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The Role of Quetiapine in the Treatment of Alzheimer's Disease

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Abstract

Behavioral and psychological symptoms in dementia (BPSD) include an array of neuropsychiatric symptoms, such as delusions, hallucinations, aggression, and agitation. In recent years, the use of antipsychotics, both conventional and atypical, has been widely debated because of concerns about their safety in treating behavioral disturbances in elderly patients affected with dementia, and the possible risks for stroke and sudden death. In this review we described the pharmacokinetic of quetiapine, its correlation in patients with Alzheimer's disease and its possible role in BPSD. Quetiapine has a bioavailability of 5-13%, about 83% is bound to plasma protein and is largely metabolized in the liver through CYP3A4, the mean plasma half-life is about 6 h and clearance is reduced by 40% in the elderly. Usually CYP3A4 inhibitors are able to increase the plasma levels of quetiapine, while CP3A4 inducers accelerating the drug clearance reduce the quetiapine plasma levels. Quetiapine does not affect metabolism of other compounds known to be metabolized by CYP system. Studies showing its effectiveness for treating BPSD and the authors'clinical experience are reported too. In conclusion, quetiapine appears to be effective for treating BPSD.

Keywords: Alzheimer's disease; Dementia; Antipsychotics; Quetiapine; Pharmacokinetic

Introduction

Although cognitive deficits are the clinical hallmark of Alzheimer's disease (AD) and related dementias, non-cognitive symptoms are common and can dominate disease presentation. Defined as behavioral and psychological symptoms in dementia (BPSD), they include an array of neuropsychiatric symptoms, such as delusions, hallucinations, aggression, and agitation. The symptoms may affect more than half of patients with dementia and contribute to patient distress [1]. Moreover, they are highly burdensome to caregivers [2,3], compromise patient safety and lead to institutionalization [4], increasing hospital length of stay [5,6]. As such, management of BPSD may help in alleviating caregiver burden [7], and in reducing healthcare costs, especially in later stages of disease [8].

In recent years, the use of antipsychotics, both conventional and atypical, has been widely debated because of concerns about their safety in treating behavioral disturbances in elderly patients affected with dementia, and the possible risks for stroke and sudden death [9-13].

Conventional antipsychotics have been widely used for BPSD; some studies showed they have an efficacy superior to placebo only at high doses, but they are associated with several and severe adverse effects. Conventional antipsychotics are D2-receptor antagonists and inhibit dopaminergic neurotransmission in a dose-related manner, whereas atypical agents cause serotonin 5-HT2A and dopamine D2-receptor antagonism [14-16]. Atypical antipsychotics showed an efficacy superior to placebo in randomized studies in BPSD treatment, with a better tolerability profile versus conventional drugs [14].

However, several placebo-controlled trials have raised concerns about their safety in elderly patients affected with BPSD [10,11].

The aim of the present study was addressed to a pharmacokinetic evaluation of quetiapine for the treatment of AD and to review its possible role for treating BPSD.

A MEDLINE search was conducted using the following key terms: elderly, quetiapine, quetiapine extended-release, effectiveness, dementia, BPSD, pharmacokinetics, age-related changes. Some personal studies were considered too. We eventually tried to draw some conclusions on the possible use of quetiapine in elderly demented patients.

Chemistry and Pharmacodynamics

Quetiapine is a dibenzothiazepine structurally similar to clozapine. It has been shown to be effective on both positive and negative psychotic symptoms, without producing extrapyramidal symptoms (EPS) [17,18]. Quetiapine is a tricyclic agent along with clozapine and olanzapine; they have their highest affinity for H1 receptors, and this is also consistent with their sedative properties [19]. Quetiapine is a lower-potency compound compared to clozapine and olanzapine, with relatively similar antagonism of 5-HT2A, D2, α1, and α2 receptors [14]. The peculiar mechanism of action of quetiapine and atypical antipsychotics might be explained through the serotonin-dopamine interactions in the nigrostriatal, mesocortical, and tuberoinfundibular pathways. In fact, in the nigrostriatal pathway, the atypical

antipsychotics bind to presynaptical 5-HT2A receptor placed on dopamine neuron. This is followed by dopamine release, so that there are usually no motor impairments, or they are at a lower extent when compared with conventional antipsychotics [9,14,15]. In fact quetiapine can be administered to patients affected with Parkinson's disease. The same mechanism at mesocortical pathway explains why atypical antipsychotics cause fewer cognitive impairment compared with conventional drugs. In tubero-infundibular pathway, dopamine inhibits and serotonin stimulates prolactin release; therefore, 5-HT2A serotonin antagonism counteracts the effects of D2-receptor blockade. Quetiapine, aripiprazole, asenapine and ziprasidone are also partial agonists at 5-HT1A receptors. Affinity for this receptor is one of the proposed mechanisms of action of quetiapine's antidepressant effects [20]. Furthermore, quetiapine and in general all the atypical drugs present the so called hit-and-run mechanism, that is they occupy D2 receptors transiently and then rapidly dissociate to allow normal dopamine neurotransmission [9]. The D2 receptor occupancy of quetiapine compared to risperidone, olanzapine and the conventional drug haloperidol [21]. The percent occupancy rate is low and this explains why quetiapine does not induce the neurological effects of haloperidol. In summary, as well as each atypical antipsychotic drug, quetiapine increases dopamine at frontocortical and nigrostriatal pathways and causes a dramatic reduction of cognitive and motor impairments when compared with conventional antipsychotic drugs. On the other hand, it reduces dopamine release at mesocortical pathway, leading to antipsychotic effects [14,16].

Quetiapine Pharmacokinetics

Speaking about quetiapine pharmacokinetics in AD, we have to take into account that most of demented patients are old and therefore there are age-related changes in pharmacokinetics. Another important factor is due to the possible drug-drug interactions, because comorbidities and polypharmacy can influence quetiapine plasma concentrations. Hypoalbuminaemia and chronic renal failure, frequently found in demented people, can alter pharmacological response; for example, elderly persons are more sensitive to benzodiazepine or antipsychotic effects, experiencing stronger sedation even with lower plasma concentrations of these drugs than those required for a sedative effect in younger persons [14].

Aging causes a number of changes in drug absorption, distribution, biotransformation and elimination [14]. Drug pharmacokinetics may change with age as a consequence of living habits in elderly individuals, such as diet, alcohol consumption, smoking, concomitant use of other drugs and genetic polymorphism of hepatic enzymes, concurrent diseases, etc. [9,22]. Overall age-related decrease in drug absorption, for the reduction in gastrointestinal motility, in splanchnic blood flow and in the absorption surface, and an increase in gastric pH is usually observed [23]. The volume of distribution is lower for water-soluble drugs and greater for lipid-soluble ones, such as quetiapine, haloperidol, chlorpromazine, diazepam, nitrazepam, amitriptyline, and lidocaine [24]. Therefore, these lipid-soluble drugs tend to accumulate in adipose tissue, resulting in increases in their plasma half-lives and their duration of action, thus boosting the risk of iatrogenic effects in elderly persons [24,25].

Another crucial point in drug kinetics is metabolism. Liver clearance of a drug depends mainly on liver blood flow, which decreases with aging, and on liver enzyme activity. Hepatic enzyme function is related to phase 1 and phase 2 reactions. In phase 1 reactions the involved enzymes are a number of haemoproteins, such as cytochrome P450 (CYP), cytochrome b5 and a flavoprotein, nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome-C-reductase. Phase 2 reactions involve acetylation and conjugation reactions with glycuronic acid, and are not influenced by increasing age, whereas phase 1 reactions are strongly influenced by aging, sex and genetic factors [14]. CYP isoenzymes have a particular role in drug metabolism, both in adults and in the elderly. In humans, more than 30 CYP isoenzymes have been identified; CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are important in the metabolism of many antipsychotics [26]. Genetic polymorphism has been described for CYP2D6 and CYP1A2 [27].

Quetiapine, administered orally as quetiapine fumarate, is rapidly absorbed in the gastrointestinal tract. Its bioavailability is 5-13% and time to reach peak blood level is about 1.5-2 h for quetiapine immediate release, and 6 h for quetiapine extended release [18,28,29]. It can be taken with food, without any changes in the absorption rate; about 83% is bound to plasma protein. Quetiapine is largely metabolized in the liver trough CYP3A4, and less than 1% of a dose is excreted unchanged. Mean plasma half-life is about 6 h and clearance is reduced by 40% in the elderly [18,28,29]. In particular, regarding quetiapine metabolism, *in vitro* studies showed that CYP3A4 is the isoenzyme involved in quetiapine sulfoxidation, N- and O-dealkylation; the 7-hydroxylation is partly mediated by CYP3A4, whereas it is unlikely that CYP2D6 is involved in the *in vivo* metabolism of quetiapine [30,31]. *In vivo* studies showed that the major metabolites are quetiapine sulfoxide, without antipsychotic activity and an acid metabolite produced by oxidation. 7-hydroxy-quetiapine and N-desalkyl-quetiapine (also called norquetiapine) are active metabolites, but with relatively low concentrations in blood [28]. Quetiapine and three metabolites in human plasma can be determined by high-performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS/ESI). Following HPLC-MS/ESI it was reported that quetiapine and quetiapine sulfoxide are the major circulating species in plasma [30]. CYP2D6 also contributes to quetiapine metabolism, though to a lesser extent. This creates small quantities of 7-hydroxy quetiapine; in addition, this isoenzyme metabolizes norquetiapine into 7-hydroxy-N-desalkyl-quetiapine, which is pharmacologically active [32]. Moreover, the plasma concentrations of 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine are about 5% and 2% respectively of those of quetiapine [33]. This means that the two metabolites are inactive in Caucasians, unless there is a low expression of this cytochrome, for example in Chinese people, where CYP3A4 expression may vary up to a 30-fold difference among individuals [30].

Recent papers reported the development of drug interactions when quetiapine is co-administered with drugs able to modulate the expression or activity of CYP enzymes [34,35].

In particular, CYP3A4 inhibitors influence drug clearance, and increase plasma concentrations of quetiapine; on the contrary, CYP 3A4 inducers accelerate drug clearance, therefore quetiapine dose may need to be increased. The main CYP3A4 inhibitors and inducers. According to the manufacturer, quetiapine does not affect the metabolism of compounds known to be metabolized by CYP1A2, CYP2C9 or CYP2D6.

The available data are sufficient to arrive at the conclusion that antidepressant activity of quetiapine is mediated, at least in part, by the active metabolite norquetiapine [36]. In fact, norquetiapine's effect as a partial agonist of 5-HT1A receptors may contribute, at least in part, to quetiapine's clinically demonstrated antidepressant and anxiolytic

action [37]. Norquetiapine has also higher affinity for the 5-HT7 receptor compared with quetiapine, which is involved in depression and sleep-related, circadian rhythm disorders [38]. As discussed above, quetiapine, and to a greater extent norquetiapine, have antagonistic properties at 5-HT2A receptors. 5-HT2A antagonists have been proposed to treat insomnia, so perhaps norquetiapine, which is also a potent H1 receptor antagonist, significantly contributes to the highly sedative effects observed during quetiapine treatment [20]. It has also been seen that norquetiapine has a great affinity for the norepinephrine (NE) transporter, which is similar to that of certain antidepressants, like nortriptyline, amitriptyline, and duloxetine [20].

Moreover, norquetiapine increases noradrenergic functioning by blocking presynaptic α2 receptors considerably more than quetiapine [20]. In experimental studies, quetiapine has been shown to prevent BDNF reduction as well as chronic stress-related cellular degeneration in the hippocampus. Therefore, this may contribute to the antidepressant effects of quetiapine in patients affected with AD.

Additionally, quetiapine has been observed to restore the activity of glutamate receptors. This may lead to a decrease in the neurotoxicity caused by an excess of the neurotransmitter glutamate [39].

Eventually, norquetiapine clearly exemplifies the case of an active metabolite that, through metabolism, can make a drug, originally introduced as an antipsychotic, in this case quetiapine, to become a useful antidepressant agent.

Clinical Efficacy

Quetiapine is a second generation antipsychotic approved for the treatment of schizophrenia, bipolar disorder and as add-on treatment of major depressive disorder. The use of quetiapine in clinical practice has extended beyond FDA-approved indications, for example generalized anxiety disorder, major depressive disorder (in monotherapy), obsessive compulsive disorder, psychosis in Parkinson's disease, and treatment of BPSD, such as agitation, aggression, depression, psychoses, and apathy [40]. For all these reasons, quetiapine may have a crucial role for its efficacy in AD patients [9].

In the case of elderly patients affected with dementia, quetiapine but in general every antipsychotic treatment, must be prescribed at the lowest effective dosage and for the shortest period possible. The severity and frequency of symptoms and the global functioning and quality of life, as reported by caregivers, must be always monitored during treatment [41-43].

In our experience, when agitation and aggression prevail, the drug to be preferred may be olanzapine, especially in the fast administration (i.e. velotab, or orally disintegrating tablets), in patients with poor compliance, or quetiapine. Clozapine and quetiapine have to be preferred in patients with Parkinsonism, even if the use of clozapine is limited by the possible onset of severe adverse events, such as agranulocytosis and myocarditis [15].

Based on the results of the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's disease (CATIE-AD), olanzapine and risperidone were significantly more effective than quetiapine and placebo when interruption of treatment due to a lack of efficacy was analyzed (22.1 and 26.7 weeks with olanzapine and risperidone respectively versus 9.1 and 9.0 weeks with quetiapine and placebo respectively). The placebo group was superior to the three drugs on the analysis of treatment interruption due to intolerability. The trial showed that there is a high rate of adversity that offset evidence of efficacy; importantly, a minority of patients can also show clinical benefits without toxicity [43,44].

Agitation often worsens some types of dementia and atypical antipsychotics are often effective, even if their use is off-label. A review performed in 2012 comparing the efficacy of off-label use of atypical antipsychotics in dementia suggested that olanzapine, aripiprazole, and risperidone have a moderate-to-high efficacy in agitation [45].

Acute onset of confusion and delusions often occur in elderly hospitalized patients and may be effectively treated with second-generation antipsychotics. On the contrary, haloperidol has long been considered the drug of choice for treating agitation and aggression. At present, olanzapine, quetiapine, and risperidone show the same efficacy profile in acute stages of disease, without inducing the neurological effects of haloperidol [46].

However, careful use of quetiapine in elderly patients with AD is strictly recommended. Importantly:

- It must be prescribed at the lowest effective dosage and for the shortest time possible;

- A balance of the risks and benefits is closely required;

- Patients need to be monitored; and

- In order to improve patient's quality of life, the use of quetiapine is justified considering the poor results of alternative treatments (other drugs and psychotherapeutic and psychosocial interventions).

Safety and Tolerability

H1 and α1 antagonism are linked to the side effects of quetiapine. The compound may cause orthostatic hypotension (because of α1-receptor blockade), especially in elderly patients [14]. Orthostatic hypotension may be associated with dizziness, tachycardia and, in rare cases, syncope. Therefore, it should be used carefully in patients with heart disease, particularly those with heart failure, previous history of myocardial infarction or conduction abnormalities [14]. Quetiapine can rarely cause EPS, such as akathisia, tremors and hypokinesia. It more frequently causes xerostomia, weight gain, constipation, somnolence and dyspepsia [47]. However, it has been shown that long-term monotherapy with quetiapine is associated with a potentially normalizing effect on weight. Weight gain can be usually observed in underweight patients, whereas weight loss can be found in severely obese patients [48]. The onset of seizures was demonstrated in 0.8% of patients treated with quetiapine. It is associated with dose-dependent reductions in total and free thyroxine and transient increases in hepatic enzymes (especially aspartate aminotransaminase).

Hasnain et al. [49], reviewed the case-report literature and found 12 case reports of QTc interval prolongation in the setting of quetiapine administration. There were no cases of quetiapine induced torsade de pointes (TdP) or sudden cardiac death (SCD) among patients using quetiapine appropriately and free of additional risk factors for QTc interval prolongation and TdP. Among the 12 case reports risk factors included female sex (nine cases), coadministration of a drug associated

With QTc interval prolongation (eight cases), hypokalemia or hypomagnesemia (six cases) quetiapine overdose (five cases), cardiac problems (four cases), and coadministration of cytochrome P450 3A4 inhibitors (two cases). There were four cases of TdP.

The long-term efficacy and safety of quetiapine in elderly patients with psychosis has been studied by some authors [50,51]. Overall recommended dosages in elderly patients are 50-300 mg/day, whereas in AD they are 25-200 mg/day [9,14].

Conclusion

Definitely, because of its decreased propensity to produce extrapyramidal symptoms, quetiapine holds promise in the treatment of elderly patients affected with BPSD [52].

Quetiapine is a lower potency antipsychotic compound with relatively similar antagonism of 5-HT2, D2, α2 and α1 receptors. H1 receptor blockade is similar for clozapine, olanzapine and quetiapine, and it is consistent with their sedative properties [14,47]. It can be used for treatment of BPSD, even if the use of antipsychotics is off label in dementia. Anyway, antipsychotics are probably the best option for short- term treatment (6-12 weeks) of severe, persistent and resistant aggression [53]. Serious adverse events are a major contraindication to long-term therapy [9].

It is metabolized via CYP3A4, so that in demented and often old patients taking several drugs, a number of interactions may be present. Age-related changes need to be carefully taken into account when quetiapine immediate or extended release is prescribed.

Therefore, since elderly demented patients are often affected with concomitant diseases and are polytreated, use of quetiapine requires a careful case-by-case assessment [54].

Some key points seem to be relevant, according to our experience:

a) Treatment with quetiapine must be started at low dosages, with gradual increases on an individual basis and titrating dosages in order to eventually decrease the possible adverse events;

b) Treatment has to be changed whenever there is no reduction in frequency and/or severity in target symptoms;

c) Wherever a sufficient control of behavioral symptoms has been obtained, the decrease in its dosage until its interruption is required;

d) Quetiapine is recommended for its sedative properties and its good tolerability compared to old antipsychotics such as promazine and haloperidol.

e) Other drugs might have the potentiality of effectiveness in BPSD, but at present there are only preliminary studies. They are paliperidone, aripiprazole, and recently asenapine (at present used only in bipolar disorder).

In conclusion, quetiapine has shown to be an effective drug for treating BPSD, even if it should be prescribed at the lowest effective dosage and for a time as short as possible, balancing risks and benefits, and continuously monitoring patients.

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