therapeutics letter
March/April 2000

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

NEW DRUGS V

Orlistat (Xenical®)

Approved indication: Management of obesity in patients with a body mass index (BMI) > 30 kg/m² or a BMI > 27 kg/m² in the presence of other cardiovascular risk factors (e.g. hypertension, diabetes, etc.).

Mechanism of action: Reversibly inhibits gastric and pancreatic lipases, decreasing the absorption of dietary fat (triglycerides) by about 30%.

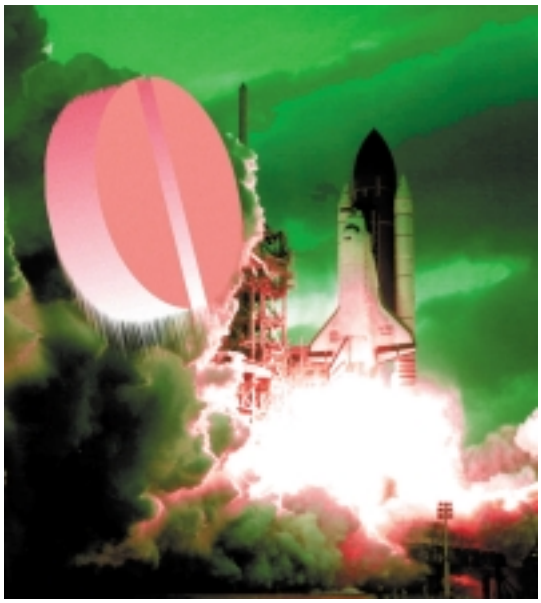
Pharmacokinetics: **About 2% of orlistat is absorbed** and this is mostly metabolized within the gastrointestinal wall. Most of the drug is excreted unchanged in the feces.

Evidence of effectiveness: Four double-blind RCTs are available to assess effectiveness.[1-4] Three of these measured weight loss over a 1-year period in 1901 obese patients with and without Type 2 diabetes (BMI > 28 kg/ m²) eating a mildly hypocaloric diet.[1-3] Pooled data from these 3 trials reveal that weight averaged 100 kg at baseline and 26.4% of patients withdrew during the first year. **In patients completing one year of the trial, the mean decrease in weight with orlistat 120 mg tid was 8.9 kg vs 5.6 kg with placebo.** The fourth trial studied the effect of orlistat on weight maintenance over a 1-year period.[4] Obese subjects who had lost >8% of their initial body weight on a hypocaloric diet over a 6 month period were randomised to placebo or orlistat. During one-year follow-up, **weight gain** with orlistat 120 mg tid was 2.6 kg, significantly less than with placebo, 4.4 kg.

Major adverse effects: Oily spotting, 27%, flatus with discharge, 24%, increased defecation, 11%, and fecal incontinence, 8%, occurred more commonly with orlistat than with placebo. More patients taking orlistat (14%) required vitamin A and D supplementation than patients taking placebo (6.5%).

Dose and cost: Available in 120 mg capsules. Recommended dose: 1 capsule tid with meals (maximum duration 2 yrs). Daily cost: $4.38.

Conclusion: In obese patients orlistat in combination with a low-fat diet (<30% of calories) reduces body weight by 3.3 kg in the first year as compared to placebo. **Adverse gastrointestinal effects are frequent and it is unknown whether orlistat affects morbidity and mortality linked to obesity.**



Raloxifene (Evista®)

Approved indication: Prevention and treatment of osteoporotic fractures in women after menopause.

Mechanism of action: Acts selectively on estrogen receptors in a manner similar to tamoxifen; they both act as agonists on bone and liver receptors and as antagonists on breast and uterus receptors.

Pharmacokinetics: About 60% of the drug is absorbed but because of extensive first-pass metabolism it has a low absolute bioavailability (2%). Half-life averages 28 hours with a wide range in different individuals. Raloxifene conjugates are mostly excreted in the feces.

Evidence of effectiveness: **Changes in bone mineral density and serum lipids do not necessarily correlate with desired clinical events**, therefore trials and data on surrogate outcomes are purposely not included in this letter. For example in one trial fluoride increased bone mineral density and increased the incidence of non-vertebral fractures[5], and in another trial estrogen/progestin treatment decreased LDL cholesterol and was not associated with a decrease in coronary events[6].

A large double-blind RCT comparing raloxifene, 60 mg and 120 mg with placebo has assessed incidence of fractures.[7] In this 3-year trial, 7705 women, >2 years after menopause, were stratified into 2 defined groups: primary prevention (low bone mineral density and no previous vertebral collapse), and secondary prevention (at least one previous vertebral collapse). Outcomes for the 2 doses of raloxifene were not different; therefore combined data for the 2 doses are presented, except where indicated.

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The primary end point was the incidence of vertebral collapse (>20% reduction in vertebral height) detected on x-ray, an event of which most patients were not aware. This end point was detected in 6.6% of patients taking raloxifene, 60 mg, vs. 10.1% of patients taking placebo. In the secondary prevention group the ARR for this end point was 6.5% and in the primary prevention group it was 2.2% .

Of the total radiologic vertebral collapses 12.3% were reported as causing back pain. These painful vertebral collapses were significantly decreased by raloxifene (0.6% vs 1.4%, ARR = 0.8%, NNT = 125 for 3 years). Non-vertebral fractures were not significantly decreased by raloxifene (8.5%) as compared with placebo (9.3%).

Major adverse effects: Thromboembolic events occurred significantly more often with raloxifene as compared with placebo (1.0% vs 0.3%, ARI = 0.7%, NNH = 143 for 3 years). Other adverse events that occurred significantly more often in the raloxifene group are listed and expressed as ARI over placebo: influenza syndrome, 2.1%, hot flashes, 3.7%, leg cramps, 3.2% and peripheral edema, 1.5%.

Note: Early breast cancer diagnoses occurred significantly less often in the raloxifene group, 0.3%, than in the placebo group, 1.1%, ARR = 0.8%, NNT = 125 for 3 years.[8]

Dose and cost: 60 mg daily. Daily cost: $1.56.

Conclusion: Raloxifene reduced radiologic vertebral collapse in both the primary (ARR = 2.2%) and secondary prevention (ARR = 6.5%) settings, but had no effect on non-vertebral fractures (including hip fractures). **Benefits for reduction in painful vertebral collapse and reduction in early breast cancer were small and of a similar magnitude to the harm of increased thromboembolic events.**

ARR - Absolute Risk Reduction
NNT - Number Needed to Treat to prevent one event
ARI - Absolute Risk Increase
NNH - Number Needed to treat to cause one Harmful event

Spironolactone (Aldactone®)

Old Drug, New Indication: Reduction in morbidity and mortality of patients with severe congestive heart failure (symptoms with slight effort or at rest).

Mechanism of action: Aldosterone receptor blocker, enhances Na^+ excretion and K^+ retention in the kidney.

Pharmacokinetics: Extensive first-pass metabolism occurs. Two active metabolites are primarily responsible for the therapeutic effects. Elimination half-life >24 hours.

Evidence of effectiveness: There is one large double-blind placebo controlled RCT in 1663 patients (73% male) with severe heart failure (LVEF <35%) being treated with loop diuretic (100%), ACE inhibitor (95%), digoxin (74%) and beta-blocker (10%).[9] **After an average of 2 years spironolactone (average dose 26 mg) was associated with a lower total mortality than placebo, 34.5% vs 45.9% (ARR = 11.4%, NNT = 9 for 2 yrs) and lower hospitalization for worsening heart failure, 26.2% vs 35.7%.**

Major adverse effects: Gynecomastia or breast pain was reported more often in men taking spironolactone (10% vs 1%, ARI = 9%, NNH = 11 for 2 yrs), but only 1% discontinued treatment due to this side effect. Spironolactone increased serum potassium on average by 0.3 mmol/L, however serious hyperkalemia was not different in the 2 groups: 14 patients on drug, 10 patients on placebo (p = 0.4).

Dose and cost: Start with spironolactone 12.5 mg daily and titrate to 25 mg. Only increase to 50 mg if there are signs and symptoms of progressing heart failure with no hyperkalemia. Monitor serum potassium, as in the trial, every 4 weeks for the first 3 months and then every 3 to 6 months.

Daily cost: $0.04 - $0.15.

Conclusion: Spironolactone added to standard therapy represents a significant advance in the management of severe CHF.

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to March 1, 2000. 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 66 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.

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