THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

NEW DRUGS IV

Donepezil (Aricept®)

Approved Indication: Symptomatic treatment of early mild to moderate Alzheimer's dementia.

Mechanism of action: Inhibits acetylcholinesterase, increasing the amount of acetylcholine in synapses and potentially enhancing brain cholinergic neurotransmission.

Pharmacokinetics: Well absorbed, eliminated by liver metabolism, half-life is 3 days. Steady state plasma concentrations are reached in 2 weeks.

Evidence of effectiveness: Three randomised controlled trials (RCTs) compared donepezil with placebo in patients with mild to moderate Alzheimer's Disease. The first trial (N=161) compared donepezil (1, 3 or 5 mg/d) with placebo in a 12-week double blind trial. Small statistically significant improvements in cognitive scores (3.2 out of 70) occurred in the 5 mg donepezil group. Caregivers (e.g. spouse) could not discern any difference.[1] A second similar 24-week trial [2] compared placebo (N=162) with donepezil 5mg/d (N=154) or 10 mg/d (N=157). Endpoint cognitive scores improved by 2.8 points in the group receiving 10 mg/d ($p<0.0001$). The third 15-week trial (N=468) compared placebo with donepezil 5 mg/d or 10 mg/d.[3] Again the 2 donepezil groups did statistically significantly better on 3 different scores, including a clinicians global assessment of change. **While of potential interest, the clinical significance of the small differences remains to be established; the studies were not designed to detect improvement in activities of daily living or delay in institutionalization.**

Major adverse effects: Cholinergic effects such as diarrhea (ARI=10%)*, nausea (ARI=13%), vomiting (ARI=8%) or muscle cramps (ARI=7%) were common at the 10 mg dose. Bradycardia, bronchospasm, peptic ulcer, insomnia, muscle cramp, fatigue, and anorexia have also been noted. Only 1700 patients with no major co-morbidities have been studied in pre-marketing clinical trials.

Dose and cost: Starting dose, 5 mg daily; assess for improvement in function and side effects after 3 to 4 weeks. Maximum dose 10 mg. Both strengths cost $4.72/day.

Conclusion: Donepezil slightly improves a measure of cognitive function and a clinician's global assessment of change in patients with Alzheimer's disease. **Further trials are required to test whether donepezil offers improvement in more clinically meaningful outcomes.**

Levofloxacin (Levaquin®)

Levofloxacin is a fluoroquinolone antibiotic, which is the levo-rotatory stereoisomer of ofloxacin (Floxin®). Antibacterial activity resides predominantly in the levo-rotatory isomer, but levofloxacin kinetics are similar to ofloxacin.[4]

Approved Indications: (not first choice) acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, complicated UTI, and skin/skin structure infections .

Mechanism of action and efficacy: Similar to other flouroquinolones, levofloxacin inhibits bacterial DNA gyrase. Enhanced efficacy, *in vitro*, to gram positive organisms as compared to ciprofloxacin and norfloxacin.

Pharmacokinetics: High oral bioavailability (99%), $t_{1/2}$ = 6-8 hrs.

Evidence of effectiveness: Once daily levofloxacin has been compared with other antibiotics in 8 RCTs; most are not double-blind. These trials show clinical efficacy ranging from 82 - 98%, which was not different from ceftriazone, or cefuroxime +/- erythromycin/doxycycline for community acquired pneumonia, cefuroxime or cefaclor for bronchitis, amoxicillin/clavulanate or clarithromycin for sinusitis, and ciprofloxacin for skin infections and UTI.

Major adverse effects: Levofloxacin has a side effect profile similar to other fluoroquinolones: gastrointestinal upset, headache, dizziness, tendinitis or tendon rupture, and hypersensitivity.

Dose and cost: levofloxacin (Levaquin®), 250 to 500 mg once daily ($4.44 to 5.01/day), ofloxacin (Floxin®, generic), 200 to 400 mg BID ($4.08 to $4.88/day), ciprofloxacin (Cipro®), 250 mg BID ($4.64/day), norfloxacin (Noroxin®), 400 mg BID ($4.52).

Conclusion: Levofloxacin is similar to ofloxacin in all respects except that it is twice as potent.

** See Therapeutics Letter 15 for definition and calculation of ARI .*

Pantoprazole (Pantoloc®)

Approved Indications: acute gastric and duodenal ulcer, severe gastro-esophageal reflux disease (GERD).

Mechanism of action: decreases gastric acid secretion by inhibition of the proton pump.

Pharmacokinetics: rapidly absorbed from the GI tract; inactivation primarily by liver metabolism; marked variation in individual metabolism ($t_{1/2}$ =1-10 hrs).

Evidence of efficacy: Five comparative RCTs with other proton pump inhibitors were identified: In two, 4-week trials of 464 patients with GERD, pantoprazole 40 mg daily and omeprazole 20 mg daily had similar healing rates at 4 weeks, 76% and 79%, respectively.[5, 6] A 4-week trial of 255 patients with acute duodenal ulcer showed that pantoprazole 40 mg daily and omeprazole 20 mg daily had similar healing rates, 95% and 89%, respectively.[7] A 4-week trial of 50 patients showed that pantoprazole 40 mg daily = omeprazole 20 mg daily as part of triple therapy to eradicate H.Pylori.[8] A small 4 week trial in 30 patients found that pantoprazole, 40 mg BID, and lansoprazole, 30 mg BID, was not as effective as omeprazole, 20 mg BID, for maintenance treatment of severe GERD complicated by a stricture.[9]

Major adverse effects: Adverse effect rates greater than placebo include: diarrhea, 1.5%, and headache, 1.3%. Concerns about long-term safety are the same as for omeprazole and lansoprazole (See Therapeutics Letters 3,9, and13, also onWeb).

Dose and cost: pantoprazole (Pantoloc®) 40 mg capsules $2.03; lansoprazole (Prevacid®) 15 mg and 30 mg $2.10; omeprazole (Losec®) 10 mg $1.83 and 20 mg $2.28.

Conclusions: **Pantoprazole is a proton pump inhibitor that is similar in efficacy, safety, cost and convenience to lansoprazole and omeprazole.**

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to Oct.1,1998. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 78 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

Quetiapine (Seroquel®)

Indication: Treatment of schizophrenia and other psychotic disorders.

Mechanism of action: The drug binds with high affinity to serotonergic, histaminergic H_1, alpha-adrenergic, and dopaminergic receptors. The role these actions play in its efficacy and toxicity is unknown.

Pharmacokinetics: Oral bioavailability is good. Inactivated primarily by liver metabolism. Elimination half-life of about 6 hours; clearance is decreased by 30-50% in the elderly.

Evidence of effectiveness: There are 3 published comparative 6-week RCTs in patients with schizophrenia. The trials are of poor quality; high drop-out rates >50%. One (N=361) compared 5 doses of quetiapine, 75, 150, 300, 600 and 750 mg/day to placebo and haloperidol, 12mg/day.[10] This study demonstrated that haloperidol and doses of quetiapine 150 mg and above were equally efficacious and significantly better than placebo. The other (N=201) compared a titrated dose of quetiapine (407 mg/day) with a titrated dose of chlorpromazine (384 mg/day).[11] This study showed no difference in efficacy parameters between quetiapine and chlorpromazine. The third study demonstrated similar effectiveness for a 225 mg BID and 150 mg TID regimen of quetiapine.[12]

Major adverse effects: The incidence of extrapyramidal side effects (akathesia, and parkinsonism) was less for all doses of quetiapine (6%) than for haloperidol (37%). However, the incidence of other side effects (postural hypotension, weight gain and elevated ALT values), were greater for quetiapine than for haloperidol. Chlorpromazine caused more postural hypotension (18% versus 5%), insomnia (16% versus 10%) and agitation (12% versus 6%) than quetiapine. Extrapyramidal symptoms were similar for quetiapine and chlorpromazine and weight gain was greater with quetiapine.

Dose and cost: Quetiapine 75 to 300 mg BID ($3.08-$8.25/day), olanzapine 10 to 20 mg daily ($7.22-14.45/day), risperidone (Risperdal®), 1- 4 mg BID ($2.06-8.20/day), and clozapine (Clozaril®), 100 mg BID to 200 mg TID ($7.62-22.86/day).

Conclusion: Quetiapine has similar efficacy and a different side effect profile to haloperidol and chlorpromazine in 6-week trials. **More and better evidence is required to demonstrate the long-term effectiveness and safety of new atypical antipsychotics.**

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