NEW DRUGS 2

Famciclovir (Famvir) and Valacyclovir (Valtrex)
Both are new antiviral prodrugs (in the same class as acyclovir).

**Indications:** Acute herpes zoster in the immunocompetent host. (Their role in genital herpes will be discussed in a future Therapeutics Letter).

**Mechanism of Action:** Reduce viral replication by inhibiting viral DNA polymerase.

**Pharmacokinetics:** Valacyclovir is a prodrug of, and metabolized to acyclovir; the oral bioavailability of acyclovir from valacyclovir is 54% as compared to 15-30% for acyclovir. Famciclovir is a prodrug for the active metabolite penciclovir; the mean oral bioavailability of penciclovir from famciclovir is 77%. Penciclovir plus acyclovir are primarily eliminated unchanged by the kidneys and have mean half-lives of 2.5 hours.

**Evidence of effectiveness:** If given within 72 hours of the first herpes zoster lesion, famciclovir 1 and valacyclovir 2 (like acyclovir 3) provide modest decreases in the time to full crusting (e.g. median 5.5 days for famciclovir, 7 days for placebo1), healing and cessation of pain. The benefit is greatest in patients with the most severe infections (many lesions and severe pain)1,3,4. At present the evidence is inconclusive as to whether any antiviral or other therapy has an effect on the overall clinical impact of postherpetic neuralgia. The new prodrugs have not been studied in children or immunocompromised hosts.

**Major adverse effects:** These drugs, like acyclovir, produce a low incidence (similar to placebo) of minor adverse effects, including diarrhea, nausea and headache.

**Dose and Cost:** Acute herpes zoster: famciclovir, 500 mg TID for 7 days ($155.61), valacyclovir, 1 g TID for 7 days ($126.84), acyclovir, 800 mg 5 times daily for 7 days ($138.60). Longer durations of therapy are not more effective; shorter courses have not been tested.

**Conclusions:** Anti-viral drugs have a modest beneficial effect if given early (rash <72 hr) to immunocompetent patients (>50 yr) with moderate to severe rash or pain associated with acute herpes zoster (shingles).

Torsemide (Demadex)
Torsemide is a loop diuretic in the same class as furosemide, bumetanide, and ethacrynic acid.

**Indications:** 1. Edema due to congestive heart failure and other conditions. 2. Hypertension.

**Mechanism of Action:** Inhibits renal sodium reabsorption in the ascending loop of Henle.

**Pharmacokinetics:** Oral bioavailability is 80%. Inactivated primarily by liver metabolism. Half-life is 3.5 hours.

**Evidence of effectiveness:** The five trials comparing torsemide with furosemide suggest that torsemide is approximately twice as potent as furosemide, possibly due to its longer duration of action. The claim that torsemide causes less hypokalemia than furosemide is not substantiated by studies where equipotent doses are used5. A low non-diuretic dose, (2.5 mg) of torsemide has an antihypertensive effect similar to low dose hydrochlorothiazide.

**Major adverse effects:** Adverse effects which have led to discontinuation of therapy include: dizziness, headache, nausea, weakness, vomiting, hyperglycemia, excessive urination, hyperuricemia, and hypokalemia.

**Dose and Cost:** Edema: Torsemide 10-20 mg daily ($0.57- $1.14/day), as compared to furosemide 20-40 mg daily ($0.01/day). Hypertension: Torsemide 2.5 mg daily ($0.20/day), as compared to HCTZ 25 mg daily (<$0.01/day).

**Conclusions:** Torsemide is a new loop diuretic which is more potent and longer acting than furosemide; however, at present there are no demonstrated therapeutic advantages of torsemide.

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Etodolac (Ultradol)


**Mechanism of Action**: A prostaglandin synthetase inhibitor with some selectivity for cyclooxygenase 2 enzymes.

**Pharmacokinetics**: Oral bioavailability is 80%. Inactivated primarily by liver metabolism. Mean half-life is 7 hours.

**Evidence of effectiveness**: In 14 randomised controlled trials (RCTs) for the treatment of osteoarthritis, etodolac was found to be similar in effectiveness and tolerability to naproxen, piroxicam, diclofenac, nimesulide and nabumetone. In 12 RCTs for the treatment of rheumatoid arthritis etodolac was found to be similar in effectiveness and tolerability to naproxen, diclofenac, piroxicam and sulindac.

**Major adverse effects**: The main adverse effects are gastrointestinal and include dyspepsia, abdominal pain, nausea, and flatulence. In a large trial 7% of patients withdrew prematurely because of GI complaints. RCTs using surrogate markers such as endoscopy scores and GI microbleeding show lower measures with etodolac than with naproxen and indomethacin. A recent systematic review has confirmed our previous Therapeutics Letter 4 demonstrating the low risk of serious GI complications in clinical practice with low dose ibuprofen (<2400mg/day). Etodolac and other new NSAIDs were not included in this review; longer clinical experience with these agents are required to determine where they fit in terms of risk.

**Dose and cost**: Osteoarthritis and rheumatoid arthritis: 200-400 mg BID ($1.60-$3.20/day), see Therapeutics Letter 4 for comparative NSAID prices.

**Conclusions**: Etodolac is a new NSAID which has similar effectiveness to other available NSAIDs. It may prove to have a relatively low incidence of serious GI toxicity, however more data are required.

Naltrexone (Revia)

Naltrexone is a long-acting pure opioid antagonist which is effective orally.

**Indications**: 1. An adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent individuals. 2. For the treatment of alcohol dependence, as a component of a comprehensive psychotherapeutic counseling program to support abstinence and reduce the risk of relapse.

**Mechanism of Action**: Competitively inhibits all opioid receptors. Opioid receptors are thought to be responsible for some of the reinforcing effects of alcohol.

**Pharmacokinetics**: Oral bioavailability is 5 to 40% due to high first pass metabolism. Inactivated primarily by liver metabolism. One major active metabolite with mean half-life of 13 hours.

**Evidence of effectiveness**: Two small RCTs compared 12 weeks of naltrexone with placebo in the treatment of alcohol dependence. In these studies naltrexone modestly increased measures of alcohol abstinence (e.g. abstinence rate for naltrexone 42%, for placebo 20%). At the present time there are no long-term follow-up data or evidence that naltrexone leads to any clinically significant outcomes (e.g. abstinence rates at one year).

**Major adverse effects**: The main adverse effects in these RCTs were somnolence, nervousness, vomiting, weight loss, dry mouth, decreased libido, insomnia, nausea, vomiting, and dyspepsia.

**Dose and cost**: Naltrexone 50 mg daily ($5.70/day).

**Conclusions**: Naltrexone is a pure long acting orally active opioid antagonist which may prove effective as an adjunct in opioid and alcohol dependence treatment programs.

Drugs to be covered in the next New Drugs Letter: alendronate (Posamax), a bisphosphonate for osteoporosis, dorzolamide (Trusopt), a topical carbonic anhydrase inhibitor for glaucoma, acarbose (Prandase), an α-glucosidase inhibitor for NIDDM, and olanzapine (Zyprexa), an atypical antipsychotic for schizophrenia.