VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

A Publication of the Department of Pharmacy

December, 1995 *Volume 2, Number 6*

INDEX

CHANGES TO FORMULARY

Additions

1. **Diclofenac Sodium 0.1% eye drops (Voltaren®)**
   - non-steroidal anti-inflammatory drug used for prevention of intra-operative pupillary constriction during cataract surgery as well as for treatment of inflammatory conditions
   - cost: $11.00/2.5mL (comparison flurbiprofen eye drops 0.03% $12.00/3mL)

2. **Amiodarone 150mg/3mL (Cordarone®)**
   - class III antiarrhythmic approved for the treatment of ventricular arrhythmias where conventional agents are ineffective
   - restricted to ICU, CCU, CSICU and Emerg
   - cost: $5.59/150mg

3. **Gabapentin 300mg, 400mg capsules (Neurontin®)**
   - adjunctive therapy for refractory partial seizures with or without generalization
   - restricted to neurology service
   - cost: $3-12/day

4. **Lamotrigine 25mg, 100mg tablets (Lamictal®)**
   - adjunctive therapy for refractory partial seizures with or without generalization.
   - restricted to neurology service
   - cost: $3-6/day

5. **Vigabatrin 500mg tablet (Sabril®)**
   - adjunctive therapy for refractory complex partial seizures ± generalization
   - restricted to neurology service

- cost: $4-6/day

6. **5-Aminosalicylic Acid 500mg tablet (Pentasa®)**
   - indicated for active and quiescent ulcerative colitis and active Crohn's disease of the small bowel and colon
   - see cost comparison, page 4

7. **Rocuronium 2mg/mL (Zemuron®)**
   - neuromuscular blocker similar in kinetics to vecuronium with a significantly shorter onset of action (1-1.5 mins)
   - cost $8.00-18.00/intubating dose (comparison vecuronium $9.00-17.00/intubating dose)

Deletions

1. **Flurbiprofen 0.03% eye drops (Ocufen®)**
   - alternative: Diclofenac Sodium 0.1% eye drops (Voltaren®)

2. **Vecuronium 10mg vial (Norcuron®)**
   - alternative: Rocuronium

UPDATED POLICY AND PROCEDURES

1. Prescription Interpretation Policy

The following PIPs have been added, unless the dosage form is specifically stated:

T If diltiazem BID is ordered, diltiazem SR is dispensed.
T If diltiazem daily is ordered, diltiazem CD is dispensed.
T If nifedipine BID is ordered, nifedipine PA is dispensed.
T If nifedipine daily is ordered, nifedipine XL is dispensed.
T If nifedipine PRN is ordered, nifedipine regular is dispensed.

2. Revised Drug Administration Policies

The following revised policies will appear in the next update of the Parenteral Drug Therapy Manual (~ Dec 1995):

Indocyanine Green may be administered by the **direct IV route by nurses in the eye care centre**.

Amphotericin B - **The IV adminstration** of amphotericin B must be **controlled by an automated infusion control device**.

Dopamine rates greater than 5mcg/kg/min may be administered in critical care areas and the **NICU**.

Nitroglycerin may be administered by the intravenous route in critical care areas, telemetry units, and the **NICU**.

Octreotide may be given by the direct IV route by nurses on general nursing units.

Meperidine may be administered by intermittent IV in 50mL IV solution over 15-30 minutes.

Hyaluronidase need only be added to subcutaneous infusions **if the infusion rate is greater than 10mL/hour.**

3. Pharmacy-Based Warfarin Dosing Service for DVT Prophylaxis in Orthopedic Patients

A Pharmacy-based warfarin nomogram has been created for deep vein thrombosis (DVT) prophylaxis in post-operative orthopedic patients. This nomogram has been endorsed by Dr. B. Masri (Orthopedics), Dr. C. Carter (Hematology) and the Drugs and Therapeutics Committee. The nomogram was initiated on W6 on November 14/95. An analysis of this nomogram will be performed 6 and 12 weeks post-inception. Pharmacists will provide warfarin service on a 7 day basis. The nomogram is designed to reach an INR of 1.6-2.3 and is therefore not appropriate for the treatment of a DVT or pulmonary embolus.

4. Patient's Own Medication

This is a reminder that when an order for a patient to use his/her own medications while in hospital is written, the medication must be sent to pharmacy for identification. A recent incident occurred when an order was written for "patient may use own Monopril® 10mg daily". On receipt of the vial of medication labelled "Monopril 10mg", the pharmacist identified the capsules as Altace® 5mg, a different ACE inhibitor. It was found that the patient had transferred his Altace® to the easier to open Monopril® bottle. The physician was contacted and the patient was switched to the formulary alternative, enalapril.

NEW DRUG AND DRUG PRODUCTS

PENTASA® (5-Aminosalicylic Acid)

Introduction

Aminosalicylic acid (5-ASA) is the active moiety of sulfasalazine, an agent traditionally used for the treatment of inflammatory bowel disease (IBD). Sulfasalazine is chemically composed of two agents: 5-ASA and sulfapyridine. However, its use is limited by a lack of efficacy in IBD involving the small bowel and by allergic side effects caused by the sulfapyridine moiety.

It is thought that 5-ASA exerts a topical anti-inflammatory effect on the bowel, where it inhibits prostaglandin and leukotriene synthesis. 5-ASA is available in different forms which deliver the drug to various parts of the GI tract. Pentasa® is a new sustained release formulation of 5-ASA.

Indications

Pentasa® is indicated for treatment of active mild to moderate ulcerative colitis and Crohn's disease involving the small bowel (duodenum, jejunum, ileum) and colon, and maintenance of remission in ulcerative colitis.

Dosage

0.5 - 1 g 3-4 times daily taken with meals and at bedtime with fluid.

Comparison of 5-ASA Products

The following table compares Pentasa® to other formulary 5-ASA products at VHHSC. The major difference between products lies in their formulation which

imparts different release times and sites of action. The release of 5-ASA from Asacol® and Salofalk® begins when the enteric coating dissolves as the pH of the gut increases. With Pentasa®, 5-ASA is encapsulated in a bead with a semipermeable membrane. Release is dependent on the rate of water absorption and the pH-dependent solubility of the encapsulated 5-ASA, imparting sustained release properties to the formulation.[1]

Table1. Comparison of Formulary 5-ASA Products[1,2]

Product	Pentasa®	Asacol®	Salofalk®
Tablet Formulation	Sustained Release	Enteric Coated	Enteric Coated
Release pH	6-7.5	7	6
Site of 5-ASA Release	Duodenum, jejunum, ileum, colon	Terminal ileum, colon	Mid-jejunum, ileum, colon
Cost/tablet	$0.56 /500mg	$0.50 /400mg	$0.52 /500mg
Other formulations	-	-	enema

Once released from the various formulations, approximately 20-30% of 5-ASA is absorbed systemically. The absorbed 5-ASA is rapidly metabolized (acetylated) by the gut mucosal wall and liver and excreted in the urine. The unabsorbed drug is excreted both as free and acetylated forms via feces.

There are no published clinical trials comparing efficacy of the different 5-ASA formulations. Studies on both healthy volunteers and patients with clinically quiescent inflammatory bowel disease (IBD) but no diarrhea showed Pentasa® to release 5-ASA sooner than Asacol® and Salofalk®.[3,4] In patients with IBD and concurrent diarrhea, the release of 5-ASA from Pentasa® exceeds that of the other formulations and is as well less affected by intestinal transit time.[3]

Adverse Drug Reactions

All 5-ASA products cause a similar incidence of side effects. The more common side effects include abdominal discomfort, diarrhea, dyspepsia, nausea, headache and rash. Rarely the drug can cause pancreatitis, nephrotic syndrome, and alopecia.

All 5-ASA products are contraindicated in patients with hypersensitivity to salicylates. Caution is recommended in the presence of renal failure or in patients suffering from peptic ulcer disease.

Conclusions

Pentasa® is a new sustained release formulation of 5-ASA. It may provide benefit over other 5-ASA products for the treatment of IBD when the small intestine is affected more proximally. In addition, release of 5-ASA from Pentasa® appears less affected in the presence of diarrhea.

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LAMOTRIGINE, GABAPENTIN, VIGABATRIN

Table 2 compares the three new antiepileptic drugs (AED) recently added to the VHHSC formulary. All three AEDs are indicated as adjunctive therapy for

refractory partial seizures with or without generalization. All three have shown good efficacy in up to 60% of patients with refractory seizures when used in combination with traditional AEDs. Lamotrigine is the only agent which when used alone was as effective as carbamazepine or phenytoin in the treatment of newly diagnosed primary generalized seizures.[1,2] The drug was also better tolerated.

Due to limited experience with these agents and lack of head to head trials comparing them to each other, it is difficult to determine which drug is most efficacious. While these agents have differing mechanisms of action, they all appear to be safe with similar side effects. Gabapentin has the advantage of not interacting with other AEDs. It does have a shorter half-life, requiring at least twice daily dosing.

Rarely, skin rashes from lamotrigine can develop into Stevens-Johnson syndrome. Also, other AEDs alter the clearance of lamotrigine, which may affect its dosage requirements. Vigabatrin may worsen myoclonus or absence seizures if used for these seizure types. While receiving this drug, patients with a history of previous psychotic illness, depression or behavioural changes may develop or experience exacerbations of these conditions. Although vigabatrin lowers phenytoin serum levels, this appears to be of minimal clinical significance.

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Sotalol-induced Torsade de Pointes

Sotalol (Sotacor®) is a class III antiarrhythmic drug which has both beta-blocking and antiarrhythmic properties. It is used for the treatment of symptomatic or life-threatening arrhythmias (both ventricular and atrial). Unlike other beta-blockers, sotalol has pro-arrhythmic properties. It can induce a polymorphic ventricular tachycardia called torsade de pointes (torsade).[1-5]

Incidence

The incidence of sotalol-induced torsades ranges from 0.5-6% and is dependent on various risk factors including dose and underlying arrhythmias. The incidence is highest in patients being treated for ventricular tachycardia or fibrillation and with doses greater than 320mg per day.[2]

Over 60% of torsade occurs within the first 3 days of therapy and over 75% occurs in the first week of treatment.[2]

Risk Factors for Torsade de Pointes

Underlying Arrhythmia: Treatment of sustained ventricular tachycardia or fibrillation.[2]

Cardiovascular History : Patients with congestive heart failure, cardiomyopathy or cardiomegaly.[2]

QT_c Interval: A prolonged baseline QT_c interval greater than 430 msec.[4,5] The incidence of torsade approaches 11% for patients with QT_c prolongation > 550 msec while on sotalol therapy.[1]

Bradycardia: A heart rate less than 50

beats per minute.[1,3]

Electrolyte disturbances: Hypokalemia and hypomagnesemia can enhance QT prolongation.[1,5]

Dose: The risk of torsade correlates directly with increasing doses of sotalol.[2] The usual initiating dose of 80mg twice daily must be adjusted in renal impairment as sotalol is primarily renally eliminated (~90%). At least 5 doses should be given at appropriate intervals prior to further dose titration.

Table 3. Dose Adjustment in Renal Failure[1,2,4]

Creatinine Clearance	Initial Sotalol Dose
> 60 mL/min	80mg q12h
30-60 mL/min	80mg q24h (or 40mg BID)
10-30 mL/min	80mg q36-48h (or 40mg daily)
hemodialysis	*40mg q24h, given post dialysis

* literature recommendations not available

Female Gender: Women account for 70% of reported cases of torsade induced by cardiovascular drugs, possibly due to their longer average QT interval compared to men.[6]

Drug Interactions: Concomitant use of drugs which can independently prolong the QT interval:

- Class 1a (e.g. quinidine, procainamide) and class III (e.g. amiodarone) antiarrhythmics[1,2]
- Phenothiazines, tricyclic antidepressants, non-sedating antihistamines (terfenadine, astemizole), erythromycin, cotrimoxazole, antifungals (ketoconazole, itraconazole)[5]
- Diuretics can increase risk by causing hypokalemia and/or hypomagnesemia[2,4]

Prevention and Management

Dose reduction or discontinuation of therapy should be considered as QT_c intervals approach or exceed 550 msec. If torsade develops during therapy, sotalol should be stopped and any electrolyte disturbances corrected. Torsades is often self-terminating. Symptomatic episodes can be controlled with intravenous magnesium sulphate, isoproterenol, ventricular pacing, or DC cardioversion.[1,5]

References

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Table 2. Comparison of three new antiepileptic drugs (AED)[3,11]

Drug	Structure/ MOA	Kinetics	Indications	Adverse Drug Reactions	AED Interactions	Dosage	COST /DAY	Advantages	Disadvantages
Gabapentin (Neurontin®)	GABA analogue/ unknown	F= 36-68% (0 order absorption) PB = min'l t1/2 5-8hrs Renal elim'n	•refractory partial ± secondary generalized (as adjunct)	Somnolence(20% - transient) Dizziness (18%) Ataxia (13%) Nystagmus (9%) Tremor (7%) Diplopia (6%)	-	900-3600mg/day in 2-3 doses	$3-12	•no AED interactions •minimal PB	•zero order absorption •BID-TID dosing •limited usage
Lamotrigine (Lamictal®)	phenyl-triazine/ stabilize neuronal membrane, 9 release excitatory neurotrans.	F= 96% PB = 56% t1/2 29 hrs Hepatic elim'n	•refractory partial ± secondary generalized (as adjunct) • primary generalized (as monotherapy) •absence	Skin rash (3-10%) Somnolence(13%) Dizziness Headache (12%) Diplopia (14%) Ataxia (11%)	•VPA increases the half-life of lamotrigine • phenytoin,CBZ, phenobarbital decrease half-life of lamotrigine	200-400mg/ day in 1-2 doses	$3-6	• high bioavailability •1-2 doses/ day •multiple indications •monotherapy (not approved)	•may cause Stevens-Johnson syndrome •other AEDs affect its clearance
Vigabatrin (Sabril®)	GABA analogue/ inhibits breakdown of GABA	F = 80% PB = min'l t1/2 7-9 hrs Renal elim'n	•refractory complex partial seizures with or without generalization (as adjunct)	Drowsiness (13%) Dizziness (<4%) Ataxia (<4%) Diplopia (<4%) Irritability Behavioural changes (4-6%)	•vigabatrin decreases phenytoin levels by 20-30% (minimal consequence)	2-3g/day in 1-2 doses	$4-6	•minimal PB •1-2 doses/day	•decreases phenytoin levels •caution in patients with psychiatric history

MOA = mechanism of action; F = bioavailability; PB = protein binding; t1/2 = half-life; CBZ = carbamazepine; VPA = valproic acid