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

This and other Drug and Therapeutics Newsletters are on the Web at www.vhpharmsci.com

Changes to Formulary

Additions

- 1. Tamsulosin 0.4mg capsule (Flomax®)**
 - Selective alpha-1 receptor blocker indicated for treatment of benign prostatic hypertrophy
 - See page 5 for review
- 2. Dapsone 100mg tablet (Avlosulfon®)**
 - Remarketed in Canada
 - Sulfone anti-infective agent indicated for treatment of leprosy, *pneumocystis carinii* pneumonia and prophylaxis of malaria

Deletions

- 1. Nefazodone 100mg tablet (Serzone®)**
 - Discontinued by manufacturer due to association with adverse hepatic events including liver failure

Updated Policies/Procedures

1. Drug Cost Containment Strategies

We are participating in the implementation of region-wide initiatives designed to reduce drug expenditures while protecting service levels. Cost containment strategies for a multitude of drugs have been identified and these are expected to yield ~\$800,000 in annual savings at the VGH site alone.

The following three strategies were launched on November 12, 2003.

Strategy # 1:

Ceftriaxone to Cefotaxime Therapeutic Interchange

Ceftriaxone is a formulary antimicrobial that replaced cefotaxime on an interchange basis in 1989. These two third generation parenteral cephalosporins are considered therapeutically equivalent. In the 2002/03 fiscal year, ceftriaxone expenditures at VGH exceeded \$250,000. The VGH acquisition cost of ceftriaxone 1g IV q24h is \$30.60/day compared to \$18.00/day for an equivalent cefotaxime dose of 1g IV q8h.

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Effective November 12, 2003, the existing therapeutic interchange was reversed and cefotaxime became the formulary parenteral third generation cephalosporin. **Prescriptions for ceftriaxone are now interchanged to a therapeutically equivalent cefotaxime dosage regimen** (Table 1). Limited supplies of ceftriaxone will be available for outpatient use by protocol only. Documentation of this interchange will appear in the health record. Microbiology will be reporting cefotaxime sensitivities when warranted. An annual cost savings of ~\$65,000 is anticipated from this strategy.

Table 1. Ceftriaxone to Cefotaxime Interchange

| Drug | Ceftriaxone IV dose | Cefotaxime IV dose | | |
|--|-------------------------------|--------------------|-------------------|------------------|
| | | CrCl > 50 mL/min | CrCl 10-50 mL/min | CrCl < 10 mL/min |
| Infections other than meningitis or CNS | 1g q12h 1g q24h 2g q24h | 1g q8h | 1g q8h | 1g q12h |
| Meningitis or CNS infections | 1g q12h 2g q12h 2g q24h | 2g q6h | 2g q8h | 2g q12h |

CrCl (creatinine clearance, mL/minute/72kg) = $\{(140-\text{age})/\text{SCr}\} \times 90$
(x 0.85 for female gender)

Strategy # 2:

IV-PO Dosage Form Conversion Service

We have been actively involved in the promotion of oral dosage forms for a variety of drugs for over a decade. When compared to parenteral therapy, the use of oral dosage forms can provide similar therapeutic outcomes, reduce risks associated with drug delivery, reduce workload and minimize unnecessary drug costs. Chart reminders, internal publications and dialogue between pharmacists, physicians and nurses have led to an increased use of oral therapy. Despite these promotional efforts, there is evidence that oral therapy remains underutilized at this hospital.

To streamline the conversion of parenteral to oral therapy, a pharmacist-managed dosage form conversion service was implemented on November 12, 2003. **All patients receiving IV antimicrobials as listed in Table 2 (page 3) will be considered candidates for oral dosage form**

conversion after 48 hours by ward-based clinical pharmacists if the following criteria are met: 1) the patient continues to need an antibiotic; 2) is clinically stable; 3) is capable of tolerating the oral dosage form; and 4) has no factors present (e.g. GI abnormalities or drug interactions) that would adversely affect oral bioavailability. Documentation of this conversion will appear in the health record and treatment courses will be monitored for oral tolerance and continued clinical response. An annual drug cost savings of at least \$100,000 is anticipated from this strategy.

Strategy # 3:

Proton Pump Inhibitor Therapeutic Interchange and IV-PO Dosage Form Conversion

There are several proton pump inhibitor (PPI) drugs on the Canadian market. This hospital considers these agents to be therapeutically equivalent and the choice of formulary agent is based upon the lowest cost alternative. The formulary parenteral PPI is pantoprazole as there are no other parenteral agents in Canada. We currently have a therapeutic interchange whereby all oral PPIs are switched to either pantoprazole (solid dosage form) or omeprazole MUPS (dissolvable dosage form). We spend ~\$140,000/year on this drug class.

Effective November 12, 2003, oral pantoprazole was deleted from formulary. **Prescriptions for an oral (including NG) PPI are now interchanged to the current low cost alternative: omeprazole MUPS 40mg as a single daily dosage regimen. For *H. pylori*, the interchange regimen is omeprazole MUPS 20mg PO/NG bid. Parenteral PPI treatment courses will also be converted to oral regimens by ward-based clinical pharmacists if: 1) patients are able to tolerate other PO/NG medications (or food); and 2) provided there is no endoscopically-confirmed high risk acute upper GI bleeding peptic ulcer disease/rebleeding within the past 72 hours.** All parenteral PPI dosage regimens (e.g. pantoprazole via continuous IV infusion, 40mg IV daily or 40mg IV bid) are candidates for conversion in accordance with the criteria. Documentation of this conversion will appear in the health record and treatment courses will be monitored for oral tolerance and continued clinical response. An annual drug cost savings of at least \$55,000 is anticipated from this strategy.

Table 2. Pharmacist-Managed IV to PO Dosage Form Conversion Service

| Drug | IV Dose | PO Dose* |
|--|--|---|
| Group 1 (Similar Area Under the Curve (AUC) achieved with oral dosage form of same drug) | | |
| Ciprofloxacin | 200mg q12h 400mg q12h | 250mg given in same interval as IV 500-750mg given in same interval as IV |
| Clindamycin | 300mg, 450mg, 600mg q8h | Same dose and interval as IV |
| Co-trimoxazole | ≤TMP 320mg/day TMP 321-640mg/day TMP 641-960mg/day TMP 961-1280mg/day | i DS q12h ii DS q12h ii DS q8h ii DS q6h |
| Fluconazole | 200mg, 400mg q24h | Same dose and interval as IV |
| Levofloxacin | 250mg, 500mg, 750mg q24h | Same dose and interval as IV |
| Metronidazole | 250mg, 500mg q6-12h | Same dose and interval as IV |
| Group 2 (Lower AUC achieved with oral dosage form of same drug) | | |
| Acyclovir | Acyclovir ≤ 270mg/day 271-540mg/day 541-810mg/day 811-1620mg/day | Valacyclovir 250mg q12h 500mg q12h 500mg q8h 1000mg q8h |
| Ampicillin | 1-2g q6h | Amoxicillin 250-500mg q8h OR Amoxicillin-clavulanate 250-875mg q8h |
| Cefazolin | 1-2g q8h | Cephalexin 250-1000mg q6h |
| Cefuroxime | 750mg q8h | Cefuroxime axetil 500mg given in same interval as IV |
| Penicillin G | 1-2 MU q6h | Penicillin V 300-600mg q6h |
| Group 3 (Different drug based on pathogen susceptibility and no contraindications to therapeutic alternative) NOTE: Prior discussion with prescribing physician is required | | |
| Cefotaxime (non-meningitis use) | 1-2g q8h | Levofloxacin 250-750mg q24h |
| Cloxacillin | 1-2g q6h | Cephalexin 250-1000mg q6h |
| Erythromycin (non-GI motility use) | 250-1000mg q6h | Clarithromycin 250-500mg q12h |
| Imipenem-cilastatin | 250-500mg q6h | Amoxicillin-clavulanate 250-875mg q8h + Ciprofloxacin 250-750mg q12h OR Ciprofloxacin 250-750mg q12h + Clindamycin 300-600mg q8h OR Ciprofloxacin 250-750mg q12h <u>or</u> Levofloxacin 250-750mg q24h + Metronidazole 500mg q12h |
| Ticarcillin-clavulanate | 2.07-3.1g q6h | As per imipenem-cilastatin |

*Dosage and interval will be adjusted for renal function as required

2. Revised Drug Administration Policies

The following revised drug administration policies have been placed in all Parenteral Drug Therapy Manuals (PDTM) and the online reference:

- **Dopamine doses \leq 5mcg/kg/minute are restricted to special and critical care units ONLY.** Low dose dopamine infusions can no longer be administered on general nursing units. Dopamine doses $>$ 5mcg/kg/minute are restricted to critical care units and NICU. Infusions must be administered via central line only.
- **Epinephrine infusions are restricted to critical care areas.** Infusions must be administered via central line only.
- The **diluent provided with glucagon injection does not contain phenol** anymore, and so **can be used to reconstitute all doses of glucagon.**
- **Labetalol infusions are restricted to special and critical care areas.**
- **Norepinephrine administration is restricted to critical care areas and NICU.** Norepinephrine must be administered via central line only.
- **Phenylephrine administration is restricted to Critical Care Areas.** Phenylephrine infusions must be administered via central line only.
- **Salbutamol may not be administered via direct IV,** only via continuous IV infusion or IM injection.
- **Nurses in the CCU** who have received the appropriate training are **authorized to administer lidocaine with epinephrine by local groin infiltration.**

3. Ceftizoxime vs Cefazolin/Metronidazole

Ceftizoxime is an anti-anaerobic parenteral cephalosporin that is used primarily for surgical prophylaxis involving intra-abdominal (and gynecological and urological) procedures. Since September 2003, there has been a nation-wide

shortage of this agent. This shortage is anticipated to continue for at least the balance of the calendar year. In the meantime, cefazolin plus metronidazole will be promoted as a therapeutic alternative to ceftizoxime.

4. Pre-Printed Orders For Chemotherapy/Immunotherapy

- Generic, pre-printed orders (PPO) are now available for physicians to use when ordering chemotherapy/immunotherapy not already on an existing PPO.
- It is mandatory for physicians to use these PPOs as they contain all the information required to safely prepare and administer chemotherapy/immunotherapy.
- Chemotherapy/immunotherapy PPOs have been supplied on the following units:
 - Cell Separator Unit
 - CTU Medicine (T4 A/B)
 - Medical Daycare (C10)Other areas can obtain a supply by calling the T15 pharmacy at local 63587.
- Nursing Resources for Administration:
 - ⇒ Sally Tomlinson, Clinical Educator, Infusion Program (604-877-5528 pager)
 - ⇒ Michael Duchnych, Clinical Educator, Leukemia/BMT Program (604-872-9790)
 - ⇒ Kathy Scarborough, Clinical Educator, CTU Medicine (604-877-3936)

5. Hospital Medication To Stay in Hospital

A reminder that hospital medication is not to go home with the patient upon discharge for the following reasons:

- The medication does not meet legal labeling requirements for an outpatient prescription.
- The medication does not meet legal PharmaNet profile entry requirements.
- Sending medication home with the patient increases hospital drug costs in the face of a severe budget deficit.

Pharmacy Awards

The following awards have been received by various members of the Pharmaceutical Sciences CSU by regional or national professional organizations.

- **Peter Zed**, Filiatrault L, Busser J. "Patient satisfaction with an emergency department-based outpatient deep vein thrombosis treatment program." Canadian Society of Hospital Pharmacists BC Branch 2003 Pharmacy Practice Award.
- **Dawn Warkentin**, Epstein JB, Campbell LM, **Yip J**, Cox V, Ransier A, Barnett MJ, Marra F. "A prospective, randomized clinical trial of valacyclovir versus acyclovir in the prevention of mucocutaneous herpes simplex virus infections in neutropenic patients." Canadian Society of Hospital Pharmacists BC Branch 2003 Publication Award for Original Research. This article was published in *Ann Pharmacother* 2002;36:1525-31.
- **Robert Balen**. "How to use email and the internet to help you keep up with the literature (part III): The therapeutic topic approach and a potential corporate strategy." Canadian Society of Hospital Pharmacists BC Branch 2003 Publication Award. This paper was published in *J Inform Pharmacother* 2002;11:500. (www.informedpharmacotherapy.com/Issue11/TIPS/Keeping_up_pt3.htm)
- Elaine Chong, **Robert Balen**, **Peter Jewesson**. "Facilitating continuing education via streaming media in a large Canadian Tertiary Care Teaching Hospital." 2003 Pharmacy Practice Commitment to Care Award for Technological Innovation.

New Drug/Drug Products

Tamsulosin (Flomax®)

Gwen Liu, B.Sc. (Pharm)

Tamsulosin has been recently added to formulary for treatment of signs and symptoms of benign prostatic hypertrophy (BPH).¹

Pharmacology

Tamsulosin is an α_1 -adrenoreceptor blocking agent that displays selectivity for the α_{1A} -adrenoreceptor subtype, which is thought to mediate contraction of prostatic smooth muscle.² Smooth muscle tone is mediated by the sympathetic nervous stimulation of α_1 -adrenoreceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra and bladder neck. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.¹ Tamsulosin and its metabolites are more specific for the prostatic α_{1A} -adrenoreceptors than any of the other α_1 -adrenoreceptor antagonists (terazosin, prazosin, doxazosin). Tamsulosin is less specific for the vascular α_{1A} -adrenoreceptors and therefore causes less orthostatic hypotension than the other α_1 -adrenoreceptor antagonists.³

Comparable Agents³

Tamsulosin has been demonstrated to be safe and effective treatment for the symptoms of BPH in both short- and long-term placebo-controlled studies.^{4,5} Table 1 compares α_1 -adrenoreceptor blockers for BPH management available in Canada.

A meta-analysis comparing terazosin, doxazosin and tamsulosin found that the efficacy of these drugs were similar.⁶ In the drug-treated patients, symptom scores decreased by 30-40% and urinary flow rates increased 16-25%. The drugs differed in their side effect profiles. The frequency of side effects with tamsulosin was similar to placebo but was 4-10% higher in men treated with terazosin and doxazosin. The most important side effects were orthostatic hypotension and dizziness. Tamsulosin has been shown to be as effective for reducing lower urinary tract symptoms of BPH with a lower incidence of adverse effects when directly

compared to terazosin.^{7,8}

Table 1. Comparison of α_1 -adrenoreceptor Blockers for Treatment of BPH

| Drug | Half-Life (hrs) | Daily Dose | Cost/day* | Pharmaceutical Coverage |
|-------------------------------------|-----------------|-------------------------|-------------|-------------------------|
| Tamsulosin (Flomax [®]) | 10-13 | 0.4-0.8mg daily | \$0.95-1.90 | No |
| Terazosin (Hytrin [®]) | 12-24 | 1-10mg daily hs | \$0.55-1.40 | Yes |
| Prazosin (Minipress [®]) | 2-6 | 2-10mg given in 2 doses | \$0.56-1.06 | Yes |
| Doxazosin** (Cardura [®]) | 9-13 | 1-8mg daily | \$0.55-1.70 | Yes |

*based on VHHSC acquisition cost

**non-formulary drug at VHHSC

Potential Risks

Overall, tamsulosin has been shown to be well tolerated in both short- and long-term safety trials.^{7,9-11} Common adverse events were rhinitis, abnormal ejaculation and dizziness. Rates of orthostatic hypotension were comparable to placebo.^{4,8,9,12} Adverse effects were generally mild, transient and self-limiting. The only drug known to have a significant interaction with tamsulosin is cimetidine which can significantly decrease tamsulosin clearance (26%) and increase area-under-the-curve (44%).^{1,13} Caution is advised when cimetidine is administered with tamsulosin doses greater than 0.4mg.¹

Potential Benefits

One major benefit of tamsulosin is its lack of specificity for the vascular α_1 -adrenoreceptor, resulting in less orthostatic hypotension and dizziness compared to other agents in this class.^{9,12} This is clinically important as orthostatic hypotension and syncope are risk factors for falling especially in the elderly. The minimal effect of tamsulosin on blood pressure is maintained in elderly patients with cardiovascular co-morbidity.^{9,10,12} Co-administration of tamsulosin with antihypertensives does not require dosage adjustment of concurrent antihypertensive drugs.¹⁰

Dosage

Tamsulosin is initiated at 0.4mg daily. Although it is recommended that it be taken after a meal, the time of administration does not appear to affect tolerability or efficacy. Dosage may be increased to 0.8mg daily depending on symptomatology and/or urine flow rates. If tamsulosin is discontinued or interrupted for several days at either the 0.4 or 0.8mg dose, therapy should be reinstated, beginning with the 0.4mg once daily dose.¹

Conclusions

Tamsulosin is the latest α_1 -adrenergic antagonist for the treatment of BPH. It has been shown to be as effective as the other α_1 -adrenoreceptor antagonists for relieving symptoms of BPH, with advantages of increased selectivity for prostatic α_{1A} -adrenoreceptors, improved tolerability (reduced incidence of orthostatic hypotension), and simple once daily dose titration.

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