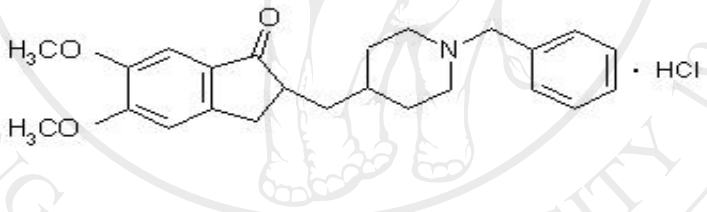
LITERATURE REVIEW

Physical and chemical properties

The chemical name of donepezil hydrochloride is (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride (14, 15).

The empirical formula of donepezil hydrochloride is $C_{24}H_{29}NO_3HCl$ (chemical structure shown below) and a molecular weight of 415.96. Donepezil HCl is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane (14, 15).



The chemical structure of donepezil hydrochloride

Mechanism of action

Donepezil HCl is a reversible inhibitor of the enzyme AChE and the postulated therapeutic effect is by enhancing cholinergic function, accomplished by increasing the concentration of ACh through reversible inhibition of its hydrolysis by AChE (14,15).

Pharmacokinetics

Absorption

Donepezil is slowly absorbed from the GI tract with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 h (10, 15-20). Its pharmacokinetics are linear over a dose range of 1-10 mg given once daily (21, 22).

Neither food nor time of administration influences the rate or extent of absorption of donepezil HCl tablets (21,22).

Distribution

Approximately 96% of donepezil is bound to human plasma proteins, mainly albumin (about 75%) and alpha 1-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL (15, 21, 22). Donepezil accumulates in plasma by 4-7 folds and steady-state is reached within 15 days (15, 21, 22). The steady state volume of distribution is 12 L/kg (15, 21, 22).

Metabolism and excretion

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified (10, 15-20). The elimination half-life($T_{1/2}$) of donepezil is about 70 h and the mean apparent plasma clearance (CL/F) is 0.13 L/h/kg (10, 15-20). Donepezil is metabolized by CYP450 iso-enzymes 2D6 and 3A4 and undergoes glucuronidation (15, 21, 22). Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as percent of the administered dose, is present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and is found in plasma at concentrations equal to about 20% of donepezil (23). Approximately 57% and 15% of the total radioactivity is recovered in urine and feces, respectively, over a period of 10 days, while 28% remains unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. (23).

Dosage and administration

The dosages of donepezil HCl shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day (15, 21, 22). The higher dose of 10 mg does not provide a statistical significantly greater clinical benefit than the 5-mg dose (15, 21, 22). There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials that a daily dose of 10 mg of donepezil HCl might provide additional benefit for some patients (15, 21, 22). Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference (15, 21, 22). Evidence from the controlled trials indicates that the 10-mg dose, with a one week titration, is likely to be associated with a higher incidence

of cholinergic adverse events than the 5-mg dose (15, 21, 22). In open-label trials using a 6-week titration, the frequency of these same adverse events is similar between the 5-mg and 10-mg dose groups (15, 21, 22). Therefore, because steady-state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4-6 weeks (21, 22)

Drug interactions

Since donepezil is metabolized by CYP2D6 and CYP3A4, there is a potential for interactions with substrates, inducers and inhibitors of these iso-enzymes (15, 21, 22). Inhibitors of CYP2D6 and CYP3A4 iso-enzymes have been shown to inhibit the metabolism of donepezil in vitro and inducers of these iso-enzyme systems may increase the rate of elimination of donepezil (21, 22). However, in vitro studies have shown that donepezil's affinity for these enzymes is low (21, 22). Co-administration of donepezil 5 mg/day and cimethidine 800 mg/day for 7 days results in approximately 10% increase in donepezil maximum plasma concentration (C_{max}) and area under the concentration time curve (AUC) (24). The pharmacokinetic profile of 5 mg/day donepezil is significantly altered with 6 days of ketoconazole co-administered at 200 mg/day (25). No significant interactions have been identified in studies evaluating donepezil co-administration with warfarin, digoxin, theophylline, risperidone and thioridazine (26, 27, 28).

Adverse effects

The most common adverse effects reported in patients taking donepezil are nausea, vomiting, diarrhea, gastric upset, dizziness, muscle cramps, fatigue, anorexia, and headache (15). These adverse effects appear more frequently with the 10 mg/day dose than with the 5 mg/day dose and are often transient of mild to moderate intensity and are related to the increased cholinergic activity of donepezil (10, 12). Many of the adverse reactions reported in clinical trials are transient and often resolved spontaneously with continued donepezil therapy (10, 12). Cardiovascular effects reported with donepezil, occurring in at least 1% of patients include hypertension, vasodilatation, atrail fibrillation, hot flashes and hypotension (15, 22). Bradycardia and syncope have also occurred during treatment in some patients with AD (15, 22).

In addition, overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions (10, 15). Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved (10). Tertiary anticholinergics such as atropine may be used as an antidote for donepezil (10).

Precautions and contraindications

Donepezil is contraindicated in patients who are hypersensitive to the drug or to other piperidine derivatives (15,22). No dosage adjustments appear to be necessary in the elderly or in patients with renal disease (13, 15, 22). In patients with hepatic disease, a study comparing 10 patients with stable alcoholic cirrhosis to 10 healthy age and sex-matched subjects showed a 20% decrease in the clearance of donepezil in patients with cirrhosis (15, 22, 29).