Review

Research progress in search for pharmacokinetics of an atypical antipsychotic: Quetiapine

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Abstract:

Quetiapine is one of the atypical antipsychotics, and mainly used in the clinical treatment of schizophrenia. It can significantly reduce the emotional symptoms related to schizophrenia, such as depression, anxiety, mania and cognitive impairment. In addition, through clinical trials, quetiapine has been found to be effective in the treatment of dementia, insomnia Alcohol dependence and other diseases also have a certain therapeutic effect, which has been widely used in clinic. This paper reviews the pharmacokinetic characteristics of quetiapine absorption, distribution, metabolism and elimination in human body, and the effects of age, liver and kidney function injury and other drug interactions on these processes.

Keywords:

quetiapine, pharmacokinetics, drug interaction

Psychosis is a kind of disease caused by many reasons, which is characterized by abnormal cognitive, thinking, intelligence, emotion and behavior as well as environment uncoordinated. Many scholars agree that psychological factors and external stimuli are the main causes of mental illness. The preferred treatment measure of psychosis is medication which is systematical and standardized with early, sufficient and sufficient treatment course, and the drugs against this disease are classified into antipsychotics and antipsychotics. (Table 1)[1].

Quetiapine developed by AstraZeneca in the UK is an atypical broad-spectrum antipsychotic of benzodiazepines (Figure 1). It was approved by FDA in 1997, and then listed in China in 2001. In order to improve patient compliance and simplify treatment, its sustained-release tablets were developed and listed in 2007. It is the only atypical antipsychotic drug approved by FDA for the treatment of bipolar disorder (depression and acute mania). Because it causes less extrapyramidal response (EPS) and does not increase the level of prolactin (PRL) with any dose, it has good tolerance and compliance. Now, it is used as a first-line drug for the

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treatment of schizophrenia. It has antagonistic effects on a variety of neurotransmitter receptors, such as dopamine D1, D2 receptors and serotonin (5-HT2) receptors, histamine receptor (H1) and adrenergic receptors α_1, α_2, but it has no affinity for cholinergic muscarinic receptor and benzodiazepine receptor.

Tab 1 The classification of antipsychotic drugs

category	Representative drugs	Receptor	Characteristic
typical	Phenothiazines(chlorpromazine, perphenazine), butyryl benzene (haloperidol), benzamides (sulpiride), dibenzoyl piperidines (pentafluorolido), thioxanthenes (chloroprothiazide ton)	Non-selective on DA	It only has obvious curative effect on positive symptoms, mostly accompanied by extrapyramidal side effects, resulting in persistent prolactin elevation
Atypical	Diphenyldiazepines (clozapine, quetiapine), phenylpropaisoxazoles (risperidone), benzodiazepines (olanzapine), quinolinones (aripiprazole), ziprasidone	Selective on Da, 5-HT2, M cholinergic receptor and norepinephrine	Multiple receptors and targets are effective for both positive and negative, which can improve cognitive symptoms with little or no extrapyramidal side effects

Quetiapine has low acute toxicity and is not accompanied by neutropenia or agranulocytosis. It has typical antipsychotic effects after oral administration (500 mg / kg) or intraperitoneal injection (100 mg / kg) to mice and rats. No teratogenic and mutagenic effects. This paper reviews the pharmacokinetic properties and possible influencing factors of quetiapine.

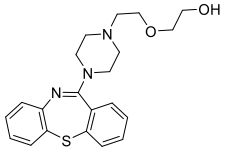

Fig 1 The structure of Quetiapine

1. Pharmacokinetics

1.1 Absorption

Quetiapine were administered orally in a single low dose, with rapid oral absorption and peak time of 1-1.5h. The absorption of quetiapine tablets after multiple doses accorded with the characteristics of linear pharmacokinetics. Sustained release preparations have been obtained clinically, but intravenous preparations have not been obtained. While bioavailability of quetiapine tablets was about 100%, food and smoking had no significant effect on its absorption. Figueroa *et al*. confirmed that extended release preparations and immediate release preparations had no effect on the total amount from absorption to elimination of quetiapine through a single-center, open-label, randomized, crossover study[2]. Quetiapine can be absorbed through the mucosa in a short time and quickly distributed throughout the body. Johansen *et al* reported a case in which a woman was sexually assaulted by a man who have taken quetiapine, and a trace of quetiapine was found in the victim's blood (0.007mg kg^{-1}) and urine (0.19mg L^{-1}) after 43 hours [3]. In addition, quetiapine can be absorbed by local administration for many times, but it can not reach the effective blood concentration. Kayhart et al. conducted a pharmacokinetic experiment which made quetiapine fumarate tablets into a unique local administration type, and

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monitored the blood concentration of five subjects who have received local treatment of quetiapine by HPLC. The effective blood concentration of quetiapine was not reached after administration, which confirmed that the local administration of quetiapine lacked systematic absorption [4].

1.2 Distribution

The results of rats experiment in vivo showed that the surface apparent distribution volume corrected for quetiapine bioavailability was small which V1/F was (8.244 ± 0.679) L·kg^{-1}, that is, quetiapine was distributed quickly but not widely in vivo[5]. For humans, quetiapine is widely distributed in the body within the range of conventional dosage, and four independent studies showed that its distribution volume is large, and the liver clearance rate is close to the liver blood flow rate[6]. For special tissues, quetiapine is not easy to penetrate and distribute. Paulzen *et al.* tested the plasma concentration of quetiapine in maternal peripheral blood, amniotic fluid and umbilical cord blood, it was found that when the daily average dose of quetiapine in maternal serum was 300mg, the average permeability of fetal blood circulation was 0.18 and 0.44 in amniotic fluid. This study confirmed that quetiapine is not easy to penetrate the placental barrier[7]. Quetiapine can also be distributed in hair. Günther *et al.* tested relevance between the dose in hair and in blood concentration by tested hairs of 22 psychiatric patients, it showed that there was a positive correlation between the drug concentration in hair and blood concentration[8].

1.3 Metabolism

Quetiapine is metabolized completely in vivo mainly through the CYP3A4 enzyme system of liver cytochrome P450. In vitro studies have found that there are more than 20 metabolites, which weresulfoxide quetiapine (SF-QTP), O-dealkylation quetiapine (OD-QTP), 7-hydroxyquetiapine (OH-QTP) and 7-hydroxy-n-dealkyl-quetiapine (ND-QTP)(Table 2). Quetiapine generates different metabolites by different enzymes, such as SF-QTP metabolites and ND-QTP are mainly catalyzed by CYP3A4. SF-QTP without pharmacological activity are the main metabolic pathway of quetiapine in vivo [9].

Drug interaction can affect the activity of metabolic enzymes and thus affect the metabolic process of quetiapine. Li *et al.* found when quetiapine is used combination with erythromycin, that metabolic clearance of quetiapine reduced from (67.2±26.6)L·h^{-1} to (34.3±12.5)L·h^{-1} ,but the blood concentration is increased from (670±314)μg·L^{-1} to (1136±459)μg·L^{-1} [10]. Carbamazepine, phenytoin and thioridazine act as enzyme inducers in combination with quetiapine to accelerate their metabolism and reduce their blood concentration. The combination with fluoxetine, paroxetine, sertraline, venlafaxine and nor venlafaxine has no significant effect on the plasma concentration of quetiapine, but the combination of quetiapine and venlafaxine will reduce the metabolic clearance of venlafaxine[11]. Therefore, the dose should be adjusted reasonably in clinical application to obtain better curative effect.

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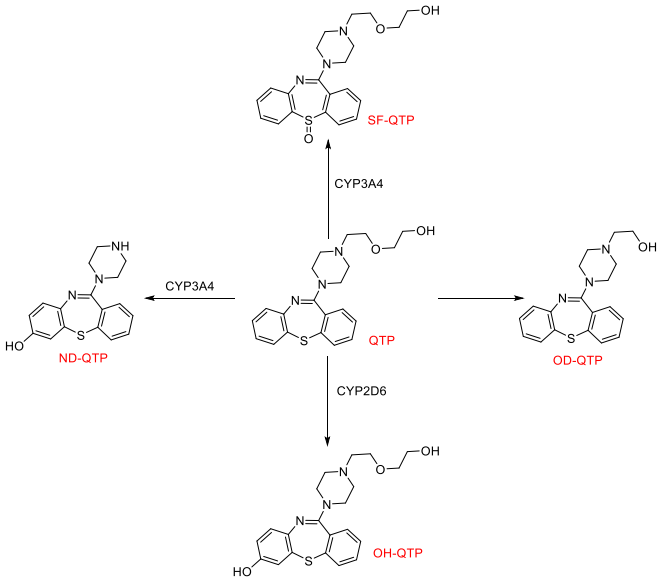

Fig 2 Structure of Quetiapine and its metabolic products

Tab 2 Main metabolites of Quetiapine

Metabolite	SF-QTP	OD-QTP	OH-QTP	ND-QTP
Antipsychotic activity	-	-	YES	YES
Enzyme	CYP3A4	-	CYP2D6、CYP3A4	CYP3A4
Metabolic pathway	Mainly pathway	-	Secondary pathway	Secondary pathway
Correlation between adverse reactions and blood drug concentration	Irrelevant	Irrelevant	Irrelevant	Irrelevant

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1.4 Elimination

Quetiapine is mainly eliminated from urine and feces in the form of metabolites, and the elimination rates of its four metabolites are similar. The results of single dose oral radiolabeled quetiapine showed that the excretion of the prototype drug was less than 1% [12]. Smoking, gender and renal dysfunction did not affect its elimination, but it would slow down in patients over 80 years old or with pathological liver injury. Clinical therapeutic dose does not cause drug accumulation in vivo [13].

2. Factors affecting pharmacokinetics

There are individual differences in clinical, that is, the plasma concentrations of different patients who take the same dose of quetiapine are different. When establishing the clinical reference value range of quetiapine plasma concentration, Liu et al investigated the range of quetiapine plasma concentration under different dose ranges. The results of multivariate analysis of variance showed that for the same patients, oral dose was the main factor who affecting quetiapine plasma

concentration [14].

2.1 Age and gender

The study showed that there was no significant difference in the plasma concentration of quetiapine, that is, age and gender were not the main factors affecting the plasma concentration. Tariot *et al*. conducted in an open experiment 151 psychiatric patients (aged ≥ 65 years) were taken 100 mg quetiapine every day during 52 weeks, and the results of BPRS evaluation showed that the drugs were effective and well tolerated. Compared with the control group of young patients who took quetiapine, the type, severity and persistence of adverse events were similar [15]. McConville *et al*. conducted a small open experiment in 10 cases to study the safety and efficacy of quetiapine in adolescents aged from 12 to 17 years, which was also no different from the control group of young patients [16]. Ma *et al*. tested the plasma concentration of quetiapine in 60 schizophrenic patients (27 males and 33 females) by HPLC to explore the influencing factors of plasma concentration. It was confirmed that there was no significant difference in plasma concentration between patients of different genders ($P > 0.05$)[17].

2.2 Genetic factors

There are great differences in the expression and activity of the same gene among different individuals. Gene polymorphisms among different individuals affect the biological activity of drug metabolism enzymes to varying degrees, and result in individual medication differences. From the perspective of genomics, whether the mutation of CYP3A4 enzyme with extremely low mutation rate and CYP3A5 enzyme with extremely high mutation rate will affect the blood concentration of quetiapine remains to be investigated in large samples. The polymorphism of ABCB1 gene lead to the change of P-glycoprotein function, which will have a corresponding impact on the efficacy of quetiapine [18].

2.3 Drug interaction

Studies show that quetiapine neither inhibits P450 isozyme nor induces CYP3A4 isozyme. Quetiapine does not interfere with plasma concentration of drugs metabolized by P450 isozymes, but drugs affecting CYP3A4 isozyme activity can affect the plasma concentration of quetiapine [19]. Omeprazole leads to the abnormal increase of quetiapine plasma concentration, which may be related to omeprazole increase the pH value of gastrointestinal tract, reduce the dissociation of weakly alkaline quetiapine and increase the absorption. In order to increase the plasma concentration the combination of omeprazole and quetiapine will compete for CYP3A4 enzyme, which further leads to the increase of quetiapine plasma concentration[20]. Quetiapine and aripiprazole are both substrates of P-glycoprotein and whic have high affinity with P-glycoprotein. They can inhibit the function of P-glycoprotein. However, contrary to aripiprazole, quetiapine can induce the expression of P-glycoprotein. Quetiapine may reduce the therapeutic effect or toxicity of aripiprazole, and aripiprazole may increase the curative effect or make the toxicity stronger, Proper dose adjustment should be paid attention to in combination. Quetiapine is prone to drug resistance in clinical application,

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while aripiprazole is not easy to drug resistance, which is related to P-glycoprotein. Amitriptyline combined with quetiapine can improve the quality of life, reduce mania and depression, inhibit immune inflammatory injury and improve the body's own antioxidant capacity[21]. Wuzhi tablets combined with quetiapine in the treatment of schizophrenic patients which can significantly improve the blood concentration of patients taking quetiapine by inhibiting liver microsomal enzyme CYP3A4 metabolic enzyme and P-glycoprotein, and have a good curative effect on liver injury in psychiatric patients[22].

2.4 Dose

An experiment using reverse high performance liquid chromatography to determine the elbow venous plasma concentration of 76 schizophrenic inpatients who taking quetiapine fumarate alone before treatment and at the 2th, 4th and 6th weeks after treatment showed that the plasma concentration of quetiapine fumarate had a good linear relationship in the range of 0.05 ~ 0.5mg Ł-1 (r = 0.9850) and the plasma concentration increased with the increase of daily dose of 50~450mg, but there was no significant correlation between gender and age [23]. A pharmacokinetic experiment of multiple administration for 16 days (twice a day for 100~375 mg and three times a day for 75 ~ 250 mg) confirmed that the pharmacokinetic behavior was linear, the values of oral clearance (CL / F), Tmax and area under dose corrected concentration time curve (AUC) had no significant difference in each dose group, the pharmacokinetic parameters of quetiapine did not depend on time or dose[24].

2.5 Smoke

In order to confirm whether smoking is a factor affecting the efficacy of quetiapine, Gong Jian et al. obtained that smoking has a slight effect on the plasma concentration of quetiapine through 63 male smokers who had quetiapine over an 8-week period, but there was no statistical significance [25]. In fact, Hickling et al. also confirmed the relationship between smoking and cognitive ability of psychiatric patients through experiments, overturning the hypothesis that smoking has an impact on drug efficacy [26].

3. Blood concentration detection method of Quetiapine

Clinical monitoring of blood concentration began with high performance liquid chromatography (HPLC) which the range of clinical reference values was determined[27]. On this basis, the scope of application was expanded, the blood concentration of several combined drugs in patients' plasma were determined simultaneously by HPLC. Liang Jun et al. simultaneously measured the concentrations of clozapine and quetiapine in human serum [28]; Shi Hongmei et al. simultaneously determined the concentrations of quetiapine and duloxetine in human plasma [29]; Chen Qingxia et al. simultaneously measured the concentrations of sertraline and quetiapine in human plasma [30]. Today, ultra high performance liquid chromatography (UPLC), reverse high performance liquid chromatography (RP-HPLC), liquid chromatography-mass spectrometry (HPLC-MS), ultra high performance

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liquid chromatography coupled with tandem mass spectrometry (UPLC-MS / MS), gas chromatography (GC), fluorescence spectrometry (FS) and other methods are widely used [31].

4. Conclusion

The treatment window of psychotropic drugs are narrow, the individual differences of patients are large, and it is very easy to cause toxic and side effects due to the dosage in the process of taking drugs. As one of the first-line drugs, quetiapine provides more superior and effective treatment options in the management of patients who have severe mental disorders. Monitoring the plasma concentration of patients who taking quetiapine, guiding medication by adjusting the dose and observing the curative effect, avoiding unnecessary adverse drug reactions, and formulating an individualized administration scheme according to pharmacokinetics. However, it is wrongly only consider the value of plasma concentration and ignore the analysis of clinical practice in clinical application. Effective plasma concentration is a relative concept, which only provides treatment reference for clinicians. Doctors must pay attention to the individualized differences of drug metabolism and the patients' own genetic factors. Clinical pharmacists are required to have a more in-depth study on quetiapine, so as to better serve the clinic.

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5. Reference

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