VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

A Publication of the Department of Pharmacy

March 1997
Volume 4, Number 1

INDEX

EDITORIAL STAFF

Karen Shalansky, Pharm.D.
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CHANGES TO FORMULARY

Additions

1. Ramipril 1.25mg, 2.5mg, 5mg capsules (Altace®)
   - Angiotensin converting enzyme inhibitor (ACEI)
   - see review, page 2

2. Zopiclone 7.5mg tablet (Imovane®)
   - non-benzodiazepine sedative-hypnotic
   - see review, page 3

3. Quinidine gluconate 80mg/mL injection
   - parenteral antimalarial drug
   - Cost: ~$62.00/day

4. Sodium phosphate injection 3mMol P/mL, 4mMol Na/mL
   - cost $3.97/10mL (comparison Potassium phosphate $0.85/15mL)

5. Hydromorphone Controlled Release 3mg, 6mg caps (Hydromorph Contin®)
   - Cost $0.90/3mg CR (comparison: $0.27/3 x 1mg tablets)

Deletions

1. Ergodryl® (ergotamine, caffeine, diphenhydramine)
   - alternatives: Ergotamine 2mg sublingual, Cafergot®

2. Levodopa 250mg tablet (Larodopa®)
   - alternatives: Sinemet®, Prolopa®

3. Quinidine Sulphate190mg/mL injection
   - alternative: Quinidine gluconate

4. Flucytosine 500mg capsule (Ancotil®)
   - discontinued by manufacturer

5. Polymyxin 50mg vial (Aerosporin®)
   - discontinued by manufacturer
   - alternative: Neosporin®

6. Hydroxypropyl Methylcellulose diagnostic agent (Methocel®)
   - discontinued by manufacturer
   - alternative: Hydroxyethylcellulose (Gonioscopic Prism®)

UPDATED POLICY AND PROCEDURE

1. Parenteral Drug Therapy Manual (PDTM) Update

All PDTMs at VHHSC have been inserted with a new January 1997 update. If there are any questions concerning this manual, please contact Dr. Karen Shalansky 875-4839 or Mr. Paul Yu 822-7084.

2. Patient Teaching Sheets

Our list of patient teaching sheets has expanded considerably. Enclosed (nursing units only) is a list of all teaching sheets available. Please use this order form to update your supplies.

RESEARCH AWARDS

We are pleased to announce that the Department of Pharmacy has won two Canadian Society of Hospital Pharmacists research awards this year. The winning project titles are:

"Cost-effectiveness analysis of azithromycin and doxycycline for *Chlamydia trachomatis* infection in women: A Canadian perspective." (Fawziah Marra, Carlo Marra, David Patrick)

"Double-blind comparison of cefazolin and ceftizoxime for prophylaxis against infections following elective biliary tract surgery." (Peter Jewesson, Grant Stiver, Amy Wai, Luciana Frighetto, Donna Nickoloff, John Smith, Linda Schwartz, Kenna Sleigh, Doni Danforth, Charles Scudamore, Anthony Chow).

NEW DRUG AND DRUG PRODUCTS

1. Ramipril (Altace®)

Ramipril is an angiotensin converting enzyme inhibitor (ACEI) used for the treatment of hypertension and CHF. It has also been shown to improve survival in post-MI patients with CHF.[1]

Comparative Drugs on Formulary

Similar to the formulary drug enalapril, ramipril is a prodrug which must be converted in the liver to the active drug ramiprilat. Ramipril is one of three ACEIs covered by reference-based pricing (captopril, ramipril, quinapril). Clinically, this drug is similar to enalapril in terms of efficacy, pharmacokinetics, side effects and proven indications.

Table 1. Comparison of formulary ACEI[2]

Drug	Captopril	Enalapril	Ramipril
Half-Life (hr)	1.7	11	**11-27**
Peak Effect (hr)	1-2	4-6	**3-8**
Duration (hr)	6-10	24	**24+**
Equivalent Daily Dose	25-37.5 mg	5 mg	**2.5 mg**
Cost/day	$0.16/25mg	$0.80/5mg	**$0.75/2.5mg**

Dosage

The dosage range for ramipril is 2.5-20mg daily given in a single or two divided doses. The target dose of ramipril for post-MI use is 5mg BID.

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Pharmacotherapeutic Specialists

2. Zopiclone (Imovane®)

Zopiclone is a short-acting non-benzodiazepine sedative-hypnotic. It is approved as an alternative in patients who require but do not tolerate benzodiazepines (BZD) or other existing less costly agents.

Pharmacology

Pharmacologic effects are related to the binding of zopiclone to sites near the BZD receptor complex and facilitation of gamma-aminobutyric acid (GABA) function. Similar to BZDs, zopiclone displays anxiolytic, anticonvulsant and muscle relaxant properties.

Comparable Formulary Agents

The pharmacokinetics of zopiclone are similar to other formulary sedative-hypnotics.

Table 2. Comparison of formulary sedative-hypnotics

Drug	Half-Life (hr)	Onset (min)	Duration (hr)	Dose (mg)	Cost/ day
Lorazepam	10-20	15-30	4-6	1-2	$0.02-0.03
Oxazepam	3-21	30-60		15-30	$0.01
Temazepam	10-20	30-45	4-7	15-30	$0.21-0.25
Chloral Hydrate	4-12	30-60	4-12	500-1000	$0.03-0.06
Zopiclone	**3.5-6**	**15-30**	**8-10**	**7.5**	**$0.57**

Zopiclone improves sleep parameters in healthy volunteers to a similar degree as other BZDs (nitrazepam, temazepam). Similar to BZDs, zopiclone delays the onset of rapid eye movement (REM) sleep, but does not affect the overall duration of REM sleep. Zopiclone has not been compared directly to chloral hydrate.

Adverse Effects/Dependence Liability

Zopiclone is well tolerated in the majority of patients. The most common side effect is a bitter/metallic taste (3.6% patients) occurring about 25 minutes after administration. Other side effects include dry mouth (1.6%), psychomotor impairment and drowsiness after awakening ("hangover effect").

Zopiclone is reported to cause less rebound insomnia and hangover effects compared to BZDs. It may induce anterograde amnesia but reportedly to a smaller extent than BZDs. Dependence liability may also be less, but more experience is required to confirm this. Serious withdrawal symptoms have not occurred after abrupt discontinuation. As well, tolerance has not been shown to develop to the hypnotic effects of zopiclone after 8 or 17 weeks of therapy.

Conclusions

Zopiclone is a non-BZD sedative-hypnotic which is comparable in efficacy to BZD hypnotic agents, although at a higher daily cost. Further studies are required regarding its dependence liability, but serious withdrawal reactions have not been reported and rebound insomnia is rare. As such, zopiclone is recommended as a second-line (alternate) agent for use in patients who cannot tolerate or who are unresponsive to BZD therapy.

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QUESTIONS

Is local instillation of antibiotics in an infected pacemaker pocket effective?

Infection remains a major complication of pacemaker implantation. Investigators have reported a post-operative infection rate of 0.6-14% in patients receiving an implanted pacemaker.[1-4] In addition, the perioperative administration of systemic antibiotics has been shown to significantly reduce the postoperative infection rate.[4] Infections associated with permanent cardiac pacing can result in potentially serious complications such as bacteremia, septicemia and endocarditis.[5-8]

Most published articles describe successful treatment of infected pacemakers with systemic antibiotic therapy directed towards the infecting pathogen.[1,3,5-14] Some authors have advocated complete removal of all foreign material combined with a course of systemic antibiotics[1], while others have successfully managed this condition with systemic antibiotics without removing the pacemaker.[3,7]

There are only two articles which deal with the local administration of antibiotics into the pacemaker pocket.[7,14] In the early 1970s, Furman et al successfully treated five local pacemaker pocket infections with wound irrigation of various antibiotic solutions (ampicillin, neomycin, bacitracin, and kanamycin).[7] In a non-comparative, non-randomized study, the prophylactic value of either perioperative local instillation of cloxacillin into the pacemaker pocket or systemic flucloxacillin was evaluated.[14] Both strategies appeared to be effective in the prevention of post-operative infections. Neither study evaluated adverse effects such as tissue irritation or the limitations of local treatment for a potentially systemic disease.

In conclusion, it appears that post-operative infections continue to be a complication with pacemaker implantation. In addition, there is significant risk of developing bacteremia, septicemia, and endocarditis in these patients once they develop an infection. Therefore, patients should be treated aggressively with systemic antibiotic therapy directed against the microbial pathogen. As with any postoperative use of antibiotic irrigations, there is no evidence to suggest that irrigations are superior to systemic therapy.[15] Given the uncertainty about the irrigating dose to administer and the lack of controlled trials documenting efficacy, systemic therapy is the preferred treatment for pacemaker pocket infections.

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What is the Role of Ondansetron for Post-Operative Nausea and Vomiting?

Postoperative nausea and vomiting (PONV) has a multifactorial etiology. Factors which are thought to contribute to the development of PONV include[1]:

a) type of anesthetic agent used
    thiopental > propofol
b) surgical procedure (incidence PONV)
    intra-abdominal surgery (70%)
    major gynecological surgery (58%)
    laparoscopic surgery (40-77%)
    ENT surgery (71%)
c) patient factors
    females > males
    previous postop emetic experience
    history of motion sickness
d) postoperative factors
    pelvic or visceral pain
    opioid administration
    movement
    hyponatremia
    premature intake of fluids/food

Consequences of PONV

Although rare, the complications of PONV can be serious. These complications include aspiration pneumonitis, wound dehiscence, bleeding, and delayed hospital discharge.

Prophylaxis of PONV

For surgical procedures associated with a high incidence of PONV or patients with a prior history of PONV, prophylactic antiemetics are beneficial.

There are several studies utilizing prophylactic treatment strategies to reduce the incidence of PONV in high risk procedures.[2-17] In four trials [2-5], propofol was used as the induction agent, which is currently the predominant induction agent used at VHHSC. Overall, droperidol 1.25mg IV was shown to be as effective as ondansetron 4mg IV when administered prophylactically either prior to or on completion of surgery.

If breakthrough PONV occurred, one to two doses of prochlorperazine 12.5mg IV/IM or metoclopramide 10mg IV/IM were sufficient to relieve symptoms.

Treatment of Established PONV

There are no trials comparing ondansetron to other antiemetic medications for the treatment of established PONV. Based on the success of prochlorperazine and metoclopramide for the treatment of breakthrough PONV in the prophylactic trials, the following algorithm has been adopted at VHHSC:

Figure 1. Role ofondansetron in the treatment of PONV

Conclusions

From the available literature, it appears that prophylactic administration of antiemetics may be warranted in patients undergoing high risk surgery or with a prior history of PONV or motion sickness. The results of these trials support that droperidol 1.25mg IV administered post-operatively is effective in preventing PONV in patients induced with propofol.

For treatment of established PONV, ondansetron is not recommended as a first-line agent. Ondansetron will be reserved for use in patients with documented failure to at least 2 prior doses of metoclopramide or a phenothiazine-type antiemetic (e.g. prochlorperazine).

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Adverse Drug Reaction Report 1996

There were a total of 21 suspected adverse drug reactions (ADRs) reported in 1996 (Table 3). The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in the determination of the incidence of adverse events.

To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to pharmacy, or call the pharmacy at local 62481 (Oak & 12th site) or local 27249 (UBC site). Pharmacists complete all ADR forms and forward copies to the BC Drug and Poison Information Centre (DPIC). DPIC forwards all reports to the Canadian ADR program in Ottawa for collation. Your continued support of the ADR program is greatly appreciated.

Table 3. ADR Report 1996

Drug	Suspected ADR (# patients)
Cloxacillin	renal impairment (1)
Diclofenac	anaphylaxis (1)
Fenfluramine	pulmonary hypertension (1) non-Q wave MI (1)
Gemfibrozil + Simvastatin	rhabdomyolysis (1)
Heparin	thrombocytopenia (1) hyperkalemia (1)
Ipratropium	Ocular pain & blurred vision (1)
Iron Dextran	headache, rash (1) rash, swollen eyes, lips (1)
Nifedipine XL	swollen lips & buccal mucosa (1)
Olanzepine	granulocytopenia (granulocyte count decreased to 1.8) (1)
Paroxetine	↑ INR with warfarin therapy (1)
Phenytoin	morbiliform rash (2)
Sertraline	acute chest pain with radiation to arms, nausea (1)
Tamoxifen	↑ INR with warfarin therapy (1)
Tinzaparin	thrombocytopenia (2)
Vancomycin	red man syndrome (2)

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