Chapter 4
The Use of Esterase Inhibitors

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4.1 Galantamine

4.1.1 A Big Picture of Galantamine

Galantamine is sold as galantamine hydrobromide tablets (4 mg, 8 mg, and 12 mg) or galantamine hydrobromide ER (extended released) capsules (8 mg, 16 mg, and 24 mg). Galantamine and galantamine ER are not equivalents – the doses are

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different and the change from one to the other should be done with care. The cholinesterase inhibitor galantamine is used as a treatment for mild-to-moderate Alzheimer's disease. It has a dual mechanism of action, being a specific, competitive, and reversible acetylcholinesterase inhibitor, and it is also an allosteric modulator at nicotinic cholinergic receptor sites, potentiating cholinergic nicotinic neurotransmission. A small number of early studies showed mild cognitive and global benefits for patients with Alzheimer's disease, and several posterior multicenter clinical trials have been published with positive findings. Galantamine has a large volume clearance, low plasma protein binding, and a high bioavailability. Short-term, double-blind, placebo-controlled studies have shown that treatment with galantamine produces small improvements on cognitive tests and global measures of change in selected patients with mild to moderately severe Alzheimer's disease and that a dose of 16–24 mg/day appears to be the most efficacious and is the maintenance dose range in most countries. The magnitude of the treatment effect is similar to that of other cholinesterase inhibitors. Adverse events experienced by patients treated with galantamine are usually mild and gastrointestinal and may improve with dose reduction [1–4, 6].

4.1.2 Protocols with Galantamine

Benefits to cognitive and affective functions were greater in patients with Alzheimer's disease who receive the galantamine plus ambulatory cognitive rehabilitation, including a set of physical therapy, occupational therapy, and speech therapy for 1–2 h once or twice a week, than in those receiving galantamine therapy only [5].

A study showed that doses of galantamine of 16 mg/day were best tolerated in the single trial where medication was titrated over 4-week periods (Table 4.1), and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably the most preferable initially [1, 5, 9].

According to several studies, the donepezil-memantine combination seems better than either drug alone for cognition in Alzheimer's disease or at least at Alzheimer's disease prodrome.

The doses used were:

- Galantamine 8 mg + memantine 10 mg.
- After receiving galantamine for 6 months, the patients received memantine 5–20 mg as well for 12 weeks, in an average daily dose of donepezil 7 ± 2.5 mg, while memantine was 16.7 ± 5.2 mg (average of 2 groups); this last study concluded galantamine + memantine is better than donepezil + memantine [13].

Table 4.1 Dosage of galantamine

	Starting dose	Maintenance dose	Increasing dose after maintenance	Observations
Galantamine	4 mg twice daily	Increase to initial maintenance dosage of 8 mg twice daily after a minimum of 4 weeks	Based on clinical benefit and tolerability, dosage may be increased to 12 mg twice daily after a minimum of 4 weeks at 8 mg twice daily	Take with meals and ensure adequate fluid intake during treatment Hepatic impairment: should not exceed 16 mg/day for moderate hepatic impairment. Galantamine and galantamine ER should not be used by patients with severe hepatic impairment Renal impairment: should not exceed 16 mg/day for creatinine clearance 9 to 59 mL/min. Galantamine and galantamine ER should not be used by patients with creatinine clearance less than 9 mL/min
Galantamine ER	8 mg/day in the morning	Increase to initial maintenance dose of 16 mg/day after a minimum of 4 weeks	Based on clinical benefit and tolerability, dosage may be increased to 24 mg/day after a minimum of 4 weeks at 16 mg/day	

4.1.3 Drug Interactions Involving Galantamine

Galantamine can interfere with the activity of anticholinergic medications [7]. Synergistic effect is observed when given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists [7].

Research was performed to find potential drug interactions with galantamine, and it was described that the most frequent pharmacodynamics interaction found was the interaction between cholinesterase inhibitors and bradycardic drugs (β-blockers, digoxin, amiodarone, calcium channel antagonists). A combination of atropinic drugs and anticholinergic medications leads to pharmacological antagonism and should not be administered together. Urinary incontinence is a well-known adverse effect of anticholinergic medications, and it counters the effects of atropinic drugs used to treat urinary incontinence. Atropinic drugs aggravate cognitive deficits (memory disturbances, confusion, and disorientation), can cause behavioral disturbances, and decrease cognitive performance in elderly patients due to their effects on the central nervous system. Sixty to 70% of the drug-drug interactions involving anticholinergic medications are pharmacodynamics [8].

4.2 Donepezil

4.2.1 A Big Picture of Donepezil

The piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase, donepezil hydrochloride, is sold as 5 and 10 mg tablets and also as 5 and 10 mg rapidly disintegrating tablets (RDT), and it is used for the symptomatic treatment of patients with mild, moderate, and severe dementia of the Alzheimer's type [9].

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate, such as bradycardia. The potential for this action may be significant to patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. Caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes can be associated with donepezil. It is recommended that donepezil do not be used in patients with cardiac conduction abnormalities (except for right bundle branch block), including patients presenting sick sinus syndrome and those with unexplained syncopal episodes [9].

Cholinesterase inhibitors can increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, such as those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs, including high doses of acetylsalicylic acid, should be monitored for symptoms of active or occult gastrointestinal bleeding. This drug can cause nausea and vomiting, being more frequent with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks, and have resolved during continued use of ARICEPT (see Sect. 4.4.5). Treatment with the 5 mg/day dose for 4–6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance [9].

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma maximum concentrations (Cmax) about 3 to 4 hours after dose administration. Plasma concentrations and area under the curve (AUC) rise in proportion to the dose administered within the 1 to 10 mg dose range studied (Table 4.2). The terminal disposition half-life (t1/2) is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple-dose administration, donepezil accumulates in plasma by four- to sevenfold; the steady state is reached within 15 days [9].

4.2.2 Protocols with Donepezil

Cognitive function shows improvement after increasing the dose of donepezil, so it is suggested that the dosage of this drug be adjusted based on the overall severity of Alzheimer's disease as well as the progression of cognitive dysfunction [12].

Table 4.2 Dosage of donepezil as a single agent

Drug	Starting dose	Maintenance dose	Observations
Donepezil or donepezil RDT	5 mg once daily	Increase only after 4–6 weeks doing the starting dose to decrease the incidence of adverse reactions and to allow plasma levels to reach steady state; 10 mg daily may be considered after that, and it is the maximum dose	It can be taken in the morning or evening, with or without food. Donepezil tablets should be swallowed whole with water, and donepezil RDT should be placed on the tongue and allowed to disintegrate before swallowing with water Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects In elderly women of low body weight, the dose should not exceed 5 mg/day since adverse events are more common in low body weight individuals, in patients 85 years old, and in females An initial dose of 1–2 mg IV of atropine with subsequent doses based upon clinical response can be used in case of overdose Hepatic insufficiency: the clearance of donepezil was decreased by 20% in patients with stable alcoholic cirrhosis Renal insufficiency: in four patients with moderate to severe renal impairment (Clcr <22 mL/mln/1.73 m^2), the clearance of donepezil was like that of 4-year-old and sex-matched healthy people [9]

Combination therapy was studied with memantine and donepezil. Tariot et al.'s study involved 404 patients with probable Alzheimer's disease who had received stable doses of donepezil for at least 3 months. They were randomized to receive memantine 10 mg twice daily or placebo. The 24-week study included patients over the age of 50 and with MMSE scores between 5 and 14 and was conducted at 37 US sites. Patients who were randomized to memantine treatment were titrated in 5 mg weekly increments, starting from a 5 mg dose daily to 10 mg twice daily. Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24. The primary efficacy measures were the change from baseline on the SIB and the ADCS-ADL19. Secondary outcome measures included the Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus), the Neuropsychiatric Inventory (NPI), and the Behavioral Rating Scale in Geriatric Patients (BGP). The combination therapy of donepezil and memantine for moderate to severe Alzheimer's disease was most effective in improving cognition, global assessment, activities of daily living, and neuropsychiatric symptoms, and the acceptability was slightly higher than that of donepezil and lower than that of memantine [10, 11].

4.2.3 Drug Interactions Involving Donepezil

Donepezil hydrochloride is about 96% bound to human plasma proteins, being about 75% to albumins and about 21% to alpha-1-acid glycoprotein over the concentration range of 2 to 1000 ng/mL. Donepezil hydrochloride is extensively and slowly metabolized, and it is also excreted in the urine. There are four major metabolites, two of them are known to be active, and there are several minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP450 isoenzymes 2D6 and 3A4, and it undergoes glucuronidation [9].

Donepezil can interfere with the activity of anticholinergic medications [7].

Synergistic effect is observed when given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists [7].

It was described that the most frequent pharmacodynamics interaction found with donepezil was the interaction with bradycardic drugs (β-blockers, digoxin, amiodarone, calcium channel antagonists). A combination of atropinic drugs and anticholinergic medications leads to pharmacological antagonism and should not be administered together. Urinary incontinence is a well-known adverse effect of anticholinergic medications, and it counters the effects of atropinic drugs used to treat urinary incontinence. Atropinic drugs aggravate cognitive deficits (memory disturbances, confusion, and disorientation), can cause behavioral disturbances, and decrease cognitive performance in elderly patients due to its effects on the central nervous system. Sixty to 70% of the drug-drug interactions involving anticholinergic medications are pharmacodynamics [8].

In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes, which, given the therapeutic plasma concentrations of donepezil, indicates little likelihood of interferences; however, it is not known whether this drug has any potential for enzyme induction. Inducers of CYP 2D6 and CYP 3A4, such as phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital, can increase the rate of elimination of donepezil. Pharmacokinetic studies demonstrated that the metabolism of donepezil is not significantly affected by concurrent administration of digoxin or cimetidine [9].

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibited donepezil metabolism in vitro, and a daily dose of 200 mg of ketoconazole can increase plasma concentrations of donepezil (administered 5 mg/day) by about 30–36% [9].

4.3 The Failure of Tacrine

Tacrine was one of the first drugs to be used for Alzheimer's disease, characterized by memory loss, cognitive disorders, and psychic changes. The success achieved by tacrine in treating cognitive and behavioral symptoms was understood as a

confirmation of the cholinergic theory of Alzheimer's disease. However, the effectiveness of tacrine for dementia symptoms remains uncertain. This can be seen in the low amount of prescription for tacrine in countries where it is approved for marketing and the lack of approval from various regulatory authorities in Europe and other countries. The uncertainty regarding the therapeutic results of tacrine may be a consequence of the difficulty in interpreting the results of clinical trials [19].

Tacrine is a drug whose mechanism of action is the inhibition of the enzyme acetylcholinesterase, which is used in the treatment of Alzheimer's dementia and can cause reversible abnormalities in liver enzymes; however, significant hepatotoxicity is uncommon. About half of patients treated with tacrine have liver enzyme abnormalities, and this most often occurs within the first 12 weeks of therapy, which resolves with drug withdrawal or dose adjustment [20].

The acetylcholinesterase (AChE) enzyme has always been considered a highly viable target for symptomatic improvement in Alzheimer's disease (AD), given the recognition of cholinergic deficit as an important, consistent, and early finding in AD. Tacrine, donepezil, rivastigmine, and galantamine have been developed and approved for the symptomatic treatment of AD [21].

Ursodeoxycholic acid reduced tacrine-induced hepatotoxicity (13 mg/kg/day for 105 days) in a pilot study in 14 patients with Alzheimer's disease. A comparative study found that serum alanine transaminase activity in 100 patients who took ursodeoxycholic acid was normal in 93% of cases, compared with 69% of patients who took tacrine alone. Regular monitoring of hepatotoxicity is necessary in patients with Alzheimer's disease where the use of tacrine has been recommended [22].

4.4 Rivastigmine

4.4.1 Pharmacology of Rivastigmine

The therapeutic class of the molecule is rivastigmine tartrate; ENA-713 is a parasympathomimetic agent or selective inhibitor of cerebral cholinesterase. The rivastigmine molecule was developed by Marta Weinstock-Rosin, professor emeritus in the Department of Pharmacology at the Hebrew University of Jerusalem, and sold to Novartis by the university's own technology transfer company, called Yissum, for commercial development. This molecule is a semisynthetic derivative of physostigmine, which is a parasympathomimetic agent of indirect action by inhibiting acetylcholinesterase. It has been available in capsules and liquid formulations since 1997. Rivastigmine was patented in 1985 and entered medical use in 1997. It was approved by the FDA (Food and Drug Administration) in April 2000. In 2006, it became the first globally approved product for the treatment of mild to moderate Alzheimer's disease and for dementias associated with Parkinson's disease [23].

The pharmaceutical forms and dosages currently available are [24]:

- Hard gelatin capsules – 1.5, 3.0, 4.5, and 6.0 mg
- Oral solution – 2 mg/mL
- Transdermal patch (patch): 5 cm^2 with 9 mg, 10 cm^2 with 18 mg, 15 cm^2 with 27 mg, and 20 cm^2 with 36 mg

4.4.2 Clinical Trials

Double-blind, placebo-controlled phase II and phase III efficacy and safety studies were performed with rivastigmine for the treatment of Alzheimer's disease. For these studies, patients with MMSE (Mini-Mental State Examination) were recruited, whose scores were between 10 and 24 points (Alzheimer's mild to moderate/severe). Already in the results of phase II, the studies showed that rivastigmine produced cognitive improvement and, according to the cognitive tests carried out in these studies, the daily activities of the patients had a positive advance. There was a noticeable improvement in the advancement of Alzheimer's disease, and it is important to emphasize that all dosages used produced an overall beneficial effect on the cognition of patients with the active drug. During the studies, some fundamental scales were used to measure this improvement, which are widely used instruments, both in the daily routine of offices and in clinical research [24]:

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is a compilation of tests, which are based on the performance of several relevant cognitive areas of the brain in patients with Alzheimer's disease, such as attention, learning, memory, and language.
- Clinical Interview-Based Impression of Change (CIBIC-Plus) is a clinical assessment of the patient's overall change in the cognitive, behavioral, and performance domains, incorporating separate patient and caregiver views. This comparison is extremely important to assess how the patient sees the reality in which he/she lives.
- Progressive Deterioration Scale (PDS) is an assessment performed only by the caregiver, measuring the patient's ability to perform daily activities, such as personal cleanliness, food, and help with household chores.

Data were collected in this study and started to appear from the 12th week of treatment, about 3 months after use with dosages between 6 and 12 mg. Cognitive improvement in global performance was observed, while patients who used placebo had cognitive worsening and global deterioration on cognitive scales, such as the ADAS-Cog., about 5 points lower than in the rivastigmine group.

Improvements in cognitive functions, such as linguistic ability, memorization, praxis, time, and spatial orientation, had improved performance. An improvement of about 15% was observed in patients who finished the 6-month treatment with

rivastigmine in these items: memorizing words, agitation, crying, delusions, inappropriate actions, hallucinations, episodes of physical/verbal violence, and tearing. Anxiety symptoms and episodes were noted.

Similar studies using cognitive scales were carried out in the patch form [24–29].

4.4.3 Carbamate

Rivastigmine is a selective carbamate-type acetyl and butyrylcholinesterase inhibitor, a parasympathomimetic agent, which facilitates cholinergic neurotransmission by the slow degradation of acetylcholine released by cholinergic neurons that have their functionality preserved, increasing the amount of this neurotransmitter in the synaptic cleft. This action makes rivastigmine have a beneficial effect on cognitive deficits, as demonstrated in the cognitive scales, as it increases the availability of acetylcholine in the cerebral cortex and hippocampus [30].

There is scientific evidence that this inhibition of the cholinesterase enzyme could also decrease the formation of beta-amyloid precursor protein (PAP) and, thus, also of amyloid plaques, which are one of the main pathological characteristics of Alzheimer's disease. An addendum: carbamates, which can also be called urethanes, are organic compounds derived from carbamic acid, nitrogenous, with anticholinesterase action, that is, capable of reversibly inhibiting the action of the enzyme acetylcholinesterase (AChE), responsible for the degradation of acetylcholine, which is a neurotransmitter, making it much more active in synaptic clefts causing cell hyperexcitation [29].

However, as described above in pharmacodynamics, rivastigmine has only a symptomatic effect and does not act on the cause of Alzheimer's disease [24].

4.4.4 Pharmacokinetics

Rivastigmine is rapidly absorbed orally, and plasma concentrations are reached in approximately 1 hour. As a result of the interaction of rivastigmine with its target enzyme, acetylcholinesterase, the increase in bioavailability is about 1.5 times greater than expected with increasing dose. The absolute bioavailability after a 3 mg dose is about 36% ± 13%. Administration of rivastigmine with food delays absorption (tmax) by 90 min, decreases Cmax, and increases AUC (area under the curve) by approximately 30% [24, 30, 31, 33].

However, transdermal absorption (adhesive/patch) is slower. After the first dose, plasma concentrations are observed after a time interval of 30 min to 1 hour after application of the patch. Plasma concentrations increase slowly and, after about 8 hours, reach levels close to the maximum; however, the maximum values (Cmax) are observed later, about 10–16 hours. After reaching the peak, plasma concentrations slowly decrease over the remaining 24 hours. When the old patch is replaced

by the new one, the initial plasma concentrations slowly decrease for approximately 40 minutes on average, until the absorption of the new application becomes faster than the elimination, and the plasma levels start to increase again and reach a new peak in approximately 8 hours. In the steady state, depression levels are approximately 50% of peak levels, in contrast to the oral dose, whose concentrations drop to virtually zero between doses. Plasma concentrations are observed with all concentrations and sizes of patches [24, 33].

The binding of rivastigmine to plasma proteins is approximately 40%, therefore weak. Rivastigmine is distributed equally between blood and plasma; in addition, the molecule easily crosses the blood-brain barrier, reaching peak concentrations within 1 to 4 hours and with a cerebrospinal fluid-plasma AUC ratio of 40% [31]. This distribution mechanism is also observed in the transdermal form. As previously mentioned, rivastigmine is rapid, with a plasma half-life of approximately 1 hour, mainly via cholinesterase enzyme-mediated hydrolysis to the decarbamylated metabolite. In vitro, the Rivastigmine shows minimal inhibition of acetylcholinesterase (< 10%). Based on in vitro studies, no pharmacokinetic drug interactions with metabolized drugs are expected by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6, and other animal studies did not show involvement of cytochrome P450 coenzymes; therefore, there was no evidence of drug interactions related to this same cytochrome in humans. The total plasma clearance of rivastigmine was approximately 130 l/h after an IV dose of 0.2 mg and decreased to 70 l/h after an intravenous dose of 2.7 mg. In the transdermal form, rivastigmine is rapidly and extensively metabolized with an apparent plasma elimination half-life of approximately 3.4 hours after removal from the transdermal patch, also via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Unchanged rivastigmine is not found in urine; renal excretion of metabolites is the main route of elimination, which is rapid and complete renal complete (> 90%) within 24 hours. Less than 1% of the administered dose is excreted in feces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease. The same type of elimination is seen in the transdermal form [24, 33].

In elderly patients, studies revealed that plasma concentrations in people over 60 years were higher when compared to younger individuals aged between 19 and 40 years, with doses of 1 mg of rivastigmine. With increasing dose, it was found that in the elderly population, plasma concentrations were about 30% higher than in a younger population. The decarbamylated metabolite did not change with the age of the patients, even those affected by Alzheimer's disease. The same was observed in patients using transdermal rivastigmine. Another population that needs more attention and care are those with renal failure, where studies have shown discrepancies in plasma levels between patients with moderate and severe renal failure, but this difference has not been clearly elucidated in these studies. What was evident is that the plasma concentrations of individuals with severe renal impairment and healthy individuals (control) were not very different, both using a dose of 3 mg. However,

individuals with moderate renal failure had 2.5 times increased plasma concentration, and decarbamylated metabolites were increased by about 50%. The same results are seen in patch form [24, 38].

In patients with mild and moderate liver failure, a plasma concentration 60% higher than in healthy individuals was observed. In this population, administration of different doses showed a mean oral clearance of rivastigmine about 60–65% lower than in healthy subjects. Pharmacokinetic changes in this type of population did not have more deleterious effects on the incidence and severity of adverse events compiled. For the transdermal form, the same effects are expected [24].

Preclinical safety studies of rivastigmine were done in relation to toxicity, mutagenicity, carcinogenicity, multiple toxicity, and reproductive and local toxicity. No signs of mutagenicity were observed in these studies; however, at higher doses, signs of chromosomal aberrations were evidenced, which the researchers concluded that this result may have been false positive and not traces of carcinogenicity, both in oral and transdermal forms. Regarding reproduction, there were no evidences of teratogenicity and adverse effects on fertility, uterine growth, or reproductive function in animals (rats) that received doses of up to 1.1 mg/kg/day. In multiple toxicity with maximum doses and different species, central and peripheral cholinergic stimulations were visualized. However, in vivo tolerability proved to be different among the species studied, with the dog being the most sensitive, even with more pronounced gastrointestinal effects. In local tolerability, mild irritation in mucous membranes and eyes was observed in rabbits. Like all medications, rivastigmine has contraindications. Its use is not recommended in patients with hypersensitivity to rivastigmine and other carbamate derivatives and excipients used in the formulation of the drug. Individuals with dermatitis or any other skin pathology are contraindicated using the patch form [24, 30, 33].

4.4.5 Adverse Events

Adverse events are expected in all use of medications: in rivastigmine, the most commonly observed were the gastrointestinal ones, such as nausea and vomiting, in about 30% of the patients observed. During clinical studies weight loss and loss of appetite were the most commonly reported events [24, 30].

According to the results of the studies, other events, less common, were observed with the use of rivastigmine capsule and oral solution:

Common adverse events, in addition to the gastrointestinal ones already reported, were agitation, confusion, nightmare, anxiety, dizziness, abdominal pain, dyspepsia, fatigue, asthenia, headache, tremors, and drowsiness. Other adverse events were observed less frequently in patients: insomnia, depression, syncope, cardiac arrhythmias, duodenal and gastric ulcers, fall, skin rash, and pruritus. Rarely, events such as hypertension, hallucinations, seizures, pancreatitis, severe (intense) vomiting

associated with esophageal rupture, hyperhidrosis, stroke, angina pectoris, and myocardial infarction were seen in patients taking the oral form.

In the transdermal form, in addition to those observed in the oral form, additional unusual events could be observed: erythema at the application site, edema, and contact dermatitis. In post-marketing, that is, when the drug is already on the market, spontaneous reports of some events were reported by users of the oral medication (oral solution and capsules); however, it is not possible to measure these frequencies nor the number of individuals involved nor the relationship with the medication in question, as these were voluntary reports of a certain population. Each country has its own agency to report such events. Spontaneous reports were dehydration, aggressiveness and agitation, extrapyramidal symptoms in patients with Alzheimer's dementia, sinus node disease, hepatitis, and Stevens-Johnson syndrome allergic (disseminated) dermatitis. In the transdermal form (adhesive/patch), urinary incontinence has been commonly reported, while other less common and rare have been reported, such as stroke, increased psychomotor activity, erythema, blisters, and edema at the application site [24, 32, 33, 36].

4.4.6 Drug Interactions

The use of concomitant medications and the drug interactions foreseen with the use of rivastigmine deserves special attention. Due to extrapyramidal symptoms, the use of metoclopramide, for example, with rivastigmine is not recommended. As described above, rivastigmine has an anticholinesterase effect and should not be administered with muscle relaxants such as succinylcholine. Rivastigmine may interfere with cholinergic medications, such as oxybutynin, physostigmine, and pyridostigmine, and also concomitant medications with rivastigmine should not be considered [24, 30, 37].

Rivastigmine should be taken away from meals.

Additive effects of bradycardia have been observed with rivastigmine and atenolol-type beta-blockers and other cardio selective beta-blockers. Smoking patients, that is, those with frequent use of nicotine, had their oral clearance of rivastigmine in about 23%. Warfarin deserves special attention, as it can present many drug interactions, when used with rivastigmine it did not increase the prothrombin time in patients using these two drugs concomitantly, in healthy volunteers [24, 36].

Drug interactions, pharmacokinetics or pharmacodynamics, which may occur with the use of commonly used and prescribed drugs such as antacids, calcium channel blockers, antihypertensives, analgesics, non-steroidal anti-inflammatory drugs, benzodiazepines, among others, were not observed in use with rivastigmine [24, 36].

4.4.7 Doses and Administration

Initial consolidated doses of rivastigmine are 1 mg, twice a day, orally and are recommended in patients especially sensitive to the effects of cholinergic drugs. Doses of 1.5 mg, twice a day, orally are commonly used in the initial treatments of Alzheimer's disease. Given the tolerability of patients, after 2 weeks of use, doses of 3 mg, twice a day, orally can be prescribed. Doses should be increased to 4.5 mg and 6 mg, at least after 2 weeks of treatment each, if there is no serious adverse event [35].

If treatment is interrupted due to any intolerability, smaller doses should be resumed. The capsules should not be broken or chewed; if there is a problem in swallowing, another pharmaceutical form should be chosen. The maximum dose to be taken orally is 6 mg twice a day. In the transdermal form (patch), the initial dose is 9 mg of rivastigmine (5 cm^2 patch); if well tolerated, the dose can be increased after 4 weeks to the dose of 18 mg (10 cm^2 patch). Dosage increases with the use of the transdermal patch should be made according to the tolerability of each patient, that is, the doses of 27 mg (15 cm^2 patch) and 36 mg (20 cm^2 patch). If treatment is interrupted due to undesirable events and effects, retreatment should be restarted with lower dosages, as recommended. Patches must be changed every 24 hours [24, 30, 35].

Symptoms related to Rivastigmine overdose were vomiting, nausea, diarrhea, tremors, headache, dizziness, drowsiness, bradycardia, mental confusion, hallucinations and general malaise. It is noteworthy that rivastigmine is an anticholinesterase drug and its overdose can result in cholinergic symptoms such as excessive salivation, vomiting, sweating, among others. Given the half-life of about 9 hours, it is important to remember that in cases of overdose, no other dose should be administered within the next 24 hours. Most symptoms of overdose are caused by symptomatic treatments, except in the cases that have severe adverse effects, in which the use of atropine is recommended. The use of scopolamine is not recommended for the treatment of symptoms of overdose related to rivastigmine [24, 30, 36].

4.4.8 Transdermal Use of Rivastigmine

The use of rivastigmine's patch in patients with Alzheimer's disease has the great advantage for those who are in more advanced stages and with swallowing difficulties. In addition, it is used every 24 hours, that is, once a day. However, this route of administration deserves special care, so that its effectiveness is fully satisfactory [38].

The recommendations are [24, 32, 34, 38]:

- The patch should be applied, preferably after showering, with clean, dry skin, and no hair.
- No product such as moisturizing cream, ointments, or lotion should be present at the patch application site.
- The patch must be changed every 24 hours, and its application must be in different places each day but on the upper and lower back, on the arm, or on the chest.
- It is important to ensure that application areas are free from friction and to avoid wearing tight clothing.
- The patch must be pressed at the administration site until the edges are fully adhered to the skin.
- If the patch comes off, a new one must be applied for the rest of this day, and then it must be changed for a new one the next day at the same time as the usual schedule.
- The skin of the elderly is thinner and drier, so care must be taken when removing the adhesive.
- Bathing, sun, or swimming should not affect the adhesive system. However, one must be careful with excessive heat.
- After removing the rivastigmine patch, fold it in half with the sticky part on the inside and press. Return the used adhesive to the original sachet, and dispose of it safely, out of reach of children. Wash your hands with soap and water after removing the adhesive.
- If there is any skin lesion, the physician must be notified promptly for a reassessment.

4.4.9 Storage

The care with the medications must be extreme, so that its effectiveness is preserved. The storage of rivastigmine in its capsule form, oral solution, or transdermal patch should be stored at room temperature, between 15 and 30 °C, in a place without humidity, without exposure to light and heat. None of the dosage forms must be frozen or cooled.

All medication must be left out of reach of people suffering from psychiatric disorders and dementias and children [24, 30].

The evolution of Alzheimer's disease is characterized by damage to various parts of the brain, and as it progresses, it causes several limitations over time, such as driving vehicles, operating machinery, and handling the stove; for example. Rivastigmine, in the first days of treatment, can cause dizziness and drowsiness, and this can cause a greater limitation for patients using this drug [24, 30, 33].

Currently, rivastigmine is still one of the few drugs used to treat Alzheimer's disease. All medications used for Alzheimer's disease neither cure the disease nor impede its progress. However, early diagnosis and treatment with already approved drugs can improve the quality of life of patients affected by this devastating disease.

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