THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

NEW DRUGS III

Alendronate (Fosamax®)

Alendronate is a bisphosphonate that inhibits bone resorption, in the same class as etidronate and clodronate.

Indication: Treatment of osteoporosis or Paget's disease of the bone.

Mechanism of action: Alendronate inhibits osteoclastic bone resorption.

Pharmacokinetics: Oral bio-availability is **very low (0.7%)** and substantially diminished by food or fluids. A proportion of absorbed drug becomes incorporated into bone. Inactivated primarily by renal elimination.

Evidence of effectiveness: Two trials compare the effectiveness of alendronate to placebo in post-menopausal women. In one methodologically weak trial[1] 994 women with extremely low bone mineral density (BMD) of the lumbar spine (> 2.5 SD below the mean) were randomized to placebo or alendronate and followed for 3 years. In those with no previous fracture (79% of total), alendronate reduced the incidence of new vertebral fractures detected by x-ray from 2% to 1%, absolute risk reduction (ARR) =1%, number needed to treat (NNT) =100 for 3 years. In the other trial[2] 2027 women with pre-existing pathological fractures were randomized to placebo or alendronate. Alendronate reduced the incidence of symptomatic (painful) fractures from 18.2% to 13.6%, ARR = 4.6%*, NNT = 22 for 3 years*. In Paget's disease one randomized trial[3] in 89 patients compared 6 months of alendronate, 40mg/day, with etidronate, 400mg/day. Decrease in alkaline phosphatase, the primary measure of effect, was greater with alendronate, 79%, than with etidronate, 44%.

Major adverse effects: The placebo-controlled trials [1,2] reported no increased evidence of adverse events including upper gastrointestinal problems with alendronate. Adverse events from post-marketing data[4] reveal a major concern with severe esophageal injury (51 reports) most often occurring during the first month of therapy.

Dose and cost: Osteoporosis: 10mg daily ($1.75/day). **Take on an empty stomach with >200ml of water in AM; remain upright for >30 minutes after ingestion to prevent esophageal injury.** Paget's disease of bone: 40mg daily ($4.66/day) for 6 months.

Conclusions: **Even in women with extremely low BMD, 100 need treatment for 3 years to prevent 1 fracture detected on x-ray. In women with a previous pathologic spinal fracture, 22 need treatment for 3 years to prevent one symptomatic fracture.**

Dorzolamide (Trusopt®)

Dorzolamide is a carbonic anhydrase inhibitor for topical ocular administration.

Indication: Chronic treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Mechanism of action: Dorzolamide is a sulfonamide which inhibits carbonic anhydrase II in the ciliary processes of the eye resulting in decreased aqueous humor secretion.

Pharmacokinetics: Dorzolamide acts locally and is absorbed systemically. The systemic effect accumulates over time, but there is no evidence in trials to date that this leads to significant metabolic acidosis. Inactivated primarily by renal elimination.

Evidence of efficacy: Dorzolamide 2% TID has been shown in double-masked placebo controlled trials to lower intraocular pressure by 3-5mm Hg[5]. When compared with timolol 0.5% BID, in a large multicentre trial (n = 184), the mean percent reduction in intraocular pressure was greater for timolol, 29%, than for dorzolamide, 24% [6]. Dorzolamide efficacy is similar to pilocarpine when used as adjunctive therapy to timolol [7].

Major adverse effects: Bitter taste occurs frequently (25%) but is usually transient. Local irritation (incidence 10%), stinging, itching, and conjunctivitis occur more frequently than with timolol[6] and may necessitate stopping therapy.

Dose and cost: Dorzolamide 2% TID ($0.90/day) as compared to timolol 0.5% BID ($0.34/day) and pilocarpine 2% TID ($0.06/day).

Conclusions: Dorzolamide provides a clear therapeutic advantage over oral carbonic anhydrase. **It should be reserved for patients in whom topical beta blockers or pilocarpine are not tolerated or ineffective.** More safety and effectiveness evidence is needed.

Acarbose (Prandase®)

Arcarbose is a new antidiabetic drug that acts by a unique mechanism of action. It inhibits hydrolysis of complex starches to glucose in the small intestine.

Indication: As adjunctive therapy to diet in the treatment of patients with non-insulin dependent diabetes mellitus (NIDDM).

Mechanism of action: Acarbose lowers post-prandial glucose concentrations by competitive inhibition of pancreatic alpha-amylase and intestinal membrane-bound alpha-glucoside hydrolases.

Pharmacokinetics: Acts locally in the gastrointestinal tract and less than 2% is absorbed in active form. Inactivated by metabolism by intestinal bacteria or eliminated unchanged in feces.

Evidence of efficacy: Over 50 published controlled trials, dating from 1979, have examined the effects of acarbose. In a Canadian multicenter randomised controlled trial[8] (354 NIDDM patients), for example, acarbose decreased HbA1C levels by 0.9% as compared to placebo over a 1 year period in 3 groups of patients already treated with diet, sulfonylureas or metformin. Acarbose has more effects on post-prandial than fasting glucose and does not lead to increase in insulin concentrations or weight gain.

Major adverse effects: Mainly gastrointestinal side effects. In the Canadian trial for example: flatulence, absolute risk increase (ARI)=34%*, diarrhea, ARI=23%, and abdominal cramps and discomfort, ARI=16%. Also noted: a low incidence of reversible elevations of serum transaminases and bilirubin.

Dose and cost: Acarbose 25-100mg TID with the first bite of meals ($0.34-0.94/day). Metformin 0.5-2.5g/day ($0.14-0.69/day). Glyburide 2.5mg daily to 10mg BID ($0.04-0.29/day).

Conclusions: Acarbose can be used as an adjunct to diet and other oral agents to achieve glucose control in patients with NIDDM. Its main disadvantages are cost and the high incidence of gastrointestinal side effects.

Olanzapine (Zyprexa®)

Olanzapine is an atypical antipsychotic drug that structurally resembles and binds to some of the same receptors as clozapine (Clozaril®).

Indication: Treatment of schizophrenia and other psychotic disorders.

Mechanism of action: The drug binds to multiple receptors: serotonergic, dopaminergic, histaminergic (H_1), α1-adrenergic, and muscarinic. 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 30 hours.

Evidence of effectiveness: There are two published randomized controlled six-week trials. One (N=335) compared three doses of olanzapine, 7±1mg/day, 12±2mg/day and 16±2mg/day, with placebo and haloperidol, 16±4mg/day[9]. The other[10] (N=1,996) compared a titrated dose of olanzapine (13.2mg/day) with a titrated dose of haloperidol (11.8mg/day). The first study showed modest efficacy for the highest dose of olanzapine (48% with >40 % improvement in Brief Psychiatric Rating Scale) which was similar to that with haloperidol (47%). In the second study the response to olanzapine was better than to haloperidol, however, the efficacy of both drugs was less than the first. The poor response to haloperidol in the second study was likely because 77% of the patients entered were intolerant or unresponsive to their last course of antipsychotic therapy. Olanzapine (mean modal dose 17 mg/day) has also been compared to risperidone (mean modal dose 7mg/day) in an unpublished 8 week interim analysis of a 28-week double-blind trial. The response rates at 8 weeks (> 40% improvement) were similar for olanzapine, 29% and risperidone, 26%.

Major adverse effects: In the RCT with haloperidol the incidence of extrapyramidal side effects (dystonia, akathesia, tremor, and hypertonia) was less for olanzapine than that with haloperidol, however, the incidence of other side effects (constipation, dry mouth, weight gain and elevated ALT values) was greater for olanzapine. In the RCT with risperidone the incidence of any extrapyramidal event at 8 weeks was greater with risperidone (27%) than with olanzapine (17%). Neutropenia has been documented with olanzapine in at least 3 cases in Vancouver[11].

Dose and cost: Single daily doses of 10 to 20mg. ($6.75-13.50/day) as compared to haloperidol (Haldol®) 5-20mg daily ($0.16-0.52/day), risperidone (Risperdal®), 1-4mg BID ($2.09-8.35/day), and clozapine (Clozaril®), 100 mg BID to 200mg TID ($7.58-22.74/day).

Conclusion: Olanzapine is effective in the symptomatic management of schizophrenia and has fewer extrapyramidal side effects in short-term trials. Long-term effectiveness and safety remain to be established. **In the meantime it should be reserved for patients who are refractory to or demonstrate significant intolerance to standard antipsychotic therapy.**

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

References:

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Tel: (604) 822•0700
Fax: (604) 822•0701
E-mail: jauca@unixg.ubc.ca
Web Site: http://www.interchg.ubc.ca/jauca/