.

CASE REPORT 2

A 51-year old female suffering from schizophrenia had been treated as an outpatient for several years by clozapine at 300mg/day. On the day of hospital admission (Day_1) clozapine plasma level was 719.0 ng/mL whereas this concentration peaked at 1359.2ng/ml at Day 7, that is to say a two-fold increase in one week at the same dosage. In both cases, clozapine dosages were performed by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS).

Drug and toxic intake	dosage	Indication	Metabolic pathways [Impact]	Impact on [Clozapine]
Clozapine	600mg/day	Resistant schizophrenia	CYP1A2, 3A4 majors CYP2D6, 2C9, 2C19	
Esomeprazole	20mg/day	Gastro-esophageal reflux	CYP3A4, 2C19 [Inhibitor]	↑↑ [Clozapine] in plasma
Oxybutynin	10mg/day	Urinary incontinence	CYP3A4 [inhibitor]	↑[Clozapine] in plasma
Tobacco Before hospitalization during hospitalization	 >25 cigs/day (Cessation)	(addiction)	CYP1A2 [inductor]	 ↓↓[Clozapine] in plasma ↑↑ [Clozapine] in plasma

Table 1. Concomitant drugs and toxic intake

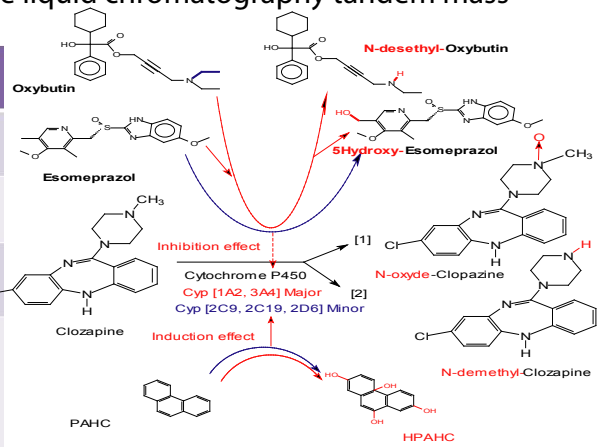

Fig.1 Metabolism Pathways

DISCUSSION

Two cases of adverse reactions were related to the metabolism variation of clozapine, mediated by several cytochrome P450 isoenzymes, particularly CYP $1A_2$ and $3A_4$ isoforms (Table 1). In the first case, the influence of concomitant medications, namely Esopremazole (Proton pump inhibitor) and Oxybutinin (Antispasmodic), on CYP $3A_4$ has led to cumulative effects. In case2, suspension of the induction of the main metabolic pathway (CYP$1A_2$), due to tobacco cessation, has resulted in an increase in clozapine plasma concentration (Figure 1). Despite a wide intra- and interindividual variability in clozapine plasma levels at a fixed dose, therapeutic monitoring of plasma concentrations is not widespread in current medical practice. The unavailability of both reliable and efficient dosage methods in routine (such as high performance liquid chromatography (HPLC-MS/MS)) and the adherence toward therapeutic guidelines could explain this paradox. In the context of hospitalization stay, it is of primary importance to consider the medical environment of schizophrenic patients to adjust their antipsychotic but also somatic treatment. Moreover, induction or inhibition of the metabolic clearance is quite dependant to the environment modifications occurring during transition from hospitalization to ambulatory care. So, a treatment previously adjusted during hospitalization could prove to be out of therapeutic range in another context.

CONCLUSION:

The therapeutic monitoring of antipsychotic drugs using plasma dosage is recommended in following cases:
- Faced with a toxic adverse event , it helps clinicians make patient's individual dose adjustment; therefore minimizing the risk of drug-induced effects and over cost of therapeutic management.
- To ensure for patients medicinal compliance, thus improving their comfort and tolerance.