VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

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. Tizanidine 4mg tablets (Zanaflex®)
- Short-acting drug for the management of spasticity
- See page 3 for review

2. Mirtazapine 30mg tablets (Remeron®)
- Noradrenergic and specific serotonergic antidepressant (NaSSA)
- See page 5 for comparison with other antidepressants

3. Zuclopenthixol decanoate 200mg/mL injection (Clopixol® Depot)
- Intramuscular antipsychotic depot formulation for chronic management of chronic psychoses

4. Sevelamer 400mg, 800mg tablets (Renagel®)
- Non-calcium-based (or electrolyte-based) phosphate binder for use in patients with end-stage renal disease
- Usual dose: 1-2 tabs of 400mg or 800mg 3 times daily with meals
- Cost: $0.75/400mg; daily cost: $2.25-9.00 (In comparison, calcium carbonate 500mg - Tums® ii TID: $0.12/day)

Deletions

1. Ancrod injection (Arvin®)
- Alternatives for management of heparin-induced thrombocytopenia: Danaparoid

2. Calcium disodium edetate (EDTA)
- Discontinued by manufacturer
- Available as Special Access Drug

2. Bethanechol injection (Urecholine®)
- Discontinued by manufacturer

4. Diazoxide injection (Hyperstat®)
- Discontinued by manufacturer

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Updated Policies/Procedures

1. Skin Tests for TB and Anergy Testing

It has come to our attention that tuberculin skin test (also known as purified protein derivative – PPD) is adsorbed in various amounts by glass and plastics. The manufacturer recommends that once tuberculin is drawn up in a syringe, it should be administered within 20 minutes to minimize reduction in potency by adsorption. As a result, Pharmaceutical Sciences CSU no longer dispenses tuberculin pre-filled syringes to the wards but instead sends the vials. The physician or authorized nurse must then draw up the dose (0.1mL) just prior to administration. This recommendation has been extended to include the other skin tests, ie. candida, trichophyton and aspergillus.

Tuberculin, candida and trichophyton skin tests have been added as wardstock to the following high usage areas: TB unit, Employee Health Unit, W10A, W10B, E5, W5, W7M, D4 and Emergency-Acute. Opened vials are stable for 30 days in the fridge.

2. Angiotensin II Receptor Blocker Interchange Policy

Effective Monday Dec 16, 2002, all angiotensin II receptor blockers, with the exception of eprosartan, will be interchanged to an equivalent dose of losartan as shown in Table 1. The physician may override this policy by indicating "do not substitute" on the prescription.

Table 1. Dosage Comparison of Angiotensin II Receptor Blockers

Angiotensin II Receptor Blocker	Equivalent Dose
Losartan (Cozaar®)	**50mg**
Candesartan (Atacand®)	8mg
Irbesartan (Avapro®)	150mg
Telmisartan (Micardis®)	40mg
Valsartan (Diovan®)	80mg

3. Revised Drug Administration Policies

- **Aminophylline** may be administered **direct IV by nuclear technologists under the supervision of a cardiologist who must be immediately available but not necessarily in the same room** at the time the drug is being administered.

- **Propofol** is **contraindicated for the sedation of children 18 years or younger receiving intensive care**.

- **Amphotericin B lipid complex** (Abelcet®, ABLC) **does not require an Infectious Diseases Consult for BMT and SOT patients**. However, a preprinted order form entitled "Treatment Amphotericin B Infusion Protocol" must be filled out for these patients.

- **Cyclosporine** is **stable for 24 hours in glass bottles**. Solutions may be prepared in **PVC bags for immediate administration** if infused in less than 6 hours.

- **Erythropoietin** administration has been associated with **pure red cell aplasia** (erythroblastopenia) after **months to years of treatment in patients with chronic renal failure**, particularly when administered via the subcutaneous route.

- There are now **2 standard concentrations for ketamine subcutaneous infusions**: **0.5mg/m**L (for doses 5-12.5mg/hour) and **1mg/mL** (for doses 13-15mg/hour).

- **Labetalol** can be diluted for IV infusion to a 0.8mg/mL, 1mg/mL, 2mg/mL and now **3mg/mL** concentration. New dosage charts have been added to those areas that use this medication.

- **Phenytoin should not be administered through a PICC line** as it blocks the line.

- **Hyaluronidase** will **no longer** be **used for extravasation of vinblastine and vincristine** due to its removal from the Canadian market.

- The **Day Bed Unit** is considered a **Special Care Area** and, as such, can administer various medications restricted to Special Care Areas.

New Drugs/Drug Products

1. Tizanidine (Zanaflex®)

Erica Greanya, BSc. (Pharm), Karen Shalansky Pharm.D., Tania Mysak Pharm.D. ,

Tizanidine is a short-acting drug that has been recently added to formulary for the management of spasticity, primarily from neurological disorders.

Pharmacology

Tizanidine is a central α_2-receptor agonist that exhibits muscle relaxant and antispastic activity.[1,2] These effects are produced through two main mechanisms. First, as an imidazoline derivative structurally similar to clonidine, its affinity for imidazoline receptors is thought to alter noradrenergic activity.[3] The main action, however, is its agonist action at central α_2-adrenergic receptors which inhibits the release of excitatory neurotransmitters, therefore producing a selective reduction of polysynaptic reflex activity.[2,3] Through these mechanisms, tizanidine has been shown to reduce mean muscle tone and reduce the frequency of muscle spasms while maintaining muscle strength.[4,5] These effects have been demonstrated primarily in patients with multiple sclerosis, spinal cord injury and cerebrovascular lesions.

Comparable Formulary Agents

Pharmacological agents used in the management of spasticity include the skeletal muscle relaxants baclofen and dantrolene as well as the benzodiazepines, usually diazepam (see Table 1).[2,4-6] Clonidine also has documented use in spasticity associated with brain and spinal cord injury, stroke, and multiple sclerosis.[7-9] Although clonidine exhibits myotonolytic action, adverse reactions including postural hypotension and rebound spasticity with dose reduction limit its usefulness in the clinical setting for the treatment of spasticity.[9] Tizanidine has been used in Europe for the treatment of spasticity since 1985. Compared to placebo, tizanidine is significantly better at reducing spasticity in patients with spinal cord injury, multiple sclerosis, stroke, and acquired brain injury.[4,10-12] While tizanidine has not been directly compared with dantrolene, no significant differences in antispastic efficacy have been noted in studies comparing tizanidine to baclofen and diazepam.[2,5,13] In terms of tolerability, tizanidine causes less muscle weakness than baclofen[5,13] and less dizziness and drowsiness than diazepam.[2]

Adverse Effects

The main side effects associated with tizanidine have been somnolence and dry mouth, which may improve with continued treatment[4,13] Also, asthenia occurred in 31% of patients in one trial.[4] Transient elevation of liver function tests (AST, ALT, total bilirubin) up to ≥ 3 times the upper limit of normal has also been reported.[4] Due to these reports, it is recommended to monitor liver enzymes at baseline and months 1, 3, and 6.[1] Tizanidine may also cause a reduction in blood pressure of up to 20 mmHg systolic and 10 mmHg diastolic.[14] This adverse effect can be explained by the structural similarity between tizanidine and clonidine. Caution should be used when tizanidine treatment is added to patients who are on concomitant antihypertensive therapy, as an additive reduction in blood pressure may occur.

Dosage

An initial dose of 4 mg up to 3 times daily as

Table 1. Pharmacokinetic and Cost Comparison of Oral Antispasticity Agents[2,4-6]

Drug	Mechanism of Action	Half-Life (hours)	Onset of Action (hours)	Mean Dose/day	VHHSC Acquisition Cost/Day
Baclofen (Lioresal®)	GABA-B agonist	2-4	1-2	10-30mg tid	$0.45-1.35
Diazepam	GABA agonist	> 24	0.5-2	5-10mg qid	$0.04-0.08
Dantrolene (Dantrium®)	↓ muscle calcium release	2.5-3	1.5-3	25-100mg qid	$1.44-3.36
Tizanidine	**Central a_2 agonist**	**2.5**	**1-2**	**4-12mg tid**	**$2.04-6.12**

needed, with gradual titration by 2-4 mg/dose increments, is necessary to minimize adverse effects.[1] Maintenance treatment with at least 8 mg up to 3 times daily, to a maximum daily dose of 36 mg, may be necessary for reduction of muscle tone in the treatment of spasticity.

Conclusions

Tizanidine is the newest addition to baclofen, dantrolene and diazepam for the treatment of spasticity associated with multiple sclerosis or spinal cord injury. Tizanidine has been shown to be as effective as baclofen and diazepam with improved tolerability (reduced incidence of muscle weakness, drowsiness and dizziness), but at a higher cost. Due to its unique mechanism of action, tizanidine may be useful as sole therapy or as adjunctive therapy in patients experiencing less than optimal therapeutic response, or dose-related side effects with other agents.

References

1. Zanaflex® Product Monograph. January 1999.
2. Lataste X et al. Comparative profile of tizanidine in the management of spasticity. Neurology 1994;44:S53-9.
3. Coward DM. Tizanidine: Neuropharmacology and mechanism of action. Neurology 1994;44:S6-11.
4. Nance PW et al. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. Neurology 1994;44:S44-52.
5. Groves L et al. Tizanidine treatment of spasticity: A meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. Adv Ther 1998;15: 241-51.
6. Abramowicz M, ed. Tizanidine for spasticity. The Medical Letter 1997;39:62-3.
7. Middleton JW et al. Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. Arch Phys Med Rehabil 1996;77:826.
8. Dall JT et al. Use of clonidine for treatment of spasticity arising from various forms of brain injury: a case series. Brain Injury 1996;10:453-8.
9. Nance PW et al. Clonidine in spinal cord injury. Can Med Assoc J 1985;133:41-2.
10. Smith C et al. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. Neurology 1994;44:S34-42.
11. Gelber DA et al. Open-label dose-titration safety and efficacy study of tizanidine hydrochloride in the treatment of spasticity associated with chronic stroke. Stroke 2001;32:1841-6.
12. Meythaler JM et al. Prospective assessment of tizanidine for spasticity due to acquired brain injury. Arch Phys Med Rehabil 2001;82:1155-63.
13. Bass B et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1998;15:15-9.
14. Barnes MP et al. A double-blind, placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. Neurology 1994;44:S70-8.

2. Mirtazapine (Remeron®)

Colette Raymond, Pharm.D.

Mirtazapine is an antidepressant with a novel mechanism of action. Table 1 (next page) outlines comparative properties of mirtazapine to other commonly prescribed antidepressant agents.

Pharmacology

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). Its mechanism of action is unique, as unlike other antidepressants, mirtazapine is not a neurotransmitter reuptake inhibitor.[1-2] Mirtazapine acts by antagonizing central presynaptic $alpha_2$ receptors and post-synaptic $5HT_2$ and $5HT_3$ receptors. As such, it enhances both noradrenergic and serotonergic $5HT_{1A}$ transmission.

Comparison to Other Antidepressants

Antidepressant effects from mirtazapine are generally detectable in 1-2 weeks.[1] In several randomized trials of tricyclic and tetracyclic antidepressants, mirtazapine has been shown to be similar in efficacy to amitriptyline, clomipramine, doxepin and trazodone.[1-5] In comparison to SSRIs, mirtazapine was superior to the comparator SSRI at one to four weeks, but not at study end (six to eight weeks).[6-8] These results suggest that mirtazapine may have an earlier onset of action than the comparator antidepressants.[9]

Role of Mirtazapine

Mirtazapine has a unique pharmacologic profile and more rapid response as compared to SSRIs. Additionally, there is evidence to support its use as add-on (augmentation) therapy for patients who do not respond to an initial antidepressant. A recent randomized, double-blind placebo controlled trial showed a benefit to mirtazapine when combined with SSRIs, bupropion or venlafaxine (response rate 64% mirtazapine vs. 20% placebo, p=0.043).[10]

Mirtazapine is similar in cost to other antidepressants, with minimal drug interactions and a comparable adverse effect profile. Of note, mirtazapine is associated with less nausea but more weight gain than comparator SSRIs, less sexual dysfunction and tremor than paroxetine, and less sweating than citalopram.[11]

Table 1. Comparative Properties of Antidepressants[12,13]

Drug	Class	Adverse Effects: Common	Adverse Effects: Rare (but significant)	Liver Enzyme Inhibition*	Comments	Dose/Day (Cost/day**)
Fluoxetine (Prozac®)	SSRI	Dizziness, Drowsiness, Hypotension, **GI distress (>30%)** Headache Dry mouth Tremor **Sexual dysfunction (30-50%)** Weight gain (with chronic use)	Movement disorders (parkinsonism, akathisia, tardive dyskinesia) SIADH Sweating	CYP 2D6 (significant)	Long half-life (up to 70 hrs and active metabolite	10-80mg ($0.55-2.24)
Paroxetine (Paxil®)	SSRI			CYP 2D6 (significant)		10-50mg ($0.80-3.28)
Sertraline (Zoloft®)	SSRI			CYP 2C19 (weak)	Peak level 30% higher with food; nausea common (>30%)	25-200mg ($0.80-3.10)
Fluvoxamine (Luvox®)	SSRI			CYP 1A2 (significant)	Most sedating SSRI; nausea common (>30%)	50-300mg ($0.83-5.28)
Citalopram (Celexa®)	SSRI			Weak	Few drug interactions	10-60mg $0.66-3.93)
Nefazodone (Serzone®)	SARI	As per SSRI (**except** sexual dysfunction 10% and minimal weight gain or tremor)	Paresthesias Hepatic failure	CYP 3A4 (significant)	Multiple drug interactions via CYP 3A4 (including grapefruit juice); twice daily dosing	100-600mg in divided dose ($0.80-4.80)
Bupropion SR (Wellbutrin SR®)	NDRI	Dizziness, Insomnia, GI distress, Constipation, Dry mouth, Tremor, Headache Sexual dysfunction (10%)	Seizures (0.15% if on < 300mg/day) Psychosis	CYP 2D6 (moderate)	No withdrawal effect usually; may promote weight loss; twice daily dosing Also indicated for smoking cessation	150-300mg in divided dose ($0.80-1.60)
Venlafaxine (Effexor®)	SNRI	As per SSRI (**except sexual dysfunction 10-30%,** sweating, and minimal weight gain or tremor	Hypertension (13% if on > 300mg/day)	Weak	Few drug interactions	37.5-375mg ($0.78-5.45)
Mirtazapine (Remeron®)	**NaSSA**	**Drowsiness Sedation (>30%)** Dry mouth Constipation **Weight gain (>4kg in 15% of patients)**	Edema Neutropenia Increased cholesterol	**Weak**	**Few drug interactions; less nausea, sexual dysfunction and sweating compared to SSRIs**	**15-45mg ($0.65-2.60)**

SSRI = selective serotonin reuptake inhibitor; SARI = serotonin 2 antagonist/reuptake inhibitor; NDRI = norepinephrine dopamine reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; NaSSA = noradrenergic/specific serotonergic antidepressant
*Cytochrome p450 isoenzymes inhibited by drug
**based on VHHSC acquisition costs

References

1. Holm KJ et al. Mirtazapine: a review of its use in major depression. Drugs 1999;57:607-31.
2. Gorman JM. Mirtazapine: clinical overview. J Clin Psychiatry 1999;60(suppl 17):9-13.
3. Fawcett J et al. A meta-analysis of eight randomized double-blind controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. J Clin Psychiatry 1998;59:123-7.
4. Stahl S et al. Meta-analysis of randomized, double-blind placebo controlled efficacy and safety studies of mirtazapine versus amitriptyline in major depression. Acta Psychiatr Scand 1997;96 (suppl 391):22-30.
5. Kasper S. Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. Int Clin Psychopharmacol 1995;10 (suppl 4):25-35.
6. Wheatley DP et al. Mirtazapine efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. J Clin Psychiatry 1998;59:306-12.
7. Benkert O et al. Mirtazapine compared with paroxetine in major

depression. J Clin Psychiatry 2000;61:656-63.
8. Leinonen E et al. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind randomized study in patients with major depressive disorder. Int Clin Psychopharmacol 1999;14:329-37.
9. Quitkin FM et al. Does mirtazapine have a more rapid onset than SSRIs? J Clin Psychiatry 2001;5:358-61.
10. Carpenter LL et al. A double-blind, placebo controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry 2002;51:183-88.
11. Thompson C. Mirtazapine versus selective serotonin reuptake inhibitors. J Clin Psychiatry 1999;60(suppl 17):18-22.
12. Kennedy SH et al. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological therapies. Can J Psychiatry;2001;46(Suppl 1):38S-58S.
13. Bezchlibnyk-Butler KS, Jeffries JJ (eds) Clinical Handbook of Psychotropic Drugs, 10th ed. Toronto:Hogrefe & Huber Publishers;2000.

Perceptions of Pharmaceutical Sciences Services at VGH: Survey Results

Katie Lacaria, Robert M. Balen, Luciana Frighetto, Tim T.Y. Lau, Terryn L. Naumann, Peter J. Jewesson

The Pharmaceutical Sciences Clinical Service Unit (CSU) is committed to optimizing patient health outcomes by addressing medication-related needs in collaboration with patients and other health care professionals. Changes in health care are significantly impacting on pharmacy practice. Pharmacist and pharmacy technician roles need to continue to evolve as a result of increasingly complex drug therapies, technological advancements, information demands, and changes in patient and professional colleague expectations. With the current limited financial resources and shortage of pharmacists, we believe that it is important to continuously evaluate current services and seek input from our patient, nurse, physician and pharmacist stakeholders for the purpose of improving these services. Accordingly, we recently conducted a survey to determine stakeholder perceptions regarding the awareness, quality and priority of the currently offered professional services.

A 32-item survey was designed to anonymously elicit opinions regarding the drug distribution, clinical, education and research services provided by the CSU. Surveys were distributed over a 90-day period (December 2001 - March 2002) to in-patients and to nurses, physicians and pharmacists affiliated with the hospital. Respondent demographics and responses were characterized using descriptive statistical analysis.

Four hundred and eighty-seven (19%) of 2,568 distributed surveys were returned. Of these, 27 surveys were excluded from analysis as respondents failed to identify their stakeholder group. Of the remaining 460 surveys, there were 38 patient, 276 nurse, 102 physician, and 44 pharmacist respondents. Response rates according to each stakeholder group were as follows: patients 32%, nurses 16%, physicians 16%, and pharmacists 50%. Patient respondents were located throughout the hospital and were hospitalized for an average of 2 weeks at the time of survey completion. For nurses and physicians, there was a balanced representation from the medical and surgical practice areas, while most pharmacists practiced on non-surgical areas. The majority of nurse and physician respondents had worked at this hospital for at least 5 years, while pharmacists had a shorter employment history.

Of the four groups surveyed, patients were the least aware of the 32 services provided. This group tended to be most familiar with traditional (e.g. dispensing) pharmacy functions only. Nurse and physician respondents tended to be well aware of the services provided, although they were less aware of services that may not typically be provided by a hospital pharmacy department such as web-based resources and an intravenous support program, and those services offered either in specific areas (e.g. group medication counseling, patient self-medication program) or to certain stakeholders (e.g. clinical drug research). While pharmacists were most aware of the services provided, they were less familiar with the intravenous support program and group medication counseling provided to psychiatry patients.

The majority of stakeholder group respondents, who were aware of, and offered an opinion about the 32 professional services, rated the quality of all these services as *excellent* or *good*. A small incidence (<5%) of poor ratings was noted for some professional services across all stakeholders groups. These services included the resolution of patient-specific drug distribution issues, patient medication counseling, intravenous support program, continuing education programs, contribution to drug therapy decision-making on rounds, production and distribution of medication administration records and medication profiles, the website, and monitoring patients for adverse drug reactions.

Respondents were asked to rank the top three most important professional services within each of the four service domains. The review of prescriptions for appropriateness; the dispensing of oral, intravenous and total parenteral nutrition preparations; the resolution of patient-specific drug distribution issues; group medication sessions; continuing education programs and the Clinical Drug Research program were ranked as the most important professional services.

In summary, this study has provided us with valuable information regarding patient, nurse, physician and pharmacist perceptions regarding the awareness, quality and priority of the services currently offered by the pharmacy department at this hospital. This information will be used in our plans to further enhance the quality, type and awareness of the professional services we provide to our patients and fellow health care professionals.

We would like to thank everyone who participated in the survey. Your contribution is greatly appreciated.

Pharmacy Awards

Several members of Pharmaceutical Sciences CSU were recipients of Canadian Society of Hospital Pharmacists (CSHP) 2002 awards for academic or professional excellence:

Anne Sawoniak B.Sc. (Pharm)

- Pharmacia/CSHP-BC Branch award for highest ranked BC residency project. Anne's project, coordinated by Karen Shalansky, Pharm.D. is entitled: Multidisciplinary Approach to Erythropoietin Resistance in a Hemodialysis Unit".

- CSHP-BC Branch Interhospital Competition for Second Highest Ranked Resident. Anne is currently working at VGH as a clinical pharmacist.

Karen Shalansky Pharm.D., FCSHP and Rubina Sunderji Pharm.D., FCSHP

- CSHP-BC Branch Publication Award, Original Research Category. Their research paper, co-authored with Zahida Esmail, Hugh Anton, Keith Chambers and William Fish, is entitled "Evaluation of captopril for the management of hypertension in autonomic dysreflexia: a pilot study". This paper has been published in Archives of Physical Medicine and Rehabilitation 2002;83:46-51.