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Research Article

A New Combinational Therapy in the Treatment of Alzheimer's Disease

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ABSTRACT
Memantine hydrochloride extended- release and donepezil hydrochloride (MH/DH), is a newly FDA approved combination drug as of the 23rd of December 2014 for use in the treatment of moderate to severe Alzheimer's disease. Alzheimer's disease affects an estimated 5.4 million Americans, 200 000 of whom are younger than 65 years. The MH/DH combination is a once a day capsule and is not intended to slow neurodegeneration in patients suffering from Alzheimer's disease.

Keywords: New Drug Update, Alzheimer's disease, Memantine Hydrochloride, Donepezil Hydrochloride.

INTRODUCTION

Dementia is a term used to describe observable decline in mental abilities, characterized by deterioration of mental function in its cognitive, emotional and conative aspects[1]. Alzheimer's disease is a progressive and possibly eventual fatal form of dementia[2]. Alzheimer's is also the most common form of dementia. It accounts for sixty to eighty percent (60- 80%) of dementia cases[3,4]. In a prospective analysis of risk factors for Alzheimer's disease done in Canada, it was found that increasing age, fewer years of education, and the apolipoprotein Ee4 allele made significant contributions to the development of Alzheimer's. According to this study, there were also no statistically significant association with family history of dementia, sex, history of depression, estrogen replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease or stroke[5].

Physiological changes of Alzheimer's disease were found to include intracellular neurofibrillary tangles (NFTs), extracellular amyloid plaques in the cortex and medial temporal lobe, and degeneration of neurons and synapses and cortical atrophy (Figure 1). It is noted that the density of NFTs correlates with the severity of dementia[2]. These changes could be due to β- amyloid protein aggregation which can lead to plaque formation; hyperphosphorylation of tau protein which causes NFTs; synaptic failure and depletion of neurotrophin and neurotransmitters; mitochondrial dysfunction; and oxidative stress[2].

Alzheimer's disease can be classified into four (4) main stages[6,7]:

Preclinical
Mild
Moderate
Severe

Preclinical Alzheimer's disease include physiological changes in the brain some ten to twenty (10- 20) years before any visible signs are observed. Memory loss is usually the first visible sign and is the main feature of amnestic mild cognitive impairment (MCI). A person suffering from preclinical Alzheimer's disease may produce normal and acceptable results when physically and mentally tested[6]. Figure 2 shows the physiological structure of the brain of a person diagnosed with preclinical Alzheimer's disease.

Mild Alzheimer's disease occurs when the cerebral cortex is affected. This leads to memory loss, confusion, taking longer to accomplish tasks, compromised/ bad decisions, loss of spontaneity and sense of initiative, and mood and personality changes, including increased anxiety. The unfortunate circumstance of this is that these early signs are commonly misconstrued for the normal signs of aging. As such, the increasing number of plaques and tangles which damages the brain may not be tested for and the disease may be left to develop[6]. Figure 3 indicates the physiological changes of the structure of the brain in someone diagnosed with mild Alzheimer's disease.

Moderate Alzheimer's disease is indicated by further damage to the cerebral cortex affecting language, reasoning, sensory processing, and conscious thought. Behavioral problems such as wandering, tearfulness, restlessness and agitation may also occur. Hallucinations, delusions, paranoia and loss of impulse control are all symptoms of moderate Alzheimer's disease[6].

Severe Alzheimer's stage is characterized by widespread

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plaque and tangles throughout the brain, as well as areas of the brain which have atrophied. Patients may become completely dependent on others for care, and experience weight loss, seizures, skin infections, difficulty swallowing, increased sleep, and lack of bladder and bowel control. Patients lose the ability to communicate and recollect[6]. Figure 4 shows the structural changes of the brain of a person diagnosed with severe Alzheimer's disease.

The primary goal of treatment of Alzheimer's disease is to maintain functioning for as long as possible whilst the secondary goal is to treat the psychiatric and behavioral symptoms. Nonpharmacological therapy does not currently exist for this disease, however, pharmacological therapy of cognitive symptoms include cholinesterase (AChE) inhibitors, memantine[8], and low dose aspirin for patients with significant brain vascular disease[6]. Pharmacological therapy of noncognitive symptoms include cholinesterase (AChE) inhibitors and memantine, antipsychotics, and antidepressants[6].

Indications and Usage

The MH/DH combination is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on [9] [10]:

• Memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg.

• Memantine hydrochloride (5 mg twice daily or 14 mg extended-release once daily) and donepezil hydrochloride 10 mg (in patients with severe renal impairment).

Patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg can be switched to the MH/DH combination 28 mg/10 mg, taken once daily in the evening. Patient should start the MH/DH combination the day following the last dose of memantine hydrochloride and donepezil hydrochloride administered separately. If a patient misses a single dose of the MH/DH combination, the next dose should be taken as scheduled, without doubling up the dose[10].

It should be noted that the MH/DH combination can be taken with or without food. The capsules can be taken intact or may be opened, sprinkled on applesauce, and swallowed without chewing. The entire contents of each capsule should be consumed; the dose should not be divided. Except when opened and sprinkled on applesauce, as described above, the MH/DH combination capsules should be swallowed whole and should not be divided, chewed, or crushed[10].

Description of Drug

The MH/DH combination contains a fixed amount of 28mg or 14mg memantine, an orally active N-methyl-D-asparate (NMDA) receptor antagonist, and 10mg donepezil, a reversible inhibitor of the enzyme actelycholinesterase[10]. The chemical name for memantine hydrochloride is 1-amino-3, 5- dimethyladamantane hydrochloride and it possesses the structural formula indicated in Figure 5.

Memantine hydrochloride has a molecular weight of 215.76 and is molecularly expressed[10] as $C_{12}H_{21}N$•Hydrochloride. It occurs as a fine white to off-white powder.

Donepezil hydrochloride is chemically expressed as 2, 3-dihydro- 5, 6-dimethoxy-2- [[1- (phenylmethyl)-4-piperidinyl] methyl]-1H- inden-1- one hydrochloride and structurally occurs as indicated in Figure 6.

Molecularly, donepezil is also known as $C_{24}H_{29}NO_3$•hydrochloride with a molecular weight of 415.96. Donepezil hydrochloride occurs in the form of a white crystalline powder[10].

Clinical Pharmacology

Mechanism of action

The MH/DH combination, as previously mentioned, contains two active ingredients which are usually combined to treat the symptoms of Alzheimer's disease. Memantine, an NMDA receptor agonist which binds preferentially to the NDMA receptor- operated cation channels. However, there is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease[10]. Donepezil is a cholinesterase inhibitor. It increases the concentration of acetylcholine in the central nervous system through reversible inhibition of its hydrolysis by acetylcholinesterase. However, there lacks evidence that neither memantine nor donepezil act to prevent or slow neurodegeneration in patients with Alzheimer's disease[10].

Pharmacokinetics

The MH/DH combination was bioequivalent to co-administration of individual memantine hydrochloride extended release and donepezil hydrochloride[10]. The Area under the Curve (AUC) and Maximum Concentration (C_{max}) were found to be similar in both fasting and fed states, when the MH/DH combination was administered[10]. Memantine is well absorbed orally and exhibits linear pharmacokinetics over the therapeutic dosage range. It is excreted predominantly unchanged in urine and has a terminal half- life of about sixty to eighty (60-80) hours. About forty- eight percent (48%) of administered drug is excreted unchanged while the remainder is converted primarily to three (3) polar metabolites which possess NMDA receptor antagonist activity: the N- glucuronide conjugate, 6- hydroxy memantine, and 1- nitroso-deaminated memantine[10]. After multiple dose administration of memantine, peak concentrations occurred around nine to twelve (9-12) hours post dose. After a single dose of memantine, there was no significant difference shown in C_{max} nor AUC in both fed and fasting states, however, peak plasma concentrations did vary at eighteen (18) hours with food, whereas without food was twenty- five (25) hours[10]. The mean volume of distribution for memantine was found to be nine to eleven (9-11) L/Kg, with low (45%) plasma protein binding. It undergoes partial hepatic metabolism though the CYP450 enzyme system does not play a significant role[10].

Donepezil exhibits linear pharmacokinetics for a dose range of one to ten (1- 10) mg administered once daily. The presence of food in the system does not affect absorption. It is absorbed with a relative bioavailability of 100% and reaches peak plasma concentrations in three to four (3-4) hours[10]. The elimination half- life was determined to be

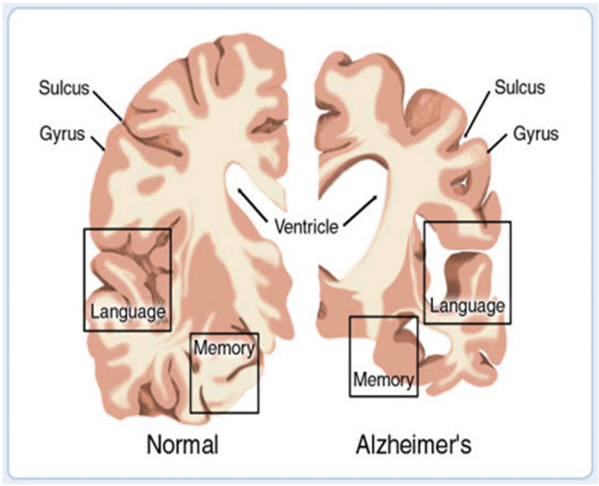

Figure 1: Physiological structures of a normal and Alzheimer's brain[7]

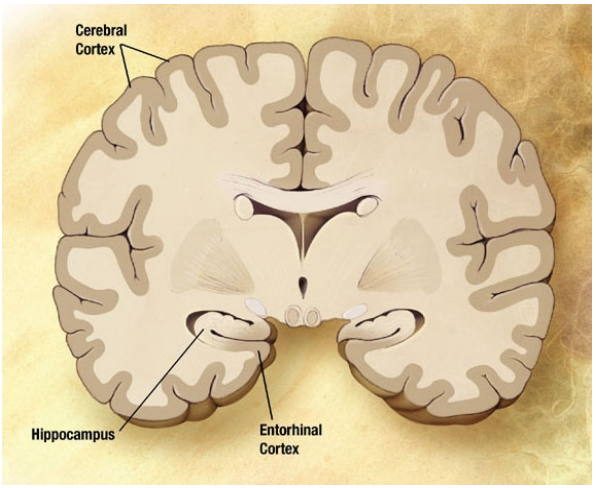

Figure 2: Physiological structure of the brain of a person diagnosed with Preclinical Alzheimer's Disease[6] Image Courtesy NIH

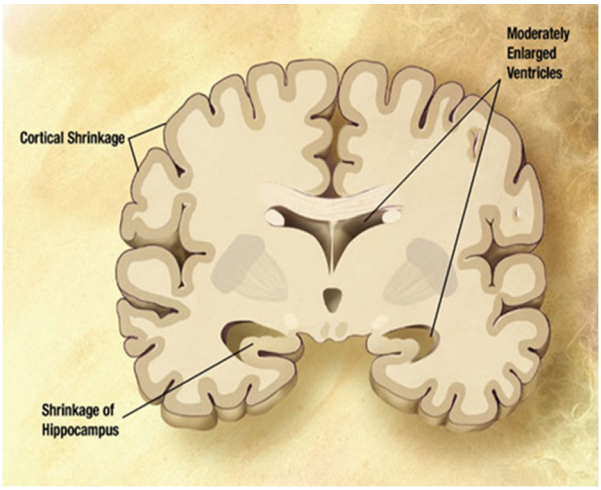

Figure 3: Physiological Structure of the Brain of a Person Diagnosed with Mild Alzheimer's Disease[6] Image Courtesy NIH

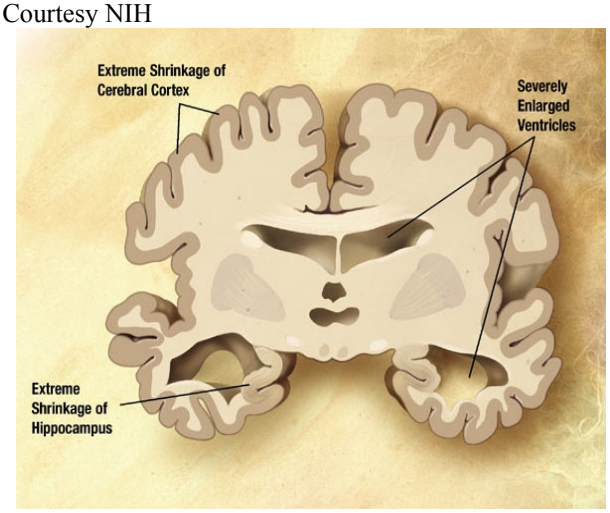

Figure 4: Physiological Structure of the Brain of a Person Diagnosed with Severe Alzheimer's Disease[6] Image Courtesy NIH

approximately seventy (70) hours and the mean apparent plasma clearance was found to be 0.13- 0.19 L/hr/Kg. Upon multiple doses of donepezil, accumulates in plasma by four to seven (4-7) fold and steady state is achieved within fifteen (15) days. The steady-state volume of distribution is twelve to sixteen (12– 16) L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (approx. 75%) and alpha-1-acid glycoprotein (approx. 21%) over the concentration range of 2-1000 ng/mL. Donepezil is metabolized to four (4) major metabolites, two (2) of which are known to be active, and a number of minor metabolites[10]. Donepezil is also excreted unchanged in the urine. There was a noted relationship between clearance of donepezil and body weight. Over the range of body weight from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/h for 70 kg individuals[10].

Special Population

Pregnancy

Pregnancy Category C: There are no adequate and/or well-controlled studies of memantine hydrochloride and donepezil hydrochloride in pregnant women. The MH/DH combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus[10].

Nursing Mothers

It is not known whether memantine or donepezil are excreted in human milk. Caution should be exercised when administered to a nursing woman[10].

Pediatric Use

Safety and efficacy of the MH/DH combination in pediatric patients have not been established[10].

Renal Impairment

A dosage reduction is recommended in patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment[10].

Geriatric Use

There were no clinically meaningful differences in most adverse events reported by patients ≥ 65 years old and < 65 years old[10].

Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The MH/DH combination has not been studied in patients with severe hepatic impairment[10].

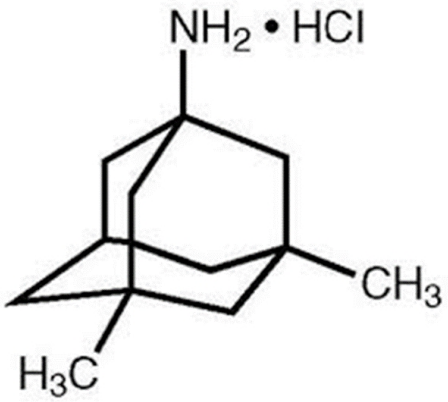

Figure 5: Structural Formula of Memantine Hydrochloride[10]

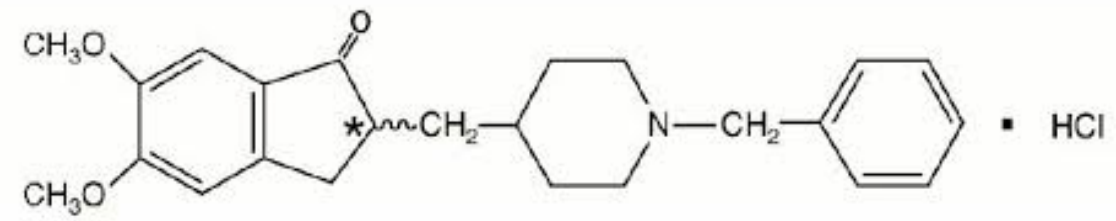

Figure 6: Structural Formula of Donepezil Hydrochloride[10]

Clinical Trials

The efficacy of the MH/DH combination for the treatment of moderate to severe Alzheimer's disease was established by demonstrating the bioequivalence of the MH/DH combination with co-administered memantine hydrochloride extended-release and donepezil hydrochloride[10]. The memantine hydrochloride studies were based on results of a double- blind, placebo-controlled trial, while the studies of donepezil were based on two double- blind, placebo- controlled trials[10].

24-week Study of Memantine Hydrochloride Extended-Release[10]

This was a randomized, double-blind clinical investigation in 677 outpatients with moderate to severe Alzheimer's disease (diagnosed by DSM-IV criteria and NINCDS-ADRDA criteria for AD with a Mini Mental State Examination [MMSE] score ≥ 3 and ≤ 14 at Screening and Baseline) receiving acetylcholinesterase inhibitor (AChEI) therapy at a stable dose for 3 months prior to screening. Approximately 68% of the patients received donepezil as the AChEI. The mean age of patients participating in this trial was 76.5 years, with a range of 49-97 years. Approximately 72% of patients were female and 94% were Caucasian. In this study, 677 patients were randomized to one of the following 2 treatments: memantine hydrochloride extended-release 28 mg/day or placebo, while still receiving an AChEI (either donepezil, galantamine, or rivastigmine). Using an LOCF analysis, memantine hydrochloride extended-release 28 mg/AChEI treatment was found to be statistically significantly superior to placebo/AChEI. It was also determined that both patients assigned to memantine hydrochloride extended-release 28 mg/AChEI and placebo/AChEI have a wide range of responses, but that the memantine hydrochloride extended-release 28 mg/AChEI group is more likely to show an improvement or a smaller decline.

6-Month Study of Donepezil Hydrochloride[10]

This was a randomized, double-blind, placebo-controlled clinical study conducted in Sweden in patients with probable or possible Alzheimer's disease diagnosed by NINCDS-ADRDA and DSMIV criteria, MMSE: range of 1-10. Two hundred and forty eight (248) patients with severe Alzheimer's disease were randomized to donepezil hydrochloride or placebo. For patients randomized to donepezil hydrochloride, treatment was initiated at 5 mg once daily for 28 days and then increased to 10 mg once daily. At the end of the 6 month treatment period, 90.5% of the donepezil hydrochloride treated patients were receiving the 10 mg/day dose. The mean age of patients was 84.9 years, with a range of 59 to 99. Approximately 77% of patients were women, and 23% were men. Almost all patients were Caucasian. Probable AD was diagnosed in the majority of the patients (83.6% of donepezil hydrochloride treated patients and 84.2% of placebo treated patients). Donepezil hydrochloride treatment was found to be statistically significantly superior to placebo and that the donepezil hydrochloride group is more likely to show a greater improvement in cognitive performance. While both patients assigned to donepezil hydrochloride and placebo have a wide range of responses, results indicated that the donepezil hydrochloride group is more likely to show a smaller decline or an improvement.

24-Week Study of Donepezil Hydrochloride[10]

In a randomized, double-blind, placebo-controlled study conducted in Japan, 325 patients with severe Alzheimer's disease received doses of 5 mg/day or 10 mg/day of donepezil hydrochloride, administered once daily, or placebo. Patients randomized to treatment with donepezil hydrochloride were to achieve their assigned doses by titration, beginning at 3 mg/day, and extending over a

maximum of 6 weeks. Two hundred and forty eight (248) patients completed the study, with similar proportions of patients completing the study in each treatment group. The primary efficacy measures for this study were the SIB and CIBIC-plus. At 24 weeks of treatment, statistically significant treatment differences were observed between the 10 mg/day dose of donepezil hydrochloride and placebo on both the SIB and CIBIC-plus. The 5 mg/day dose of donepezil hydrochloride showed a statistically significant superiority to placebo on the SIB, but not on the CIBIC-plus.

Adverse Effects

The MH/DH combination may cause serious side effects, including[10]

• Muscle problems if you need anesthesia

• Slow heartbeat and fainting. This happens more often in people with heart problems.

• More stomach acid. This raises the chance of ulcers and bleeding especially when taking the MH/DH combination. The risk is higher for patients who had ulcers, or take aspirin or other NSAIDs.

• Nausea and vomiting

• Difficulty passing urine

• Seizures

• Worsening of lung problems in people with asthma or other lung disease.

The following are serious adverse reactions to the MH/DH combination[10]

• Cardiovascular Conditions

• Peptic Ulcer Disease and Gastrointestinal Bleeding

• Nausea and Vomiting

• Genitourinary Conditions

• Seizures

• Pulmonary Conditions

Warnings and Precautions

Anesthesia

Donepezil hydrochloride, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia[10].

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil hydrochloride[10].

Peptic Ulcer Disease and Gastrointestinal Bleeding

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Clinical studies of donepezil hydrochloride in a dose of 5 mg/day to 10 mg/day have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Patients treated with the MH/DH combination should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs)[10].

Nausea and Vomiting

Donepezil hydrochloride, when initiated, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil hydrochloride, patients should be observed closely at the initiation of treatment[10].

Genitourinary Conditions

Although not observed in clinical trials of donepezil hydrochloride, cholinomimetics may cause bladder outflow obstruction. Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine[10].

Seizures

Cholinomimetics, including donepezil hydrochloride, are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease[10].

Pulmonary Conditions

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease[10].

Contraindications

The MH/DH combination is contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation[10].

Drug Interactions

Use of Memantine with Drugs That Make the Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse reactions. Urine pH is altered by diet, drugs (e.g., carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g., renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions[10].

Use of Memantine with Other N-methyl-D-aspartate (NMDA) Antagonists

The combined use of memantine hydrochloride with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution[10].

Effect of Other Drugs on the Metabolism of Donepezil

Inhibitors of CYP3A4 (e.g., ketoconazole) and CYP2D6 (e.g., quinidine), inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. Inducers of CYP3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil[10].

Use of Donepezil with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors, including donepezil hydrochloride, have the potential to interfere with the activity of anticholinergic medications[10].

Use of Donepezil with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors, including donepezil hydrochloride, are given concurrently with succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists such as bethanechol[10].

CONCLUSION

A cholinesterase (AChE) inhibitor and memantine combination is commonly prescribed for the treatment of Alzheimer's disease. This establishes the basis for the importance of a combination drug of both donepezil, a cholinesterase inhibitor, and memantine. The MH/DH combination is also ideal in that it is a once daily dosage, for use in Alzheimer's disease, a disease which is associated with both noncompliance and memory loss. The combination holds no more adverse effects or limitations than the individual dosing of donepezil and memantine and with time and more clinical trials, this MH/DH combination can prove promising for the future in Alzheimer's treatment and it is certainly not a combination to be forgotten.

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