THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Review and Update

• What is our position on Reference Based Pricing?

None. The Therapeutics Initiative is at arms length from government and other vested interest groups, and is not involved with the government's Reference Based Pricing policy. Our function is unbiased review of evidence and communication of therapeutic recommendations to physicians, pharmacists and government.

• How do we minimize bias?

Before making assessments of therapeutic effectiveness, we review all relevant published clinical trials and the best available clinical epidemiologic and pharmacologic evidence. The Therapeutics Letter is reviewed by the members of the Scientific Information and Education Committee (SIEC), plus relevant subspecialists and 6 other primary care physicians, before distribution.

• How do we ensure relevance to patients?

The SIEC is comprised mostly of practising physicians and pharmacists, including three representatives of the BCMA. We recognize that each patient represents a unique problem and decisions about each patient's therapy must be founded on the patient's individual needs. Our assessments apply to most but not all patients.

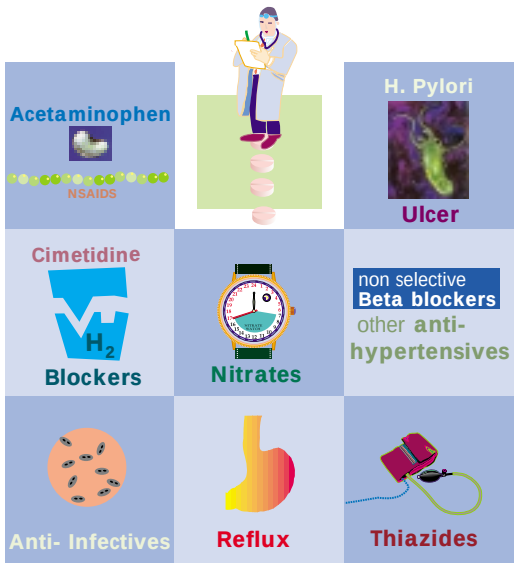
• What has changed in the last year?

Therapeutic guidelines may change with time because clinical evidence is constantly evolving. Below we review the recommendations published in our first year, including some updated information based on feedback which we have received from you.

• Letter 1: H2 Blockers, Oct.'94

The 4 available histamine-2 receptor blockers are used to suppress acid production in the treatment of upper gastrointestinal disorders. Our conclusion was that the 4 drugs had similar pharmacokinetic, effectiveness, and safety profiles. They differ in dose with the average maintenance dose of cimetidine, 400 mg, being roughly equivalent to 150 mg of ranitidine, 20 mg of famotidine and 150 mg of nizatidine. Because cimetidine is much less expensive in British Columbia than the others, it provides better value for the money. Cimetidine does have a greater potential to inhibit the metabolism of other drugs, but this is only clinically significant with the following three drugs: warfarin, phenytoin, and theophylline.

Other groups, including the Centre for Evaluation of Medicine in Ontario and the North Shore Community Drug Utilization Program in British Columbia, have independently reviewed the H_2 blockers and come to the same conclusion. Cimetidine and famotidine have recently become available over-the-counter in the United States, further demonstrating their excellent safety profile.



• Letter 2: H. Pylori and Peptic Ulcer, Nov.'94

The eradication of *H. pylori* reduces duodenal ulcer recurrence from a rate of >50% per year to <10%. We recommended a one week course of triple therapy: bismuth subsalicylate 30 ml, tetracycline 500 mg, and metronidazole 250 mg,QID, which produces a >90% *H. pylori* eradication rate. Acid suppressants are not required unless needed for management of symptoms in the first week. In contrast, two drug regimens for two weeks (e.g. omeprazole and amoxicillin) are associated with reduced eradication rates (<60%).[1]

The evidence for *H. pylori* association with gastric ulcer is not as strong. However, a recently published study in 100 patients with gastric ulcer has shown that one week of triple therapy (outlined above) compared with 4 weeks of omeprazole, 20 mg per day, produced similar ulcer healing, 84.4% and 72.5%, greater *H. pylori* eradication, 91.1% versus 12.5%, and fewer recurrent gastric ulcers at 1 year, 4.5% versus 52.2% (p=0.001). **Patients with duodenal and gastric ulcer, who have been effectively treated, no longer require chronic acid suppressive medications.**

• Letter 3: Gastroesophageal Reflux, Dec.'94

This common symptom is frequently intermittent, and, thus, can usually be managed by prn antacids or H_2 blockers in addition to eliminating precipitating factors. In the less common patient with persistent daily symptoms we recommended a 6-8 week trial of cimetidine, 400 mg BID. In the refractory patient, where severe erosive esophagitis

is demonstrated on endoscopy, omeprazole, a proton pump inhibitor, has proven to be the most effective treatment. Some of these patients require long-term omeprazole therapy. Long term omeprazole therapy is not recommended for patients with no demonstrable pathology because of the potential risks of long term acid suppression associated with this potent drug (e.g. B12 deficiency, gastric dysplasia, carcinoid tumors etc.)

• Letter 4: NSAIDs for Osteoarthritis, Feb.'95

NSAIDs provide symptomatic benefit, are commonly associated with GI complaints and have a 1% incidence of serious gastrointestinal complications. To minimize the risk we recommended replacing the NSAID with acetaminophen, which has been shown to be as effective for symptom relief as NSAIDs in 50% of patients and without the GI toxicity. When an NSAID is proven to be required we recommended low doses of the relatively safe and most cost effective preparations, enteric coated ASA, ibuprofen and naproxen, whenever possible.

We mentioned the randomized controlled trial in which misoprostol 200 mcg QID, reduced the incidence of serious GI complications by 0.4% as compared to placebo. This study is now published.[3] A preliminary economic analysis of the study[4] reveals that this small benefit does not justify the cost in the majority of cases (>$250,000 per complication prevented). It is justifiable in the small subgroup of high risk patients with a history of peptic ulcer or gastrointestinal bleeding and/or elderly patients with concomitant cardiac disease.

A recent randomized placebo controlled trial shows that misoprostol 200 mcg BID or TID offers substantial protection against endoscopically visualized NSAID ulcers and is better tolerated than the QID regimen.[5]

• Letter 5: Anti-infective Guidelines, March'95

The booklet Anti-infective Guidelines for Community Acquired Infections, prepared by the Ontario Anti-infective Review Panel, is organized in a user friendly format, grouped under Respiratory, Skin, Genitourinary, and CNS infections. The drugs of choice for each infection are provided in tables under probable organisms, antibiotic choices, usual dosage, and cost per day.

• Letter 6: Nitrates for Stable Angina, May'95

Management of angina pectoris must be done in a regimen that prevents the development of tolerance and subsequent loss of effectiveness. For daytime dosing we recommended isosorbide dinitrate (ISDN) BID at 0800 and 1400h.The half-life of the active metabolite, isosorbide 5-mononitrate, is 5 hours, making this regimen effective in most patients. In occasional patients a TID regimen at 0700,1200,and 1700h is required. For daytime dosing it is important that no long acting nitrate be given after 1700h. Not included in the letter, is the use of nitrates for the occasional patient who develops angina at night. ISDN at bedtime should be tried first, but may not be long enough acting to cover a patient during 8 hours sleep. The preparations, which have a significantly longer duration of action than ISDN, nitroglycerine ointment, nitrate patches or oral delayed release isosorbide-5-mononitrate (IMDUR) may be useful in these patients. It is essential that the nitrate patches be removed after a maximum of 12 hours, and that no long acting nitrate be administered during the day.

• Letters 7, 8: Treatment of Hypertension, June-Aug.'95

These letters emphasized choosing antihypertensive drugs primarily based on the results of randomized controlled trials measuring morbidity and mortality. The evidence at the present time demonstrates that low dose thiazides are effective in reducing the incidence of myocardial infarction, stroke, and overall mortality in patients with mild to severe hypertension. The amount of evidence in favor of beta blockers is less and we have little data on what dose is optimal or whether cardioselectivity and partial agonist activity are beneficial. There are no randomized controlled trials in hypertension measuring morbidity and mortality associated with ACE inhibitors and calcium channel blockers.

The case control study which we referred to in Letter 8 has now been published.[6] This study shows that for the treatment of hypertension calcium channel blockers (verapamil, diltiazem, and nifedipine) are each associated with a 60% increased risk of myocardial infarction (MI) compared with thiazides and beta blockers. When the dose response relationship was evaluated, higher doses of calcium channel blockers increased the risk of MI compared with beta blockers where higher doses decreased the risk. Another interesting observation from this study is that ACE inhibitors alone were associated with an MI risk similar to diuretics and beta blockers.

References

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2. Sung JJY, Chung SCS, Ling TKW et al. *Antibacterial treatment of gastric ulcers associated with Helicobacter pylori.* N Engl J Med 1995; 332:139-42.
3. Silverstein FE, Graham DY, Senior JR et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995; 123:241-249.
4. Levine JS. *Misoprostol and nonsteroidal anti-inflammatory drugs: a tale of effects, outcomes and costs.* Ann Intern Med 1995, 123:309-310.
5. Raskin JB, White RH, Jackson JE et al. *Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens.* Ann Intern Med 1995;123:344-350.
6. Psaty BM, Heckbert SR, Koepsell TD et al. *The risk of myocardial infarction associated with antihypertensive drug therapies.* JAMA 1995; 274:620-625.

The Therapeutics Initiative was established to disseminate up to date evidence based drug therapy information to physicians and pharmacists. We are also committed to evaluating the effectiveness of all our educational activities using the Pharmacare data base. The data will be in a form such that individual physicians, pharmacies or patients will not be identified. If you do not wish to be part of this evaluation process, please notify us and you will be excluded from the evaluation.

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