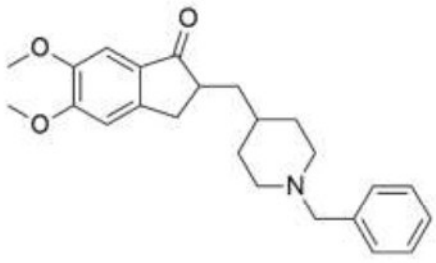
2. Drug Profile

2.1 Introduction

Donepezil is a synthesized small molecule, pipiderine-derived and reversible acetyl-cholinesterase inhibitor approved by the United States Food and Drug Administration (US-FDA) for the symptomatic treatment of AD [1,2]. The first class of drugs approved for the symptomatic treatment of Alzheimer's type of dementia are acetyl-cholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine) [3–5]. Eisai received approval from the US-FDA in the year 1996 for donepezil under the brand name of Aricept, it is co-marketed with Pfizer. Donepezil is the most widely used drug molecule in this class which has proven its efficacy over patients at stages of AD such as mild, moderate and severe conditions [6–8]. The primary pharmacological action of donepezil is to trigger central cholinergic neurotransmitters by inhibiting acetyl-cholinesterase enzyme [8,9]. However, it has been reported for potential efficacy over the amyloid clearance and inhibiting glutamate excitotoxicity which is directly related to the pathophysiology of AD [10]. Moreover, it also used for the improvement of neurocognitive function in the patients received with radiation therapy for brain metastases or brain tumors and in opioid treatment of cancer pain to reduce sedation [11].

2.2 Drug properties

General Name	:	Donepezil
IUPAC Name	:	2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one
CAS registry number	:	120011-70-3
Empirical Formula	:	$C_{24}H_{29}NO_3$
Structure	:	
Molecular weight	:	379.2 g/mol (base) 415.2 g/mol (hydrochloride salt)
Therapeutic class	:	Anti-Alzheimer's
Appearance	:	White to off-white crystalline powder

Solubility	:	It is less soluble in water (base), but its HCl salt is very soluble in water
Melting point	:	220 ºC (base)
pKa	:	8.9
Partition coefficient (Log P)	:	4.7
BCS Classification	:	Class I
Chirality	:	Racemic mixture
Proprietary names	:	Aricept, Aricept ODT (Eisai Co., Ltd.)
Marketed as	:	5mg, 10mg, 23mg tablets (film-coated and orally disintegrating)

2.3 Therapeutic indications and dosage

Donepezil tablets are used for the symptomatic treatment of AD and its therapeutic efficacy has been established in the patients at all stages of AD. It has been reported that, this molecule has contraindications for the patients with hypersensitivity due to its piperidine derivative [1]. Moreover, cholinesterase inhibitors exhibit vagotonic effects in the atrioventricular and sinoatrial nodes that might lead to heart block or bradycardia [12]. The primary mechanism of action is to inhibit cholinesterase enzyme which will increase gastric acid secretion thereby promotes the risk for developing ulcers, gastric irritation, gastrointestinal bleeding, nausea, diarrhea etc. These side effects appear more frequently in case of higher dosage (10mg/day or 23mg/day) rather than lower dosage (5mg/day).

2.4 Mechanism of action

Donepezil is a chemically synthesized small molecule, piperidine derivative and an acetylcholinesterase inhibitor with neuroprotective activity. Acetylcholinesterase is an enzyme which degrades acetylcholine released from the presynaptic neuron. Donepezil is an acetylcholinesterase inhibitor, which blocks the hydrolysis of neurotransmitter acetylcholine and thereby increases its neurocognitive activity. It has been reported that, the activity with respect to acetylcholinesterase inhibition is more specific in the brain for this molecule [8,13]. Moreover, it shows enhanced neuroprotective property by upregulating the nicotinic receptors particularly in cortical neurons of the brain. It also slows down the fast-transient potassium currents, rectifier potassium currents and inhibits voltage-activated sodium currents, but unfortunately this action has no contribution to the clinical effects [8].

2.5 Pharmacokinetics

Donepezil displays complete absorption with the relative bioavailability of about 100%. It follows a linear pharmacokinetic profile on oral administration with a daily unit oral dose range of 1 to 10 mg. The peak plasma concentration was obtained in 3-4 h and previous reports have shown that neither the food consumed or the time of administration of donepezil affected the extent or the rate of absorption. The mean apparent plasma clearance of the molecule was 0.13 L/h per kg body weight with its elimination half-life about 70 h [1,14]. This molecule is capable of accumulation in the plasma by over 4 to 7 times after multiple dose administration and the steady state concentration of the same will reach after 15 days. The drug has exhibited extensive distribution to different organs of the body including the brain. This was confirmed by the steady state volume of distribution being 12 L per kg body weight. Although, research work has indicated that the mean cerebral spinal fluid concentration is about 15.7% of the mean plasma concentration. Furthermore, albumins and alpha-acid glycoprotein are the major proteins found in human plasma to show extensive binding (96%) with donepezil [1].

The drug undergoes metabolism via the action of CYP 450 isoenzymes 2D6 and 3A4 and is subjected to glucuronidation reaction. These metabolic pathways are extensive in nature yielding four primary metabolites, of which two are active. Other minor metabolites may also be formed but they have not yet been identified. Donepezil is later excreted in an intact form via the urinary route. On administration of ^{14}C-labeled donepezil, the radioactivity results exhibited the existence of intact donepezil (53%) and 11% of the molecule was 6-O-desmethyl donepezil that is an active metabolite known to be an acetyl-cholinesterase inhibitor, to the magnitude as that of the parent molecule in vitro. Across a period of 10 days, an estimate of 57% of total radioactivity was found from urine while 15% was in feces. Moreover, 28% of the total radioactivity was unrecovered and 17% of the administered dose was recovered in the unchanged form in urine [2,7].

2.5.1 Special population

(a) Hepatic disease

Liver is the most important site of metabolism for donepezil. So, patients suffering from hepatic diseases might showcase a modification in its pharmacokinetic parameters. In a research work by Tiseo *et al.,* on administration of 5 mg dose via the oral route, the maximum plasma concentration was found to be 37.5% higher in patients afflicted with liver ailments as compared to healthy controls. In another study, there was an improvement in particular pharmacokinetic parameters

like area under the curve (AUC), C_{max}, Css and half-life when 5 mg/kg dose was administered to a small group of patients having mild-to-moderate liver issues and healthy volunteers across a period of 4 weeks [2,14].

(b) Renal disease

Similar pharmacokinetic parameters and profiles at dose of 5 mg in healthy controls and patients of moderate-to-severe renal diseased condition were noticed. Besides, both the groups showed similar steady-state pharmacokinetics and pharmacodynamics (red blood cell acetylcholinesterase inhibition) profiles and insignificant distinction in side effects for a multiple dosing study across a month [14].

2.6 Pharmacodynamics

Loss of cholinergic cells in the basal portion of forebrain and uniform decrease in all the brain biomarkers except butylcholinesterase was reported in AD patients. This holds at least some evidence that, the behavioral and cognitive symptoms are regulated through cholinergic hypothesis. Donepezil exhibits its enzyme inhibiting property by strongly binding to anionic sites present over the acetylcholinesterase enzyme. Hence, it shows strong acetylcholinesterase inhibitory action, rather than butyrylcholinesterase inhibition. Moreover, the binding ratio of donepezil over acetylcholinesterase to butyrylcholinesterase is about 1265:1. The key pharmacodynamic action of donepezil is acetylcholinesterase inhibition that is highly selective to brain tissue rather than other acetyl cholinesterase inhibitors. Due to its short binding time over acetylcholinesterase enzyme, it is classified under reversible inhibitor category [15].

2.6 Drug-drug interactions

AD patients suffer from multiple comorbidities and hence are subjected to a cocktail of drugs. Hence the phenomenon of drug interactions is a vital consideration in the case of donepezil. Studies have been conducted on the possible pharmacokinetic interactions with atypical antipsychotics, selective serotonin reuptake inhibitor (SSRI) antidepressants, memantine etc. The results of these studies displayed an absence of adverse reactions or any clinically significant pharmacokinetic interactions [2,16].

2.7 Marketed formulations

Donepezil is commercially available in the different dosage forms and strengths mentioned below;

- ARICEPT® is a film-coated tablet with a dose of 5 or 10 mg of donepezil hydrochloride

- ARICEPT® ODT (oral disintegrating tablet) having a dose of 5 or 10 mg of donepezil hydrochloride
- ARICEPT® SR film-coated sustained release tablets with a dose of 23 mg of donepezil hydrochloride

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