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Mini Review

Pharmacokinetic and Pharmacodynamic Characteristics of Donepezil: From Animal Models to Human Applications

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ABSTRACT

Alzheimer's disease is associated with a decline in Acetylcholine (ACh) levels, leading to cognitive impairment. Donepezil, an acetylcholinesterase (AChE) inhibitor, treats Alzheimer's disease by slowing ACh degradation, thus decelerating symptom progression. The pharmacokinetic characteristics of donepezil have been studied in experimental animals and humans, providing insights into its distribution, metabolism and excretion. Donepezil rapidly crosses the blood-brain barrier (BBB) and is primarily metabolized in the liver, with metabolites showing minimal brain permeability. In rats, the maximum concentration of donepezil in the brain occurs two hours after administration, and the increase in ACh in the brain roughly coincides with plasma levels. Similar linear pharmacokinetics have also been observed in humans. However, species-specific differences in hepatic metabolism and plasma protein binding contribute to the variations in clearance between rats and humans. Once-daily dosing in clinical settings is supported by its long half-life ($t_{1/2}$) of approximately 80 h. Cardiotoxicity has been observed when donepezil is co-administered with cilostazol, an antiplatelet agent that inhibits efflux transporters, leading to donepezil accumulation in the heart. Clinical studies indicate that although combination therapy improves cognitive function in patients with mild dementia, it may pose a risk of cardiovascular side effects. Pharmacokinetic/Pharmacodynamic (PK/PD) modeling has provided valuable insights into the relationship between plasma pharmacokinetics and AChE inhibition profiles, aiding the development of new dosage forms such as transdermal patches. These findings contribute to the understanding of the efficacy of donepezil and its potential drug interactions, providing more effective treatment strategies for Alzheimer's disease, especially in cases of polypharmacy.

Keywords: Donepezil; Acetylcholinesterase inhibitor; Pharmacokinetics; Experimental animal; Modeling

INTRODUCTION

In recent years, the prevalence of Alzheimer's disease has continuously increased. This neurodegenerative disorder results from a reduction in ACh levels in the brain due to various factors, leading to substantial impairment of the cholinergic system [1-4]. Treatment typically involves prolonged therapy aimed at slowing down disease progression [5,6]. Donepezil, a commonly prescribed medication for Alzheimer's disease, works by inhibiting AChE enzyme in the brain, reducing the decline in ACh levels, thus decelerating disease progression [7-9]. Common adverse effects of donepezil, related to its cholinergic effects, include nausea, vomiting, and diarrhea [10,11]. More serious side effects, such as bradycardia, arrhythmias and heart block, have also been reported [12].

Additionally, pharmacokinetic studies of donepezil in both animal models and human participants, using pharmacokinetic modeling, provided information on the correlation between pharmacokinetics and AChE inhibition across different administration routes. This review also explored the side effects and potential drug interactions that may pose challenges in clinical practice. These findings are expected to enhance our understanding of the efficacy of donepezil, especially in the cases of changes in disease state or when predicted drug interactions alter its pharmacokinetics.

LITERATURE REVIEW

Pharmacokinetics and efficacy of donepezil in experimental animals

In a basic pharmacokinetic study of donepezil in rats, including plasma kinetics and tissue distribution, the drug was substantially distributed to the liver, a major metabolic organ, as well as in the adrenal glands, heart and brain [13]. Following intravenous administration, donepezil was rapidly distributed to the heart and lungs, with concentration-time profiles similar to those in plasma. Peak concentration in the brain was observed approximately 2 h after administration. Donepezil is predominantly metabolized

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in the liver, yielding 14 metabolites, with the primary metabolite being 6-O-desmethyl donepezil (DMDon) [14]. However, its plasma concentration is only approximately one-thirtieth that of donepezil [15]. These metabolites are further processed *via* glucuronidation before excretion into bile and urine, with some entering the enterohepatic circulation [15-18]. Additionally, oral administration of donepezil leads to rapid absorption, with the maximum plasma concentration occurring 30 min after administration and nearly complete absorption [15,16].

The distribution of donepezil and DMDon in the brain has been previously evaluated in rats [15]. Donepezil readily crosses the BBB, reaching concentrations in the brain that are about twice as high as those in plasma. After the oral administration of ^{14}C-labeled donepezil, the plasma donepezil levels declined more quickly than the radioactivity levels, whereas brain radioactivity paralleled the plasma levels of donepezil. This indicates that most of the brain radioactivity was due to donepezil and that the metabolites did not effectively pass through the BBB, given their low permeability. Similar findings were observed in dog studies, where over 80% of the brain radioactivity was attributable to donepezil [17]. Consequently, DMDon had a minimal impact on brain efficacy. Cholinesterase enzyme includes the subtypes AChE and Butyrylcholinesterase (BuChE). Donepezil selectively inhibits AChE, which is more prevalent in the brain than BuChE, which explains why the activity of donepezil in the brain is stronger than its plasma activity owing to the cholinesterase subtype distribution [7,19].

Following a 30-min intravenous infusion of donepezil in rats, the plasma concentration-time curve of donepezil and corresponding changes in ACh levels in the hippocampus were studied over time using microdialysis [20]. The ACh levels in the brain began to rise shortly after administration, reaching their peak at 45–60 min, and then gradually declined slightly, lagging behind the plasma donepezil concentration before returning to baseline. These results are consistent with those of Kosasa et al. who reported that orally administered donepezil was rapidly absorbed, leading to a rapid increase in ACh levels in the cerebral cortex, with a minimum effective dose of 2.5 mg/kg or less in rats [21].

Pharmacokinetics and efficacy of donepezil in humans

Rogers et al. reported that when donepezil was orally administered to humans at doses ranging from 2.0 to 6.0 mg (from low to typical clinical doses), the plasma concentration was dose-dependent, demonstrating linear pharmacokinetics [22]. Clearance was almost consistent across different doses. Maximum plasma levels were achieved approximately 4 h after administration, and the $t_{1/2}$ of the drug was around 80 h, indicating slow elimination and supporting the possibility of once-daily dosing. It took approximately 14 days to reach a steady state due to the long $t_{1/2}$. This tendency did not change with repeated administration [23]. The accumulation rate after repeated administration was calculated from the pharmacokinetic parameters obtained after a single administration. The calculated pharmacokinetic profiles largely agreed with the observed values. The clearance of donepezil from the human body is very slow and differs from that in rats. One of the factors contributing to this result is the difference in hepatic metabolic activity between these species. Hepatic clearances calculated using the well-stirred model and *in vitro* enzyme kinetic data in rats and dogs were 14.4 and 7.4 times larger than that in humans, respectively [24]. In addition, plasma protein binding of donepezil was slightly higher in humans than in rats and dogs (88% *vs.* 74%, respectively). Donepezil metabolism is complex, resulting in various metabolites such as hydroxylated, N-oxidized, N-dealkylated, and O-dealkylated forms, which are primarily processed by CYP3A4 and CYP2D6 enzymes in human liver microsomes [25,26]. Nevertheless, inhibitors of CYP2D6 and CYP3A4 have minimal impact on pharmacokinetics of donepezil in patients with Alzheimer's disease [27]. Donepezil is known to metabolize into the active compound DMDon, with the parent drug efficiently crossing the BBB and achieving concentrations in the brain that are approximately double those in the plasma, whereas the metabolites do not readily cross the BBB [15,28]. Based on these reports, plasma donepezil concentration is considered important for ACh profiles in the brain. The absence of hysteresis and the linear correlation between plasma concentration and AChE inhibitory activity suggest that the effects increase with plasma levels until a steady state is reached.

The effect of AChE inhibition was proportional to plasma levels, similar to findings in rat models. A substantial correlation was observed between the area under the plasma concentration-time curve (AUC) and the area under the effect-time curve (AUE), particularly after repeated dosing [23]. The relationship between the AUC and AUE of AChE inhibitory activity after repeated administration was almost linear (r^2=0.919). Simulations indicated that the AUC and AUE of donepezil were consistent with the observed measurements, showing that the effect increased proportionally with rising plasma concentrations towards a steady state without any time lag.

Cardiotoxicity of donepezil with cilostazol co-administration and its clinical efficacy

Cilostazol, an antiplatelet agent, is known to enhance cerebral blood flow and reduce amyloid-β protein deposition, which is implicated in Alzheimer's disease-related cognitive decline [29,30]. The combination of donepezil and cilostazol has been found to be particularly effective for patients with mild dementia [31]. However, interactions between the two drugs can lead to cardiovascular side effects, possibly due to transporters inhibition [32]. Therefore, it is important to explore the relationship between the pharmacokinetics and effects of donepezil, along with the changes in its pharmacokinetics and the emergence of both therapeutic and adverse effects when combined with cilostazol.

Donepezil has been associated with cardiotoxicity when co-administered with cilostazol in clinical practice [12]. In an *in vitro* study using Madin-Darby canine kidney epithelial cells, donepezil was shown to be a substrate for efflux transporters, including breast cancer resistance protein and P-glycoprotein, which facilitate drug excretion in organs such as the liver, kidneys, brain and heart [32]. Cilostazol is known to inhibit these transporters, resulting in reduced excretion of donepezil from the heart, leading to its accumulation and potential cardiotoxicity. Based on plasma concentrations when the two drugs were administered together at clinical doses and the 50% inhibitory concentration of cilostazol for these transporters, the observed *in vitro* drug-drug interactions could potentially occur in clinical settings. In rat studies, tissue concentrations of donepezil were compared when administered alone and in combination with cilostazol. Initially, there was no substantial difference in tissue concentrations shortly after administration, but donepezil levels markedly increased in the combination group after 300 min. Interestingly, this increase in

tissue concentration occurred without substantial changes in plasma levels. This suggests that donepezil accumulate in the brain and heart without altering its plasma concentration, potentially leading to side effects or enhanced effects in these organs in clinical settings.

In a retrospective study involving patients with mild to severe dementia, Ihara et al. examined the outcomes of the Mini-Mental State Examination, comparing donepezil monotherapy with donepezil and cilostazol [31]. Over a period of 2–2.5 years, cognitive decline was more pronounced in the donepezil only group in patients with mild dementia, while the combination therapy group showed only slight deterioration and improvements in orientation and recall, marking a substantial difference between the two groups. However, no differences were noted between the groups in patients with moderate to severe dementia, where cognitive decline occurred. Therefore, the combination of donepezil and cilostazol may be particularly beneficial in slowing the progression of symptoms in patients with mild dementia.

Pharmacokinetic and pharmacodynamic modeling of donepezil in rats

After drug administration, plasma concentration is commonly measured as an indicator of efficacy. However, the relationship between the drug concentration in plasma (pharmacokinetics) and therapeutic or adverse effects (pharmacodynamics) is complex and not always directly proportional. Several factors can influence this relationship, including the temporal delay between concentration in plasma and at the target site of action, as well as the mechanisms through which the drug exerts its effects. PK/PD analysis provides insights into the effects of many drugs by relating their pharmacokinetic properties to their pharmacodynamics. Kiriyama et al. analyzed the time course of the effect in relation to the plasma concentration profile of donepezil, using the pharmacokinetics of donepezil in rats and the ACh concentration profile in the hippocampus [20]. The plasma kinetics of donepezil, as described by the two-compartment model, and the ACh concentration profile in the brain, as described by the indirect response model, were in good agreement with the actual measured values.

Moreover, a pharmacokinetic study in humans indicated that the pharmacokinetic profile after oral administration aligns well with a saturable Michaelis-Menten model, which accounts for hepatic first-pass metabolism [33]. In this study, the optimal pharmacokinetics of donepezil patches after transdermal administration were examined through modeling. In recent years, transdermal patch administration has become a convenient route for patients with Alzheimer's disease. In this study, we examined the optimal dosing schedules of a donepezil patch regimen compared to an oral regimen using a constructed pharmacokinetic model, which included Michaelis-Menten metabolism. Despite species-specific variations in pharmacokinetic and pharmacodynamic between rats and humans, our results provide foundational insights for human applications and offer valuable information for future PK/PD analyses.

CONCLUSION

The pharmacokinetic characteristics of donepezil have been investigated, revealing different pharmacokinetic properties in experimental animals and humans. The relationship between the pharmacokinetics, efficacy, and side effects of donepezil has been clarified through various experiments using animal models. In the future, by applying model analyses to interpret human phenomena based on experimental animal results and by considering pharmacokinetic efficacy and side effects, it is believed that pharmacokinetic changes can be predicted for polypharmacological therapy, under pathological conditions, with changes in the administration route or dosage form, and that further predictions of pharmacological effects in such cases will also be possible.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest concerning this study.

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