drug information perspectives

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Contents

RIVASTIGMINE

TRADE NAME(S): Exelon

CLASSIFICATION
- Anticholinesterase
- Acetylcholinesterase inhibitor
- Cholinergic
- Dementia therapy

ACTION
- Pseudo-irreversible (slowly reversible) acetylcholinesterase inhibitor, thus increases the level of acetylcholine in neuronal synaptic clefts in the brain. Maximum dose produces 62% enzyme inhibition with more potent inhibition of the G1 form than the G4 form.
- Inhibits butyrylcholinesterase; maximum dose produces 62% enzyme inhibition; clinical relevance unknown.
- Increases REM sleep density.
- Increases regional cerebral blood flow.
- A carbamate.

PHARMACOKINETICS
Half-life:
- Parent drug: 1-1.5 hours (oral), 3.4 hours (transdermal, after patch removed). Main metabolite: 3 hours (oral).

Absorption:
- Rapidly absorbed orally. Cmax attained after 0.5-1.5 hours (oral) or 8-16 hours (transdermal).
- Almost 100% absorbed orally, but due to rapid first-pass metabolism the oral bioavailability is 36%. From transdermal patches about 50% of the drug is absorbed over 24 hours.
- Bioavailability is non-linear above 3mg; doubling a 3mg dose triples bioavailability.
- Administration with food slows and increases oral bioavailability.

Distribution:
- Protein binding 40%.

Metabolism:
- Extensively metabolized by cholinesterases. The main metabolite is weakly active.

B.C. Drug and Poison Information Centre
1081 Burrard Street, Vancouver, B.C. V6Z 1Y6
Phone: (604) 682-2344; Ext: 62126 Fax: (604) 806-8262

- No metabolism by P450 enzymes.

Elimination:
- Almost entirely eliminated as metabolites in urine.
- Plasma clearance is dose-dependent.

Special populations:
- ***Elderly***: Plasma levels increase 30% in elderly males.
- ***Hepatic impairment***: Mild to moderate hepatic impairment: Increased bioavailability 2-fold. Severe hepatic impairment: No data.
- ***Renal impairment***: Moderate renal impairment: Increased plasma levels 2.5-fold. Severe renal impairment: Mixed data: No increase in plasma levels, or increased bioavailability, or increased half-life of main metabolite.
- ***Smokers***: Increased clearance by 23%.

USES AND EFFICACY

Uses: The symptomatic treatment of **mild to moderate Alzheimer's disease**. Temporarily stabilizes cognition, or modestly improves it by approximately 1 point on ADAS-cog compared with baseline (3 points better than placebo), over 6-9 months. Activities of daily living improve. Behavioural symptoms may improve but this is less well documented. Response rate: clinically meaningful response (at least 4 point improvement on ADAS-cog) occurs at 6 months in approximately 10% more patients (29% versus 19%) than with placebo.

Clinical course:
- Maximal inhibition of cholinesterase occurs about 6 hours after a 6mg dose and lasts about 12 hours, longer than suggested by its half-life due to the drug's slowly reversible inhibition. Cognitive function improves within 12 weeks after the initial dose, peaks at 12 weeks, then declines gradually to baseline levels after 9 months, with further decline thereafter.

Major clinical trials

B303, B351 and B352 Trials (1998): The results of three randomized, double-blind, placebo-controlled trials were pooled to demonstrate the effects of rivastigmine low dose (1-4mg/day), high dose (6-12mg/day) or placebo in over 3300 patients with mild to moderate Alzheimer's Disease. After 26 weeks, cognition, as measured by Observed Case analysis of ADAS-cog results, stabilized or improved in patients given rivastigmine compared with those given placebo (difference 2.6-4.9 points). Activities of daily living scores also improved. In the B352 study, 35% of patients receiving the high dose range discontinued treatment, mainly due to side effects. An open-label extension revealed that the initial improvement in cognition lasted approximately 38 weeks. Approximately 38% of patients stabilized or improved, while only 19% had a clinically meaningful improvement.

Dementia in Parkinson's disease (2004): A randomized, double-blind, placebo-controlled study in 541 patients with mild to moderate dementia found a 3 point improvement on ADAS-cog compared with placebo after 24 weeks (NNT=19). Patients were slowly titrated over 16 weeks to the highest tolerated dose up to 12mg/day. Tests of executive function, a predominate dysfunction in Parkinson's disease, showed small but significant improvements. The withdrawal rate due to adverse effects was higher in the rivastigmine group (17% versus 8%, NNH 11), mostly due to nausea, vomiting and tremor. Hallucinations may have been reduced. Study limitations: Use of last observation carried forward data may bias results in favour of the treatment group in a degenerative disease especially if there is a higher dropout rate in the treatment arm.

Comparisons

Versus donepezil:
- No evidence of a difference in cognitive effects in Alzheimer's disease. Initial dose titration may be easier and quicker with donepezil. GI toxicity may be less common with donepezil. Some patients who do not tolerate or respond to donepezil may tolerate or respond to rivastigmine.

Versus galantamine:
- No data.

Advantages:
- This treatment is well tolerated after the initial dose titration period
- Available as an oral solution and a transdermal patch
- Multiple dose strengths available may facilitate slow dose titration to tolerance

- Short half-life allows rapid resolution of side effects
- Lack of P450 metabolism reduces drug interactions

Disadvantages:
- Not studied in severe Alzheimer's disease
- Slow dose titration of at least 8 weeks required to avoid frequent side effects
- Twice daily dosing required (except for the transdermal patch)

Place in therapy:
- In mild-to-moderate Alzheimer's disease, small but genuine improvements or stabilization in cognition and daily function have been documented objectively.
- The majority of responders are stabilized at, or slightly above, their initial level of cognition for up to 38 weeks.
- With continued therapy, the disease progresses, but patients on average have better scores on ADAS-cog than expected if they had not been treated.
- However, the response rate is only about 10% better than with placebo, and very few patients display a striking improvement.
- Benefits are highly variable with a subgroup attaining a clinically meaningful response. Treatment should be continued in responders and discontinued in nonresponders.
- The drug helps only the symptoms and does not alter the course of the disease.
- There is no evidence that treatment delays institutionalization.

Investigational/Unapproved Uses:
- ***Autism***: May be beneficial; more study needed.
- ***Frontotemporal dementia***: Limited data suggest slight benefit on behavioural symptoms.
- ***Lewy body dementia***: Effective in reducing apathy, anxiety, confusion, delusions, visual hallucinations, sleep disturbances and motor dysfunction in preliminary studies, with little worsening of motor function. Some authorities recommend a trial with slow titration and careful monitoring.
- ***Mild cognitive impairment***: A related drug, galantamine, has been shown to be ineffective in two controlled studies. In the studies the risk of death was increased, mainly from cerebrovascular or cardiovascular causes.
- ***Parkinsons Disease with dementia***: Approved in the United States for mild to moderate dementia in patients with Parkinson's Disease. The benefit is modest, highly variable, and may decline after 24 weeks; side effects include increased tremor, increased salivation, and worsening of motor function. These patients may have a greater cholinergic deficit than patients with Alzheimer's disease.
- ***Schizophrenia***: Abnormal cholinergic transmission at nicotinic receptors may exist. May help some aspects; more study needed.
- ***Traumatic brain injury:*** No benefit in a study conducted more than 12 months after injury.
- ***Vascular dementia***: Some suggestion of benefit in executive function and behavior in patients with subcortical vascular dementia, but randomized, double-blind, placebo-controlled trials are needed.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindications:
- ***Hypersensitivity*** to rivastigmine or other carbamates
- ***Cardiac conduction abnormalities*** including sick sinus syndrome and history of unexplained syncope (vagotonic effect can cause heart block)
- ***Severe hepatic impairment*** (no data)
- ***Children*** (no data)
- ***Mild cognitive impairment*** (increased risk of death in a similar drug, galantamine)

Precautions:
- ***Coronary heart disease and heart failure*** (vagotonic effect can cause heart block)
- ***GI bleeds, GI ulcers*** (risk due to cholinergic increase in gastric acid secretion; monitor for GI bleed)
- ***Urinary tract or GI obstruction*** (theoretical risk due to cholinergic effect; increased activity may be harmful; possible urinary obstruction)
- ***Seizure history, epilepsy*** (seizures may occur)
- ***Asthma, COPD*** (theoretical risk due to cholinergic effect; may precipitate bronchoconstriction)
- ***Slow dose titration*** (follow guidelines to avoid side effects)
- ***Overdose***: atropine is antidotal

- ***Smokers*** (may have less benefit)
- ***Avoid sudden withdrawal*** (drug withdrawal syndrome has been reported in related drugs)
- ***Monitor body weight*** (weight loss may occur)
- ***Report*** unexpected or serious reactions to the Canada Vigilance Program (Health Canada's postmarketing surveillance program).

PREGNANCY AND LACTATION
- No teratogenic effects known in animals. No data on effects during pregnancy in humans. Assess risk:benefit.
- No data on excretion into breast milk or effects on nursing infants. Not recommended during lactation due to potential cholinergic effects.

SIDE EFFECTS
- Common effects are cholinergic, most commonly nausea, mainly during initial dose titration.

Cardiovascular: Bradycardia, atrial fibrillation (frequent); arrhythmias, heart block (infrequent); multiple case reports of hypertension, myocardial infarction, chest pain, stroke, heart failure. QT prolongation (1 case with positive dechallenge).

CNS: Dizziness (up to 20% versus placebo 10%); somnolence (5% versus placebo 2%); syncope (frequent); tinnitus (frequent); headache (19% versus placebo 8%); fatigue (10% versus placebo 3%); multiple case reports of hallucinations, aggression, seizures, insomnia, confusion, agitation.

Gastrointestinal: Dose-related, partly centrally mediated due to stimulation of muscarinic receptors in the chemoreceptor trigger zone, usually transient, more common in women, occurs in up to 57% of patients during initial dose titration phase, versus placebo 31%. Nausea (up to 50% versus placebo 10%), vomiting (up to 34% versus placebo 6%; may be severe if gradual dose titration is not done; one case of esophageal rupture), diarrhea (up to 17% versus placebo 9%), anorexia (up to 14% versus placebo 2%); abdominal pain (up to 12% versus placebo 3%); dyspepsia (8% versus placebo 4%). Weight loss (2%; more than 7% of body weight in 24% of women taking 6-12mg/day versus placebo 6%); upper and lower GI bleeds (multiple case reports, <1% versus placebo 0%). Fecal incontinence (frequent).

Other: Many case reports of pneumonia, falls (some fatal), fractures, and lack of efficacy. Multiple case reports of weakness, aggravated condition, memory impairment, pancreatitis, extrapyramidal disorder, apraxia. Tremor (3% versus placebo 1%). Fatigue (8% versus placebo 4%). Increased sweating (3% versus placebo 1%); Stevens Johnson syndrome.

INTERACTIONS

DRUG	EFFECT	MECHANISM	IMPORTANCE
Anticholinergic drugs including tolterodine	Decreased anticholinergic effect; decreased cognitive benefit; seizures when discontinue anticholinergic drug	Antagonism	Caution
Antipsychotic drugs (haloperidol, risperidone, D2 blockers)	Parkinsonism	Increased cholinergic activity	Caution

DRUG	EFFECT	MECHANISM	IMPORTANCE
Beta blockers	Bradycardia	Additive	Caution (theoretical)
Calcium channel blockers	Bradycardia	Additive	Caution (theoretical)
Cholinergic drugs	Increased cholinergic effect	Additive	Caution
Digoxin	Bradycardia	Additive; no kinetic interaction	Caution (theoretical)
Muscle relaxants, depolarizing (succinylcholine)	Prolonged muscle relaxation	Additive cholinesterase inhibition; decreased succinylcholine metabolism	Caution, monitor
Nicotine	Decreased rivastigmine levels	Increased clearance	Caution
NSAIDs	Risk of GI bleed	Increased gastric acid secretion	Caution, monitor

Interactions lacking
A lack of pharmacokinetic interaction has been documented with
- Diazepam
- Digoxin
- Drugs that inhibit butyrylcholinesterase (fluoxetine, haloperidol, thioridazine)
- Fluoxetine
- Warfarin

DOSAGE
Guidelines
- Administration with food or antiemetic drugs and giving adequate fluid intake may reduce GI side effects.
- Start at a low dose and slowly raise the dose to avoid severe vomiting, especially in patients with a low body weight.
- If doses are missed for several days, restart at the lowest dose and titrate up slowly.
- Adjust dose to patient tolerance. If nausea or vomiting occur, skip several doses and restart at the same or next lower dose to avoid severe vomiting.
- Switching from other cholinesterase inhibitors: A washout period of 7-14 days is required if the patient was not tolerating the initial drug. Then start rivastigmine at the lowest recommended dose for that age, hepatic function and renal function, maintain this dose for at least 4 weeks, then increase at 4 week intervals if tolerated.

Adults:
- Alzheimer's Disease:
- Oral: Initial dose 1.5mg twice daily with food. After at least 2 weeks, if tolerated, increase dose to 3mg twice daily. After at least a further 2 weeks, if tolerated, increase dose to 4.5mg twice daily. After at least a further

2 weeks, if tolerated, consider increasing to a maximum of 6mg twice daily.
- Range 6-12mg/day.
- ***Transdermal***: Initially one Exelon Patch-5 applied once daily. If tolerated, increase after a minimum of 4 weeks to one Exelon Patch-10 applied once daily. Switching from the oral form: If the patient is taking less than 6mg/day orally, switch to one Exelon Patch-5 applied once daily, starting the day after stopping oral therapy. If the patient is taking 6mg/day or more orally, switch directly to one Exelon Patch-10 applied once daily, starting the day after stopping oral therapy.

- ***Parkinson's Disease with dementia***: As for Alzheimer's disease, with slower titration, increasing the dose at a minimum of 4 week intervals.

Elderly:
- ***Oral***: Over 85 years with low body weight, especially females: Initially 1.5mg once daily with food. Increase dose slowly.

Hepatic impairment:
- Moderate impairment (Child-Pugh score 7-9): Oral: Initially 1.5mg once daily with food. Increase dose slowly.
- Contraindicated in severe hepatic impairment.

Renal impairment:
- ***Oral***: Initially 1.5mg once daily with food. Increase dose slowly.

NURSING IMPLICATIONS
The oral forms of this medication should be taken with food to reduce any stomach irritation and to improve absorption.

For transdermal application, see PATIENT INSTRUCTIONS. Note that applying the patch to the patient's back is recommended if there is a concern that the patient might remove the patch. Application to the abdomen or thigh is not ideal since less drug will be absorbed.

Maintain adequate fluid intake to avoid dehydration.

The most common side effects are nausea and vomiting. These effects will often disappear with time. If severe vomiting, weight loss or any worsening of the patient's condition occurs, inform the physician.

Therapeutic benefit when used in Alzheimer's disease may include an improvement in activities of daily living, such as improved attentiveness, memory and ability to converse, and improved behaviour.

See PATIENT INSTRUCTIONS.

PATIENT INSTRUCTIONS
Rivastigmine (ri-va-STIG-meen) is a drug most commonly used to treat the symptoms of Alzheimer's disease.

Before taking this medication, be sure that the physician is aware if you have: kidney problems; liver problems; heart disease; bladder obstruction; stomach ulcers; epilepsy or seizures; asthma or COPD; planned surgery; or if you take other drugs, or smoke.

This medication should be used exactly as prescribed by the physician. It is taken every day for best results. Do not stop taking it suddenly; consult your physician if you wish to stop taking it.

The oral form of this medication should be taken twice a day, with the morning and evening meals. Taking it with food should reduce stomach irritation and will also increase its absorption.

Oral solution: use the oral syringe provided to measure the correct dose. The dose may be mixed with water, soda or juice, or swallowed directly from the syringe.

Transdermal patch: Remove any previous patch and discard it by folding it in half with the adhesive sides together and discarding it safely, since it still contains active drug. Apply the new patch to the upper or lower back, the upper arms or chest. The skin should be healthy, with no creams or powder that could interfere with the ability of the patch to adhere. Change the site of application daily, not repeating the same site for 14 days. Wash your hands afterwards. Apply a new patch once a day around the same time of day. Bathing or swimming are fine, but avoid prolonged exposure of the patch to heat. If the patch falls off, apply a new patch for the rest of the day, and then replace it at the usual time of day.

If a dose is missed, take it if it has only been a few hours. Otherwise, skip that dose and take the next one at the usual time. Don't take a double dose to make up for a missed one.

If a few days of therapy are missed, contact your physician to find out how to restart the medication.

This medication can interact with other medications. Inform your physician and pharmacist of all other medications that you are taking.

Side effects are usually mild and temporary. Tell your physician if you develop any unexpected or serious effects after starting this medication, especially weight loss, worsening of your condition, black stools, stomach pain, or falls.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, at room temperature away from heat, light and moisture, and out of the reach of children.

PRESENTATION
Capsule: 1.5, 3, 4.5, 6mg.
Oral solution: 2mg/mL (120mL).
Transdermal patch: Exelon Patch-5 (5 cm squared, contains 9mg base, releases 4.6 mg/24 hours. Exelon Patch-10 (10 cm squared, contains 18mg base, releases 9.5mg/24 hours.)

References are available on request.