

PHARMACOKINETIC INTERACTIONS OF NEW ANTIPSYCHOTICS WITH OTHER PSYCHOTROPIC DRUGS

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Abstract: *The development of the new antipsychotics in the last decades, their intensive study and increased use in clinical practice have revealed a broad spectrum of data on drug-drug interactions with other psychotropic agents. Most of clinically significant pharmacokinetic interactions are those at the biotransformation level. Co-administration of inducers or inhibitors of major enzymes involved in antipsychotic drugs metabolism may lead to correspondent changes of their plasmatic concentration, possible associated with reduced effectiveness, or increased risk of adverse effects, respectively. The best defence against these equally important, unwanted consequences is awareness of this issue. Knowledge of the pharmacokinetic interaction profile of individual drugs may help clinicians in choosing the best therapeutic option for distinct patients.*

Key words: *antipsychotics, pharmacokinetic interactions, CYP enzymes.*

1. Introduction

After a half of century since chlorpromazine was the first drug used for specific antipsychotic action, despite extensive research and great advances made in this area, schizophrenia has remained the most devastating of the mental illness. The development of newer, “atypical”, antipsychotics, has offered some real benefits, but has also posed a variety of new problems, whilst issues of efficacy and safety are still far from having idealistic values. Under these circumstances, modification of plasmatic concentration of an antipsychotic, especially for those with a narrow therapeutic index, by concurrent administrated drugs poses a supplementary challenge to clinicians, by lowering the effectiveness of the antipsychotic, or, by contrary, by increasing the risk of adverse

effects. Given the broadening spectrum of antipsychotics indications, especially after the introduction of “atypicals”, there is an increased number of patients with a variety of psychiatric disorders, and, possible, comorbidities, for whom issues of drug-drug interaction might be of clinical significance. The present paper summarises present data on newer antipsychotics pharmacokinetics, the pharmacokinetic drug interactions of proven clinical significance, as well as aspects which need further pharmacological and clinical research.

2. Biotransformation of Antipsychotics

Antipsychotics are generally metabolised through cytochrome P450 (CYP) microsomal monooxygenases mediated oxidation processes, and glucuron-conjugation processes, mediated by

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enzymes of UDP-glucuronosyl-transferase (UGT) system.

The cytochrome P450 system consists of a superfamily of isoenzymes, situated in the smooth endoplasmic reticulum from the liver and other extrahepatic tissues, which mediate oxidative reactions. These enzymes are divided into families, subfamilies and isoenzymes. The main CYP enzymes involved in drug biotransformation include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Variability of expression and activity of each enzyme isoform may lead to significant differences in drug response among individuals. The variation in individual response to drug is the result of complex interaction between genetic, pathophysiological and external factors, including co-administration of other drugs [26].

Uridine diphosphate-glucuronosyl-transferases (UGT) are enzymes located in the endoplasmic reticulum, mainly from the liver, but also from extrahepatic tissues, such as kidney, intestine, skin, lung, prostate and brain. They catalyse reactions of glucuronidation which decrease toxicity and facilitate elimination of substances, by generating products with increased polarity, compared to the parent compound. In most cases glucuronidation processes of antipsychotics occur after the first phase of biotransformation, the oxidation. Some of antipsychotics, like olanzapine, may be directly glucuronidated, without previous oxidation. Although less studied than CYP-enzymes, UGT enzymes have been lately divided in more than 33 families, from which UGT1 and UGT2 seem to have the most important role in drug metabolism [26].

Most antipsychotics are extensively metabolized (excepting amisulpride) by oxidation and glucuronidation, resulting inactive compounds, which are urinary (sometimes biliary) eliminated. Active metabolites like dehydro-aripiprazole,

which counts for 40% of circulatory aripiprazole, are exceptions. The main CYP enzymes involved in antipsychotic metabolism are: CYP1A2, CYP2D6, and CYP3A4 [15].

Clozapine is metabolized mainly by CYP1A2, with some contribution of CYP2C19, CYP2D6, and CYP3A4. Olanzapine has a common pathway of metabolism with clozapine, by CYP1A2 oxidation; CYP2D6 and CYP3A4 contribute to a lesser extent to olanzapine oxidation. Despite being the main oxidising enzyme, the influence of CYP1A2 on olanzapine metabolism is weaker than that on clozapine metabolism, because olanzapine has an alternative, secondary pathway of direct glucuronide conjugation, followed by excretion of the soluble metabolite [15], [29].

Risperidone is primarily metabolized by CYP2D6 and to a lesser extent by CYP3A4. Its active metabolite, 9-hydroxyrisperidone is marketed as a new antipsychotic, paliperidone. Once ingested, paliperidone undergoes directly phase 2 metabolism (conjugation reactions) or is excreted unchanged in the urine, which makes it the antipsychotic with the lowest potential of inducing pharmacokinetic drug-drug interactions [15]. A similar, very low, potential of interaction with other drugs is that of ziprasidone, which has 2 pathways of metabolism: the main one (metabolises 2/3 of circulating ziprasidone) is catalysed by aldehyde oxidase system, and the minor pathway (1/3 of ziprasidone) is through CYP3A4 enzymes. As aldehyde oxidase system is a non-CYP system, non-saturable and non-inhibitable, the influence of inhibitors or inducers on CYP3A4 has minimal influences on plasma level of ziprasidone [15].

Another antipsychotic with minimal potential of clinical significant metabolic drug-drug interactions is amisulpride, which is 50% excreted unchanged in the urine [26].

Quetiapine is metabolized to an inactive metabolite mainly by the CYP3A4 enzyme, being therefore highly susceptible to influences of CYP3A4 inducers or inhibitors. CYP3A4 and CYP2D6 are important enzymes in the metabolism of aripiprazole. The predominant active metabolite, dehydro-aripiprazole, represents 40% of the circulating dose of aripiprazole [26].

An interested area of pharmacokinetic drug-drug interaction research during last years is that involving P-glycoprotein (P-gp). P-gp, also called ABCB1, ATP-binding cassette sub-family B member 1, is a multidrug efflux transporter with various roles in absorption, distribution, and excretion of drugs. Of special importance for central nervous system acting drugs is P-gp action of limiting the access of drugs to the brain via the blood-brain barrier. The clinical implications of combining two drugs which are substrates for P-gp and their possible competition are not known yet, but they might significantly increase the complexity of pharmacokinetic interaction issue. For some drugs it might not be appropriate to adjust the dose when co-administering them based exclusively on plasmatic concentration, if drug concentrations in the brain are not considered [1]. P-glycoprotein has been involved in multidrug resistant diseases, including schizophrenia or neuro-degenerative diseases [1], [18]. Novel antipsychotics demonstrated (up to now) to be substrates for ABCB1 transporters are olanzapine, quetiapine, risperidone, and paliperidone [32].

3. Pharmacokinetic Interactions with other Psychotropic Drugs

Most clinical significant pharmacokinetic interactions with newer antipsychotics occur at the metabolic level. Compared to first generation antipsychotics, such as phenothiazines, which are potent inhibitors of some CYP enzymes (CYP2D6), the

newer agents have the advantage of not significantly affecting the activity of CYP enzymes, therefore they do not interfere with the biotransformation of co-administrated drugs [20], [22]. In turn, co-administration of inducers or inhibitors of major enzymes involved in new antipsychotics metabolism may modify their plasma concentration, with potentially significant effects. Co-administration of an enzymatic inducer (mainly CYP3A4 inducers) may reduce plasma level of the antipsychotic, with negative consequences on effectiveness. Co-administration of an enzymatic inhibitor may increase plasmatic level and the risk of adverse effects of the antipsychotic, being the most frequent mechanism of serious, possible life-threatening drug-drug interactions [3]. The probability that such influences became clinical significant is influenced by multiple factors, including genetic variability of isozymes, alternative metabolic pathways of the antipsychotic, the narrow/wide therapeutic index of the antipsychotic. For antipsychotics such as olanzapine, mainly metabolised by glucuronide conjugation, co-administration of CYP inhibitors might have no significant clinical consequences. Co-administration of CYP inducers may pose problems in case of all second generation antipsychotics, but the effect will be of much greater significance in case of quetiapine, mostly dependent on CYP3A4 for its metabolism [26]. An advantage of newer antipsychotics, compared to older ones, is their broad therapeutic index, especially concerning extrapyramidal effects. There are though some exceptions, such as the case of risperidone for which the risk of extrapyramidal effects is dose-dependent in doses exceeding 6mg/day [22], or clozapine with a much narrower therapeutic index, compared to olanzapine, for which the risk of neurotoxicity is

higher at plasmatic levels above 1000 ng/ml [6].

As co-administration of two antipsychotics is not very commonly used in clinical practice, except for some refractory cases, there are few studies to investigate their pharmacokinetic interaction. Studies investigating the consequences of clozapine-risperidone co-administration have produced conflicting results: some reports of an increase of plasmatic concentration of clozapine when co-administrated with risperidone [13], [28] were followed by studies that found no such influences [7], [17]. One study investigating pharmacokinetic parameters of quetiapine after adding haloperidol, risperidone, or thioridazine, found no changes induced by haloperidol or risperidone, but a 68% increase of quetiapine clearance induced by thioridazine [16]. One hypothesis to explain this interaction might be that thioridazine, although a potent inhibitor of CYP2D6, might be also an inducer of other metabolic pathways involved in quetiapine biotransformation. On the other hand, thioridazine and other phenothiazines, known as CYP2D6 inhibitors may increase plasmatic concentration of antipsychotics dependent on these enzymes for biotransformation, such as risperidone, and, to a lesser extent, aripiprazole, effects which have been demonstrated by pharmacokinetic studies [30], [33].

In various psychiatric conditions with co-existing psychotic and depressive symptoms, in strategies of improving negative symptoms of schizophrenia or in obsessive compulsive disorder, a combination of newer antidepressant with novel antipsychotic may be used. The most widely used antidepressants, the selective serotonin reuptake inhibitors (SSRIs), are potent inhibitors of CYP enzymes: fluoxetine and paroxetine strongly inhibit CYP2D6, fluvoxamine is a potent inhibitor

of CYP1A2 and CYP2C19, while fluoxetine and fluvoxamine are moderate inhibitors of CYP2C9 and CYP3A4, and sertraline is a moderate inhibitor of CYP2D6 [26]. Numerous studies have revealed clinical significant pharmacokinetic inhibition of novel antipsychotics metabolism by selective serotonin reuptake inhibitors. Fluoxetine was found to increase plasmatic level of clozapine (more than 40%) and risperidone (more than 70% elevation) [25], [34]. Pharmacokinetic interaction between fluoxetine (and its metabolite norfluoxetine which may also inhibit CYP3A4), and risperidone explains previously reported clinical observations that patients treated with risperidone developed gynaecomastia, urinary retention, or Parkinsonism when fluoxetine was added to their treatment. According to pharmacokinetic data, a lower dose of risperidone dosage is recommended in case of co-administration of fluoxetine. One of the most intensely studied pharmacokinetic interactions is that between fluvoxamine and clozapine. Pharmacokinetic studies have demonstrated a 5 to 10 fold increase in plasmatic levels of clozapine after fluvoxamine co-administration, in some cases the increased level being associated with occurrence of extrapyramidal effects [5], [24], [27]. The interaction has been explained by the inhibitory effect of fluvoxamine on CYP1A2, but also on CYP2C19 and CYP3A4, additionally involved in clozapine biotransformation [26]. Careful clinical and plasmatic level monitoring of clozapine, and possible dose reduction of clozapine, is advisable if used together with fluvoxamine. Given the magnitude of fluvoxamine-clozapine interaction, an augmentation strategy has been proposed, by which lower doses of clozapine could be used for antipsychotic effect, if co-administrated with fluvoxamine [27]. Such a strategy could be used only with clozapine level monitoring,

by specialized clinical pharmacologists. Similar interactions have been reported for fluvoxamine and olanzapine, with increased plasmatic levels of olanzapine and possible occurrence of adverse reaction, probably through inhibition of CYP1A2 [8]. The magnitude of the later interaction is much lower, compared to that with clozapine, given the alternative pathways of metabolism for olanzapine, including UGT system which is not influenced by fluvoxamine. Co-administration of fluvoxamine and olanzapine requires, though, careful clinical monitoring for adverse effects.

Apart from SSRIs, the only new antidepressant found to interact with antipsychotics was nefazodone, a serotonin 5-HT₂ receptor antagonist that also inhibits serotonin and noradrenaline reuptake, which is a potent inhibitor of CYP3A4. As expected for an enzymatic inducer, nefazodone may increase plasmatic levels of clozapine and norclozapine associated with adverse reactions such as anxiety, dizziness and mild hypotension [11].

Antiepileptic drugs, especially those with mood-stabilizing effects, and antipsychotics are often prescribed together, and their combination may affect their efficacy or their toxicity. These interactions mostly depend on the induction or inhibition of the cytochrome P450 isoenzymes, but other important mechanisms may be involved, such as influences on UGT system enzymes or on protein binding [2]. Carbamazepine is a potent inducer of various drug-metabolizing enzymes including CYP (CYP3A4, CYP2C9, CYP2C19 and, possibly CYP1A2), as well as UGTs. Numerous studies have reported a clinical significant decreased plasma level of novel antipsychotics when co-administrated with carbamazepine, as well as increased plasmatic concentration and toxicity of

antipsychotic after discontinuation of carbamazepine. The level of plasma concentration decrease is different for various antipsychotics, depending of their metabolic pathways, from 50% for clozapine, 50-70% for olanzapine, risperidone, and aripiprazole to 80% for quetiapine, which is mainly dependent on CYP3A4 for biotransformation [4], [26], [32]. Higher or lower doses of antipsychotic may be needed to maintain the antipsychotic effect when given together with carbamazepine, or to avoid toxic reactions when carbamazepine is interrupted, respectively. Apart from their pharmacokinetic interaction the association between carbamazepine and clozapine is to be avoided due to possible additive hematological adverse effects. Lower influences of carbamazepine have been reported on ziprasidone metabolism (plasmatic level reduced by 20-40 %) [26]. Even though paliperidone metabolism seems not to be significantly influenced by carbamazepine, carbamazepine was reported to increase (35%) renal clearance of paliperidone probably as a result of induction of renal P-gp by carbamazepine [10]. Several reports have suggested that valproate may slightly increase serum quetiapine and clozapine levels. Valproate is known as an inhibitor of several enzyme systems including UDP, and CYP, but the mechanism and the clinical significance of previously mentioned interactions have not been elucidated yet [32]. As expected considering their known potent inductor effect on multiple metabolizing enzymes, phenobarbital and phenytoin may increase the clearance and decrease plasmatic concentration of clozapine, olanzapine, risperidone, or quetiapine, requiring dose adjustment.

Frequently used in psychiatry, the association between benzodiazepines and antipsychotics has not been found to induce pharmacokinetic interactions. Co-administration of a benzodiazepine with a

novel antipsychotic is generally well tolerated, with the exception of clozapine. There have been reports of lethargy, ataxia, loss of consciousness [12] and even respiratory arrest [21] at 24-48 hours after clozapine was added to benzodiazepine treatment. In order to avoid such reactions, probably of idiosyncratic nature, avoidance of benzodiazepines is recommended one week before and one week after the treatment with clozapine is started.

Unlike first generation antiepileptics, the newer ones (lamotrigine, oxcarbazepine, gabapentine, topiramate) have a lower potential of interaction with novel antipsychotics. An isolated case report suggested that lamotrigine may increase clozapine levels, but this has not been later confirmed. One possible explanation of such an interaction could have been competitive inhibition of UGT4 enzyme, for which both drugs are substrates [32].

In dementia patients, antipsychotics are commonly used together with cholinesterase inhibitors, such as donepezil, rivastigmine, galantamine, and tacrine. Pharmacokinetic studies performed have not revealed significant interactions between risperidone and donepezil [19], rivastigmine [31], or galantamine [9]. Reported cases of worsening extra-pyramidal effects on adding donepezil to risperidone treatment [14] seem to have a pharmacodynamic explanation, such as that of a striatal cholinergic-dopaminergic imbalance caused by the association between and dopaminergic blocking and a cholinesterase inhibitor drug.

Conclusions

The developments of new antipsychotics in the last decades, their intensive study and increased use in clinical practice have revealed a broad spectrum of data on drug-drug interactions with other psychotropic agents. Most of clinically significant pharmacokinetic interactions are those at the

biotransformation level. Co-administration of inducers or inhibitors of major enzymes involved in antipsychotic drugs metabolism may lead to correspondent changes of their plasmatic concentration, possible associated with reduced effectiveness, or increased risk of adverse effects, respectively. The clinical consequences of these interactions are influenced by multiple factors, including genetic variability of isoenzymes, pharmacokinetic particularities of drug metabolism, or drug therapeutic index. The picture is even more complex if influences of other factors, such as those recently involved in drug distribution to brain tissue (glycoprotein P) are taken into account. The amount of information that must be taken into account while prescribing psychotropic drugs is growing day by day, and only awareness of this issue and detailed, constantly up-dated information on drugs pharmacokinetic and pharmacodynamic mechanisms may help clinicians in choosing the best therapeutic option for distinct patients in order to avoid unnecessary side effects and to improve the effectiveness of drug treatment.

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