VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

A Publication of the Department of Pharmacy

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In This Issue...

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics Committee (D&T) and Medical & Academic Advisory Council (MAAC).

This and other D&T Newsletters are on the Web at **www. vhpharm-sci.com**

Changes to Formulary

Additions

1. Clopidogrel 75 mg tablet (Plavix®)

- antiplatelet agent similar to ticlopidine but with a more favourable side effect profile
- restricted to neurology, vascular surgery, cardiology, and cardiovascular surgery
- Cost: $2.44/day (75mg daily) versus ticlopidine $1.48/day (250 mg bid)
- See page 3 for drug review

2. Terazosin 1, 5 mg tablets (Hytrin®)

- postsynaptic alpha-1 adrenergic blocker
- indicated for the symptomatic treatment of benign prostatic hyperplasia (BPH) and treatment of mild-moderate hypertension
- Cost: $0.55-1.40/day (1-10 mg hs) versus prazosin $0.56-1.06/day (1-5mg bid)
- see page 4 for drug review

Updated Policies/Procedures

1. Modification of Drug Status

- The current restrictions for **fentanyl patches** are relaxed to include Palliative Care Unit and Acute Pain Service.

2. Expansion of TPN Prescribing Privileges

- Dr. J Jastrzebski, Division of Nephrology, may prescribe Intradialytic Parenteral Nutrition (IDPN) for the Vancouver Hospital hemodialysis patient population.

3. Parenteral Drug Therapy Manual (PDTM)

- All PDTMs at VHHSC were updated in March 1999. For any questions regarding this manual, please contact Dr. Karen Shalansky at (604) 875-4077.

4. Revised Drug Administration Policies

- **Intravenous methylprednisolone doses of greater than 250mg** must be administered over at least **30 minutes**. Exception: Acute spinal cord injury bolus of 30mg/kg over 15 minutes.

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- **Morphine, meperidine and fentanyl** may be administered **IV direct over at least 1 minute.** For **fentanyl, a maximum of 25mcg/dose per 10 minute interval may be given IV direct** on general nursing units. Nurses in Critical Care Areas, Burn Unit, *in vitro* Fertilization Clinic and Palliative Care Unit have no dose limitations for fentanyl.

- **Abciximab** dosage regimen guidelines have been updated to **weight-based dosing**: 0.25mg/kg IV over one minute (given 10-60 minutes prior to PTCA) followed by a continuous infusion of **0.125mcg/kg/minute** (**maximum 10mcg/minute**) for a total of 12 hours. Refer to PDTM for dosing chart.

- **Nitroglycerin weight-based dosage** regimen guidelines have been added: Initiate with 0.2mcg/kg/min and increase in increments of 0.1mcg/kg/min every 3-5 minutes until response; if no response noted at 0.3mcg/kg/min, increments of 0.2-0.4mcg/kg/min can be used.

- **Amiodarone dosage** regimen guidelines for the treatment of ventricular and supraventricular arrhythmias has been **updated** according to the recent American Heart Association guidelines: **Initial rapid loading dose of 150mg over 10 minutes, followed by a slow loading dose of 360mg over 6 hours, then a maintenance infusion of 30mg/hour.** Refer to PDTM for dilution and administration rates.

- The **dosage** regimen guidelines for **calcitonin for pain relief of osteoporotic vertebral fractures** has been added: **20-100 units SC daily**.

- The **dosage** regimen guidelines for **aprotinin for orthotopic liver transplantation** has been added. Refer to PDTM for details.

- **Dosage regimens for all narcotics** listed in the PDTM (anileridine, fentanyl, hydromorphone, meperidine, morphine) have been updated to optimize acute pain management and reflect current literature-based recommendations. Please refer to individual monographs.

5. Revised *Helicobacter pylori* Treatment Regimen

The preprinted orders for management of *Helicobacter pylori*-associated peptic ulcer disease have been modified to be consistent with the 1998 Canadian *Helicobacter pylori* Consensus Conference.[1] In particular, clarithromycin dosage can be reduced to 250mg bid po x 7 days when used in combination with metronidazole and a proton pump inhibitor. In contrast, a higher dose of clarithromycin appears to be optimal when combined with amoxicillin and a proton pump inhibitor. The following 3 regimens now appear on the preprinted orders.

- **Regimen 1 - Quadruple Therapy**
  (acquisition cost/7 days ~$36.00; success rate 94-98%)

1. Bismuth Subsalicylate 30mL QID po x 7 days
2. Metronidazole 250mg QID po x 7 days
3. Tetracycline 500mg QID po x 7 days
4. Omeprazole 20mg BID po x 7 days

- **Regimen 2 - Triple Therapy**
  (acquisition cost/7 days ~$42.00; success rate 86-91%)

4. Metronidazole 500mg BID po x 7 days
2. **Clarithromycin 250mg BID po x 7 days**
3. Omeprazole 20mg BID po x 7 days

- **Regimen 3 - Triple Therapy**
  (acquisition cost/7 days ~$65.00; success rate 86-91%)

3. Amoxicillin 1g BID po x 7 days
2. Clarithromycin 500mg BID po x 7 days
3. Omeprazole 20mg BID po x 7 days

Reference

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New Drug/Drug Products

CLOPIDOGREL (Plavix®)

Mario de Lemos, Pharm.D. student, Rubina Sunderji, Pharm.D.

Clopidogrel is a new antiplatelet agent with a similar chemical structure and mode of action to ticlopidine.[1,2] Clopidogrel inhibits platelet aggregation by irreversibly inhibiting the adenosine diphosphate (ADP) pathway for platelet activation, thus suppressing the activation of the glycoprotein IIb/IIIa receptor. Unlike aspirin (ASA), clopidogrel does not affect the cyclo-oxygenase pathway and thromboxane-A2.

Role of Antiplatelet Agents

Low dose ASA is indicated for secondary prevention of mycocardial infarction (MI), stroke and other vascular events in patients with symptomatic atherosclerotic disease.[3,4] Ticlopidine represents a formulary alternative to ASA in patients who cannot tolerate or have failed ASA.[4] It is also used in combination with ASA for the prevention of stent thrombosis. However, hematological adverse effects of ticlopidine (e.g. neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP)) necessitate close CBC monitoring. Clopidogrel does not appear to cause these hematological effects and thus offers a safer, but more expensive alternative to ticlopidine.

Clinical efficacy: Prevention of Vascular Events

ASA prevents approximately 15 secondary ischemic events annually per 1000 patients with atherosclerotic disease.[5] A comparative study of ASA 650mg bid and ticlopidine 250mg bid in 3069 patients within 3 months of transient ischemic attack (TIA) or minor thrombotic stroke showed a significant benefit of ticlopidine over ASA.[6] The 3 year event rate for fatal or non-fatal stroke was 10% for ticlopidine and 13% for ASA (p=0.024, number needed to treat, NNT = 33).

Recently, a large randomized, controlled trial (CAPRIE) in 19,185 patients with previous stroke, MI or peripheral vascular disease ccompared clopidogrel 75mg/day to ASA 325mg/

The incidence of severe neutropenia with clopidogrel was similar to ASA (0.04% vs 0.02% for ASA)[7] and less than that reported with ticlopidine (0.8%).[4,6] Unlike ticlopidine, clopidogrel has not been reported to cause TTP.[16] Consequently, clopidogrel does not require the hematological monitoring (every 2 weeks for 3 months) as is necessary with ticlopidine.

Formulary Status

Both clopidogrel and ticlopidine are restricted to the divisions of neurology, vascular surgery, cardiology, and cardiovascular surgery.

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Table 1. Comparison of Antiplatelet Agents

Antiplatelet Agent	Dosing Regimen	Daily Cost†	PharmaCare Coverage
Clopidogrel	75mg daily	$2.44	No
Ticlopidine	250mg bid	$1.48	Yes
Enteric Coated ASA	81mg daily 325mg daily	$0.09 $0.01	Yes

† based on VHHSC acquisition costs

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TERAZOSIN (Hytrin®)

Edith St Pierre, B. Pharm., M.Sc., Debbie Partridge, B.Sc. (Pharm)., Karen Shalansky, Pharm.D.

Terazosin causes smooth muscle relaxation in the peripheral vasculature, resulting in arterial and venous dilation. As well, this drug relaxes smooth muscle of the bladder neck and prostate. Terazosin is indicated for the treatment of mild-moderate hypertension and for the symptomatic treatment of benign prostatic hyperplasia (BPH).

Pharmacology

Terazosin is a long-acting selective postsynaptic alpha-1 adrenergic antagonist. For the management of BPH, terazosin causes relaxation of the smooth muscle in the bladder neck, prostate capsule and prostatic urethra.[1-5] This relaxing effect helps reduce outflow obstruction, improve peak urine flow rate and decrease other symptoms of BPH such as hesitancy, urgency, frequency, terminal dribbling, incomplete empyting and nocturia.[5,6] Terazosin is effective in approximately 60-70% of patients[6] with relief of symptoms occurring as early as 2-4 weeks following initiation of therapy[6].

Unlike finasteride (Proscar®), terazosin has no effect on prostate size nor on the concentration of prostatic specific antigen.[6] It neither arrests nor retards the progression of BPH.[1,4]

Comparison of Selective Alpha-1 Antagonists

Terazosin is a structural analogue of prazosin with similar pharmacological effects (Table 2). Compared to prazosin[8], terazosin has been more widely studied in controlled trials for the management of BPH, has a longer half-life allowing once daily dosing and is approved by the Health Protection Branch for the management of this condition. Doxazosin, a newer alpha-1 blocker, is also structurally similar to terazosin and appears to be similar to this agent in its effects on BPH.[9]

Tamsolusin is the newest alpha-1 antagonist which selectively blocks the alpha-1a adrenoreceptor subtype that predominates in the prostate. This agent has the potential to cause less orthostatic hypotension compared to terazosin[6,10,11], but this advantage has not been clearly proven and there are no adequate head-to-head trials using equipotent doses of both agents for BPH.

Dosage Regimen for BPH

The starting dose is 1mg daily at bedtime, increasing to 10mg/day at stepped intervals (2mg, 5mg, 10mg) every 1-2 weeks.[1,2] Dosages of 5-10mg are usually necessary for a clinical response. To minimize the risk of hypotensive side effects, this dose is best taken at bedtime.[1]

Adverse Effects

The most common side effects of terazosin are related to its potential blocking effect of the vascular smooth muscle. Terazosin can cause dizziness (14%), asthenia (9%), headache (6.4%), somnolence (4.5%), postural hypotension (3.8%) and "first dose" hypotension and syncope (0.7%).[6] These side effects, which appear to be dose related, can be largely alleviated by bedtime administration and slow dose titration. Use caution in patients with renal or liver impairment (40% renally eliminated).[1]

Conclusion

Terazosin, a long-acting postsynaptic alpha-1 adrenoreceptor antagonist, significantly improves the symptoms of BPH in approximately 60-70% of patients. Prazosin, although structurally similar to terazosin, has not been as well studied for the management of BPH and must be administered at least twice daily, placing the patient at increased risk of postural hypotension if switched over from bedtime dosing of terazosin. Tamsolusin, a newer more selective alpha-1a blocker in the prostate, could potentially exhibit a better safety profile (less hypotension), but further studies must be carried out to estab-

(continued from page 4)

lish its superiority over terazosin.

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Table 2. Comparison of Selective alpha-1 Antagonists for BPH

Drug Name	Daily Dose	Half-Life (hrs)	Cost/ day†	PharmaCare Coverage
Terazosin‡ (Hytrin®)	1-10mg daily hs	12-14	$0.55-1.40	Yes
Prazosin‡ (Minipress®	2-10mg given in 2 doses	2-6	$0.56-1.06	Yes
Doxazosin (Cardura®)	1-8mg daily	9-13	$0.55-1.70	Yes
Tamsolusin (Flomax®)	0.4-0.8mg daily	10-13	$0.95-1.90	No

† based on VHHSC acquisition costs
‡formulary drug at VHHSC

Herbal Interactions with Warfarin

Mario de Lemos, Pharm. D. student, Rubina Sunderji, Pharm.D.

Several case reports of interactions between various herbal products and warfarin have been reported recently.[1-12] As warfarin has a narrow therapeutic window, it is important to be aware of these potential interactions to prevent anticoagulant under- or overdosage. Table 3 summarizes interactions between commonly used herbal products and warfarin.[1-17]

Case reports

Heavy use of garlic (*Allium sativum*) supplement was associated with one case of spontaneous spinal epidural hematoma[1] and two cases of prolonged clotting time with increased postoperative bleeding.[2,3] The authors suggest that garlic supplements should be stopped for at least 10-14 days prior to surgery.[2,3] Although none of these patients were receiving concurrent warfarin, it is prudent to avoid garlic supplements in patients taking warfarin. Ginkgo (*Ginkgo biloba*) at a daily dose of 80-160 mg was associated with 5 cases of hemorrhage: subdural hematoma (2)[4,5], hyphema (1)[6], intracerebral hemorrhage (1)[7] and subarachnoid hemorrhage (1)[8]. In three of these cases, the time to onset of the adverse effect was relatively short from the time of starting Ginkgo, from 1 week[5] to less than 2 months[6,7]. Although only one case involved concurrent warfarin[7] and another involved aspirin[6], patients taking warfarin should avoid Ginkgo due to the possible increased risk of hemorrhage. Danshen (*Salvia miltiorrhiza*) was found to potentiate anticoagulation in three patients stabilized on warfarin.[9-11] The INR was increased from around 2.0-3.0 to over 5.5 after taking danshen for 2-4 weeks. Ginseng was reported to reduce INR from 3.0-4.0 to 1.5 in a patient stabilized on warfarin after taking ginseng capsules for 2 weeks.[12]

Other commonly used herbal products which have NOT been reported to interfere with warfarin include alfalfa, bee pollen, betel nut, blue-green algae, chamomile tea, devil's claw, dong quai, evening primrose oil, kelp, milk thisle, royal jelly, saw palmetto, St. John's wort, and valerian.[13-16] A lack of reported cases however does not imply the safety of these products when administered with concurrent warfarin, as few of these combinations have been studied specifically to determine the impact of herbal medications on anticoagulation. For example, some herbs (e.g. chamomile[14]) contain coumarins although their effects on the anticoagulant system is unknown.[17]

Table 3. Drug Interactions between Warfarin and Herbal Products

Herb	Common Usage	Interaction	Evidence of Interaction
Danshen[9-11,18]	Coronary heart disease, supplement post surgery	↑ INR by ↓ warfarin elimination; also ↓ platelet aggre-	case reports (see text)
Echinacea purpurea[19]	Stimulates immune response to infections	↑ INR by ↓ warfarin metabolism by ↓ CYP3A4	potential†
Feverfew	Migraine, rheumatoid arthritis	↑ risk of bleed by ↓ platelet aggregation	potential†
Garlic[1-3]	Atherosclerosis, hypertension	↑ risk of bleed by ↓ platelet aggregation	case reports (see text)
Ginger	Nausea	↑ risk of bleed by ↓ platelet aggregation	potential†
Gingko biloba[4-8]	Dementia	↑ risk of bleed by ↓ platelet aggregation	case reports (see text)
Ginseng[12]	Stress, physical endurance	↓ INR, unknown mechanism	case reports (see text)
Green tea & herbal teas made with tonka beans, melilot or	Beverage	↓ INR due to high vitamin K content	potential†

† Interaction based on *in vitro* studies with herb

Conclusion

Due to the limited data available, patients should be advised about the potential interaction of herbal products with warfarin.

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Further references available on request.

Grapefruit Juice-Medication Interactions

Karen Shalansky, Pharm. D.

When ingested together, grapefruit juice can interact with various medications, resulting in potentially toxic drug levels and adverse effects.

Certain bioflavonoids contained in citrus juices can affect drug metabolism. The major bioflavonoid in grapefruit juice is naringin, which is partially metabolized by enteral bacteria to form naringenin.[1,2] Naringenin is a potent inhibitor of the cytochrome p450 liver enzymes: CYP1A2, CYP3A3 and CYP3A4. There is however, considerable inter-individual variability in the effects of grapefruit juice on drug metabolism, in part due to 1) amount of naringenin formed by an individual, 2) amount of naringin present in a brand of grapefruit juice, 3) dilution of grapefruit juice used, and 4) other substances in grapefruit juice accounting for the interaction.[2]

Table 4 lists drugs whose levels may significantly increase if given concomitantly with grapefruit juice. CSU Pharmaceutical Sciences will place a label stating "Do not take with grapefruit juice" if a patient is ordered any drug listed below.

Table 4. Grapefruit Juice-Drug Interactions

Drug	Significance
Dihydropyridine Calcium Channel Blockers: -amlodipine† -felodipine -nicardipine -nifedipine†	AVOID grapefruit juice OR monitor for decreased BP, increased HR if taken together
Terfenadine	AVOID grapefruit juice as may result in cardiotoxicity (prolonged QT interval)
Cyclosporine†	AVOID grapefruit juice, unless prescribed to specifically increase cyclosporine levels
HMG-CoA Reductase Inhibitors (Statins)‡: -atorvastatin -cerivastatin -lovastatin -simvastatin†	AVOID grapefruit juice as potential for myopathy or rhabdomyolysis¶
Cisapride†	AVOID grapefruit juice as potential for cardiotoxicity (torsades de pointes, prolonged QT interval)¶
Benzodiazepines -triazolam -oral midazolam†	AVOID grapefruit juice or monitor for increased sedation if used together
Quinidine†	AVOID; significance unknown
Saquinavir	AVOID; signficance unknown
Estrogens -ethinyl estradiol† -17ß estradiol	AVOID - significance unknown

† formulary drugs at VHHSC
‡ fluvastatin and pravastatin are not affected by CYP3A4 inhibitors[3]
¶ theoretical risk as these adverse reactions have occurred with other

For further information on this topic on line, refer to: *www.powernetdesign.com/grapefruit/*

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Infusion Program Updates

A reduction in available nursing resources has resulted in the need to reduce the IV Resource Nurse support hours.

IV Resource Nurse support has not been available on a 24 hr/day basis since 1991. Prior to March 1, 1999, this service was provided for 16 hr/day on a 7 day/wk basis. For the immediate future, this service will continue to be provided 8 hr/day (M-F) and 16 hr/day (S-S). A formal request to implement an 11.5 hr/day on a 7 day/wk schedule has been initiated and it is anticipated that this will become effective as soon as it is approved by B.C.N.U..

The daily workload statistics gathered by the IV Resource Nurses over the past 5 months reveals that a mean of 2 consults are being documented every service hour. A random sample of 50 interventions during this period also reveals that 98% of these are related to peripheral IV starts and that approximately 35% of these involved veins that were described by the IV Resource Nurses as "visible" and considered to be of either "good" or "fair" status. In over 50% of the consults reviewed, no previous attempts to start the IV appeared to have been made by a unit nurse.

Below are recommendations to address IV access issues when the service is not active:

1. Prepare the patient to facilitate catheter insertion.

   It is usually easier to start an IV when the head of the bed is raised and a hot pack is applied to the entire arm and hand for ten minutes prior to cannulation.

2. Use #24 gauge x 19 mm needle catheters for select patients with difficult IV access.

   Please stock #24 gauge x 19 mm Needle IV Cath. (stock #28562) on your unit. Flow rates of 25 mL/min (1500 mL/hr) can be achieved with these catheters. Although blood products cannot be infused through this catheter, it is easier to insert than larger gauge needles and provides excellent vascular access for antibiotics, other drugs or hydration therapy. A #24 gauge catheter is also useful for the pre-operative patient with difficult vascular access. If necessary, the anaesthetist can insert a larger catheter or central line once the patient is in the operating room.

3. Use the subcutaneous route of administration when appropriate.

   The subcutaneous route is often appropriate for short or long term hydration when vascular access is not possible. See Patient Care Guidelines M 100 (May 1998) for detailed instructions on the use of this technique. An infusion rate of 50 mL/hr is recommended to commence therapy and a subsequent infusion rate of 50-120 mL/hr is possible. When the IV Resource Team is not available, subcutaneous infusions are easily and quickly initiated with a butterfly needle. This route provides an excellent method of hydration and can be used as an interim measure until peripheral vascular access can be achieved.

4. Enhance your parenteral therapy skills.

   The Infusion Program offers a continuing education series on the third Wednesday of every month. These classes are open to all staff who require parenteral therapy skills in their current role. The 1999 Infusion Program Continuing Education calendar has recently been distributed. Group requests for education can also be made by contacting an Infusion Program clinical nurse educator (875-4706).

The current distribution of resources within the Infusion Program is continually being reviewed. Any input on this issue is appreciated.