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 Therapeutic Newsletters are published on our website at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. **Salmeterol 25mcg/puff inhaler (Serevent[â])**
   - long-acting beta-2 agonist
   - indicated for long-term maintenance treatment of asthma and chronic obstructive pulmonary disease (COPD)
   - see page 3 for review

2. **Latanoprost 0.005% eye drops (Xalatan[â])**
   - prostaglandin $F_{2\alpha}$ analogue for reduction of intraocular pressure in patients with open-angle glaucoma
   - see page 4 for review

Deletions

The following drugs have been deleted by the manufacturer or have had minimal to no usage over the past 3 years:

1. **Piroxicam capsules (Feldene[â])**
   - alternatives: diclofenac, ibuprofen, indomethacin, naproxen, sulindac

2. **Ketoprofen tablets (Orudis[â])**
   - alternatives: see above

3. **Magaldrate suspension (Riopan[â])**
   - alternative: Diovol Plus®

4. **Echothiophate eye drops (Phospholine Iodide[â])**
   - discontinued by manufacturer

5. **Acetazolamide injection (Diamox[â])**
   - discontinued by manufacturer

Updated Policies/Procedures

1. **Drug Formulary 2001**

All VHHSC formularies have been updated with the 2001 version. In addition to revisions to formulary drugs (white pages), several policies

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have been added to the policy and procedure section (green pages) and new charts to therapeutics tools (yellow pages). If there are any questions regarding this update, please call Dr. Karen Shalansky, (604) 875-4839.

2. Conscious Sedation and Driving

Patients who undergo procedures on an ambulatory basis and receive drugs for conscious sedation that may impair their ability to operate a motor vehicle (e.g. benzodiazepines) should be advised to avoid operating such a vehicle until the calendar day after the procedure. This should permit any residual effects of the drugs to subside.

3. Patient's Own Medication Policy Update

To expedite the administration of medications, the policy governing Patient's Own Medication has been modified to:

a) authorize pharmacists to write an order in the health record indicating that a patient may take their own medication as prescribed by the physician;
b) authorize patients in the Surgical Day Care Centre to take their own medication as prescribed without prior identification by a pharmacist.

4. Revised Drug Administration Policies

All Parenteral Drug Therapy Manuals (PDTM) have been updated with the May 2001 version. The following changes have been incorporated into this update:

- **Methotrexate** may be administered **subcutaneously**, specifically for the control of inflammatory rheumatoid arthritis.

- Multiple vitamin infusion **(MVI) must be diluted in not less than 500mL IV solution** for peripheral or central line adminstration.

- **Enoxaparin** may now be administered for both the prevention **and treatment** of **deep vein thrombosis and pulmonary embolism**. Tinzaparin also remains on formulary for these indications.

  The manufacturers recommend **maximum doses for enoxaparin (100mg/12 hours or 180mg/24 hours) and tinzaparin (18,000 units/day)**; however, **dosage should be individualized** and higher dosages may be administered.

- Both **oral and intravenous** formulations of **azathioprine (Imuran®)** are now considered **cytotoxic agents**. As such, cytotoxic precautions must be followed per Occupational Health and Safety Manual guidelines, Policies Section, OHS # 13 for administration and disposal. Also refer to Table G of the PDTM for specific parenteral administration guidelines. The following Table is a list of cytotoxic agents at VHHSC.

Table 1. Cytotoxic Agents at VHHSC

ORAL/TOPICAL	PARENTERAL	
Azathioprine	Amsacrine	Etoposide
Busulfan	L-Asparaginase	Fludarabine
Chlorambucil	Azathioprine	Fluorouracil
Cyclophosphamide	Bleomycin	Ganciclovir
Etoposide	Carboplatin	Mechlor-
Fluorouracil cream	Carmustine	ethamine
Ganciclovir	Cisplatin	Melphalan
Hydroxyurea	Cladribine	Methotrexate
Lomustine	Cyclophosphamide	Mithramycin
Melphalan	Cytarabine	Mitomycin C
Mercaptopurine	Dacarbazine	Mitoxantrone
Methotrexate	Dactinomycin	Teniposide
Mitotane	Daunorubicin	Thiopeta
Thioguanine	Doxorubicin	Vinblastine
	Epirubicin	Vincristine

5. Switch to Losec MUPS® Formulation

We have switched our omeprazole formulation (Losec®) to Losec MUPS® (Multiple Unit Pellet System). The advantage of the MUPS® formulation over traditional Losec® is that the tablets are designed to disperse rapidly in water or fruit juice. Each Losec MUPS® water-soluble tablet contains 100 enteric coated micropellets of omeprazole. The acid-resistant micropellets dissolve at a pH above 5.5, thus preventing premature breakdown of omeprazole in the stomach and subsequent inactivation by gastric acid.

Dissolution of the tablets in water occurs within 2 minutes and the resultant suspension can be administered via a tube as narrow as 8 French without clogging. The micropellets stay intact in

sterile water. The suspension is stable for 30 minutes.

Losec MUPS® is available in 10mg and 20mg strengths for hospital use only. Only the MUPS formulation will be available at VGH site while both omeprazole products will be stocked at UBC site. Since Losec MUPS® is not yet available in the community, traditional Losec® will continue to be dispensed by retail pharmacies.

Pharmaceutical Sciences CSU will no longer prepare omeprazole suspension. This was previously undertaken using traditional Losec®, but was very time consuming and required dissolution in sodium bicarbonate. Instructions on how to administer the new Losec MUPS® via suspension will be attached to the prescription label.

6. Prescription Interpretation Protocol: Methadone Solution 10mg/mL

Pharmaceutical Sciences CSU currently purchases a manufactured methadone 10mg/mL solution. If methadone in Tang is prescribed for an in-patient, the pharmacist is authorized to dispense methadone oral solution. This policy only applies to in-patients for whom nurses administer medication doses. Patients taking methadone home on passes will receive methadone in Tang as required by the College of Physicians and Surgeons.

New Drug/Drug Products

1. Salmeterol inhaler (Serevent®)

Shakeel Bandali, B.Sc.(Pharm), Karen Shalansky, Pharm.D., Alan Low, Pharm.D.

Background and Indications

Both salmeterol and formoterol (Foradil®, Oxeze®) are long-acting, selective β_2 receptor agonists indicated for the management of uncontrolled asthma as an alternative to increased doses of inhaled corticosteroids.[1,2] Studies have shown that combination therapy of an inhaled long-acting β_2-agonist with moderate doses of an inhaled corticosteroid (800mcg/day budesonide or equivalent) is steroid-sparing and provides similar or better control of asthma symptoms and lung function compared to high dose inhaled corticosteroid therapy alone.[1-3] A reduction in corticosteroid dose allows for prevention of potential systemic adverse effects such as osteoporosis, growth retardation in children, and glaucoma. Salmeterol should be considered as an adjunct to inhaled corticosteroid therapy, not as a replacement.[4,5]

Long-acting β_2-agonists are also used for control of exercise-induced asthma.[6] The longer duration of salmeterol allows more prolonged activity compared to short-acting β_2-agonists (Table 1).[1]

Salmeterol is also indicated in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[7] A 16-week study in COPD patients showed a significant increase in forced expiry volume in 1 second (FEV_1) in patients receiving salmeterol 50mcg twice daily compared to placebo.[8] Two cross-over studies with salmeterol in COPD patients, however, failed to show significant improvement in FEV_1.[9,10]

Table 1. Comparison of Short- and Long-Acting β_2-Agonists

Drug	Salbutamol (Ventolin®)	Terbutaline (Bricanyl®)	Salmeterol (Serevent)	Formoterol (Oxeze®, Foradil®)
Class	SA	SA	LA	LA
Onset (mins)	< 5	< 5	10-20	1-3
Duration (hrs)	4-6	4-6	12-18	12-18
Formulary Status	F	F	F	NF
Cost*	$3.00/100 mcg/dose MDI (200 puffs	$3.84/500 mcg/dose turbuhaler (50 puffs)	$24.90/25 mcg/dose MDI (60 puffs**)	$42.30/12 mcg/dose turbuhaler (60 puffs)

SA = short-acting; LA = long-acting; F = formulary; NF = non-formulary; MDI = metered dose inhaler
*based on VHHSC acquisition costs
**the dose of salmeterol is 2 inhalations, thus this dosage form represents a 30 dose unit

Comparable Formulary Agents

There are no other long-acting β_2-agonists on formulary at VHHSC. Salbutamol and terbutaline are short-acting selective β_2-agonists, and in asthma, are indicated solely for relief of acute asthmatic episodes.[1] Salmeterol is a long-acting, selective β_2-agonist acting on respiratory smooth

muscle and lung mast cells to produce bronchodilation.[1,2] In contrast to short-acting agents, this drug offers more effective protection against histamine-induced bronchoconstriction resulting in a longer duration of bronchodilation of at least 12 hours (Table 1). Salmeterol is a partial β_2-agonist, whereas, formoterol is a full agonist at beta receptors which may account for its faster onset of action compared to salmeterol and also a greater potential for adverse effects.[1] Despite the faster onset of formoterol (1-3 minutes), long-acting β_2-agonists are not recommended for the relief of acute asthmatic symptoms; a short-acting β_2-agonist still needs to be employed for relief of acute symptoms.

Potential Risks

In controlled, multi-dose clinical trials, the most frequent adverse effects of salmeterol were headache (4.2%), palpitations (1.5%), and tremor (1.4%).[1,7] Other adverse effects include tachycardia, immediate hypersensitivity reactions, including urticaria, rash and bronchospasm.[7] The bronchodilating and symptom-relieving effects of salmeterol can mask increasing inflammation and delay awareness of worsening asthma.[11,12]

Dosage

The usual dose of salmeterol is 50mcg (2 puffs) twice daily in patients 12 years and older.

Conclusion

The evidence for long-acting β_2-agonists supports its use in patients with uncontrolled asthma currently receiving moderate doses of inhaled corticosteroids. Salmeterol offers a prolonged duration of action as well as a steroid-sparing effect. Salmeterol should not be used for acute attacks (i.e. should not replace short-acting β_2-agonists), nor should this agent be used as a substitute for inhaled corticosteroid therapy. While the benefits are conflicting, salmeterol may be beneficial in some patients for the management of COPD.

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2. Latanoprost 0.005% eye drops (Xalatan®)

Vivian Leung, B.Sc. (Pharm)
Reviewed by Dr. M Potter, Ophthalmologist

Drug therapy for glaucoma is designed to reduce intraocular pressure (IOP) and slow the progression of visual loss. IOP reduction may be achieved by limiting the production of aqueous humor in the eye or increasing its outflow. Latanoprost is the first agent in the class of prostaglandin $F_{2\alpha}$ analogues for the management of open-angle glaucoma and ocular hypertension. It acts by increasing aqueous humor outflow.[1,2] Formulary agents for the management of open-angle glaucoma are summarized in Table 1.

Potential Advantages

Clinical trials indicate that latanoprost once daily is equal or superior in efficacy to a standard regimen of timolol twice daily.[3-5] In many patients, timolol therapy alone may be insufficient to lower IOP and dual therapy using a drug with a different mechanism of action may need to be employed. Latanoprost monotherapy was found to be comparable to the combination timolol 0.5%-pilocarpine 2% (Timpilo 2®)[6,7] and the addition of latanoprost to timolol 0.5% was superior to Timpilo 2®[7]. As well, latanoprost is less likely to cause systemic side effects compared to timolol.[8,9] Although administered topically, timolol may cause decreased pulse rate and induce bronchoconstriction in patients with reactive airways disease.[10] Latanoprost also compares favourably to dorzolamide[11,12], a topical carbonic anhydrase inhibitor, and brimonidine[13], an α_2-agonist.

Table 1. Formulary Options for Open-Angle Glaucoma

Drug Class	Primary Action on Aqueous Humor[2]	Formulary Agents	Cost*
β-blockers	Decreased inflow	Timolol (Timoptic®) Levobunolol (Betagan®) Betaxolol (Betoptic®)	$8.35/ 5ml (0.5%) $7.91/3ml (0.5%) $11.27/5ml (0.25%)
Prostaglandin $F_{2\alpha}$ analogue	Increased outflow	Latanoprost (Xalatan®)	$26.00/5ml (0.005%)
Carbonic Anhydrase Inhibitors	Decreased inflow	Dorzolamide (Trusopt®)** Acetazolamide SR tab (Diamox®) Methazolamide (Neptazane®)	$16.50/5mL (2%) $1.46/day (500mg bid) $0.80/day (100mg bid)
Cholinergics	Increased outflow	Pilocarpine (Isopto Carpine®) Carbachol (Miostat®)	$3.50/15ml (2%) $12.76/15ml (3%)
α_2-agonist	Decreased inflow	Apraclonidine (Iopidine®) Brimonidine (Alphagan®)**	$21.27/5ml (0.5%) $16.50/5mL (0.2%)

*based on VHHSC acquisition costs
** non-formulary

Potential Risks

Increased iris pigmentation is observed in 5-15% of patients on latanoprost.[9] Concentric increases in colour typically appears after six months of treatment and may be irreversible.[14] This effect is more common in patients with multi-coloured irises and may be attributed to an increase in melanin.[9] Patients should be informed of the possibility of heterochromia between the eyes if treated with latanoprost in only one eye.

Dosage and Duration

The dose of latanoprost is one drop to the affected eye once daily in the evening. Evening administration has been shown to be superior to morning dosing.[3,15,16] Latanoprost exerts IOP-lowering effects for 20 to 24 hours after a single dose with maximum reduction in IOP occurring in 8 to 12 hours.[17]

Conclusions

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue represents a unique, albeit expensive class of drugs for the management of open-angle glaucoma and ocular hypertension. Once daily dosing in the evening has proven effective as monotherapy or add-on therapy to traditional antiglaucoma medication. Iris pigmentation is the most common adverse effect which may be irreversible.

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New Advanced Cardiac Life Support (ACLS) Guidelines: Implications for Change at VHHSC

Peter Zed, Pharm.D., Richard Slavik, Pharm.D., Jane de Lemos, Pharm.D., Rubina Sunderji, Pharm.D., John Fenwick, M.D.

Introduction

In August 2000, the American Heart Association published an update to the Advances Cardiac Life Support (ACLS) guidelines.[1] These international guidelines were developed using the principles of evidence-based medicine and recommendations were classified using a strength of evidence scheme. The recommendations confirm safety and effectiveness for many approaches, acknowledge ineffectiveness for others and introduce new treatments that have survived intensive evidence-based evaluation. The Resuscitation Committee at VHHSC has made several recommendations regarding application of these new guidelines for in-hospital ACLS protocols. These recommendations received approval by the Drugs and Therapeutics Committee and are summarized below. Please refer to the complete guidelines for further details on these recommendations.[1]

Amiodarone

Amiodarone has received most of the attention and has had the most significant impact in the new ACLS guidelines. Amiodarone is included in the ACLS algorithms for ventricular fibrillation/ pulseless ventricular tachycardia (VF/pVT) (Class IIb level of evidence), stable monomorphic VT (Class IIb), stable polymorphic VT (Class IIb), stable narrow-complex tachycardia and atrial fibrillation (AF)/flutter (AFL) (Class IIa in patients with preserved cardiac function and Class IIb in patients with an ejection fraction (EF) < 40% or heart failure).[1] The most significant change will be for its use as a 300mg IV bolus in VF/pVT as it has become the drug of first choice ahead of the former first line agent lidocaine following initial shocks and a single-dose of either IV epinephrine or vasopressin. The evidence for this stems from a single out-of-hospital VF/pVT study, the ARREST trial, and remains the only published data for use of amiodarone with cardiac arrest.[2] In this trial of 504 patients, amiodarone was superior to placebo in survival to hospital admission (44% vs. 34%, p=0.03), but there was no overall survival benefit to hospital discharge compared to placebo at 13.4% and 13.2%, respectively.

Amiodarone has also been recommended in the new ACLS guidelines for management of supraventicular arrhythmias.[1] Several randomized trials have suggested that IV amiodarone is superior to placebo[3-7] or digoxin[8,9] for acute ventricular rate control in patients with AF. Observational data suggest that IV amiodarone may also be safe in critically-ill patients on vasopressor agents or in patients who are intolerant or resistant to conventional rate control agents.[10-14] There have been 8 prospective, randomized, controlled trials that suggest that IV amiodarone is no more effective than placebo or rate control agents for acute conversion of AF to normal sinus rhythm (NSR) within 24 hours.[3-5,8,9,15-17] Many studies evaluating conventional doses of IV amiodarone are underpowered; however, the largest trial by Galve et al. was powered to rule out a clinically significant benefit.[5] Three of the 8 trials administered higher than conventional doses of IV amiodarone (> 1500mg/day) to patients with persistent or chronic AF and showed similar conversion rates to placebo or digoxin after 24 hours.[9,16,17] Despite ongoing oral amiodarone therapy in two of these trials, it took up to 4 weeks before conversion rates associated with amiodarone were higher than those associated with placebo.[16,17] Intravenous amiodarone has been shown to be effective for conversion of paroxysmal supraventricular tachycardia (PSVT) and Wolff-Parkinson White (WPW) Syndrome to NSR.[1] Thus, at VHHSC, it is recommended that IV amiodarone be used for supraventricular arrhythmias as follows: (i) IV amiodarone may be used for acute ventricular rate control within the first 48 hours of arrhythmia onset in patients with AF or AFL in whom other rate control measures are ineffective or contraindicated (Class IIb); (ii) IV amiodarone should be reserved for attempted conversion of symptomatic AF or AFL resistant to electrical cardioversion in patients with an EF < 40% or clinical heart failure (Class IIb); and (iii) IV amiodarone may be used as an alternative to electrical cardioversion for attempted cardioversion of narrow complex supraventricular tachycardias in patients with or without WPW and an EF < 40% or clinical heart failure (Class IIb).

Amiodarone is not yet available as pre-loaded syringes but is supplied as 50mg/ml (3ml) ampules which have been added to all ACLS carts at VHHSC. For all indications other than VF/pVT, amiodarone is recommended at a dose of 150mg IV over 10 minutes followed by repeated 150mg IV

doses if the rhythm persists or initiation of a continuous infusion at 1mg/minute (60mg/hour) x 6 hours then 0.5mg/minute (30mg/hour) to a maximum daily dose of 2.2g. To administer amiodarone in VF/pVT arrest, 300mg amiodarone is administered by IV push followed by 20 ml of IV fluid (NS or D5W). To mix amiodarone for subsequent infusion, 2 x 100mL bags of D5W with written instructions have been added to all ACLS carts.

Bretylium

Bretylium has been dropped from the VF/pVT and stable VT algorithms due to a worldwide shortage of this agent resulting from insufficient raw materials. Thus, although bretylium remains acceptable to use it is no longer recommended and has been removed from all ACLS carts at VHHSC.

Vasopressin

Vasopressin, the natural substance antidiuretic hormone, becomes a potent vasconstrictor when used at much higher doses than normally present in the body. Vasopressin possesses positive effects that duplicate the effects of epinephrine without the potential adverse effects. Vasopressin received a Class IIb recommendation for use as an alternative to epinephrine following initial defibrillation in VF/pVT. It is recommended as a one-time 40 units IV bolus dose. The support for this recommendation comes from a small (n=40) study by Lindner *et al*. in which vasopressin showed a trend in improving survival to hospitalization (vasopressin 70% versus epinephrine 35%, p = 0.06), and overall survival to discharge at 40% and 15%, respectively (p = 0.16) for out-of-hospital VF/pVT arrest.[18] Also taken into consideration for this recommendation is the soon to be published Canadian prospective, randomized, double-blind study (n=200) comparing vasopressin to epinephrine during in-hospital VF/pVT arrest in which no difference was found between these two treatment groups with respect to overall survival.[19]

There has been some debate regarding the results of these two trials and the fact that the Lindner trial[18] was underpowered to provide a definitive answer. However, one difference in these trials is the fact that patients in the Lindner trial experienced a much more prolonged VF/pVT arrest and may have been refractory to cathecholamines but responded to vasopressin. In contrast, the Canadian study[19] was an in-hospital study with early initiation of vasopressin, a scenario in which patients are as likely to respond to either agent. Animal and clinical studies as well as *in vitro* studies suggest that vasopressin may be especially useful when the duration of cardiac arrest is prolonged, because the adrenergic pressor response in severe acidosis is blunted while vasopressin remains effective.

Based on the fact that the largest trial of in-hospital cardiac arrest patients failed to demonstrate any benefit of vasopressin over epinephrine, it was recommended that epinephrine continue to be the vasoconstrictor of choice and as such vasopressin has not been added to VHHSC ACLS carts.

Epinephrine

Despite the immense amount of animal research and lower level human research which exists for epinephrine in cardiac arrest, there is no evidence to support epinephrine over placebo in human cardiac arrest. Consequently, although still recommended in the new guidelines, epinephrine has been given a Class Indeterminate for cardiac arrest.[1]

Research on high-dose epinephrine has not yet shown that routine use of initial and repeated doses can improve survival.[20] However, there is some evidence which suggests that in cardiac arrest, survivors that receive high-dose epinephrine have more post-resuscitation complications than survivors that received standard epinephrine doses.[21] Because of the potential for harm, high-dose epinephrine is not recommended (Class Indeterminate). Epinephrine should be used only at standard doses of 1.0mg every 3-5 minutes as indicated in cardiac arrest.[1]

Conclusion

Based on the updated ACLS 2000 guidelines, amiodarone has been added to all VHHSC ACLS carts for the management of VF/pVT arrest. Bretylium has been removed from all ACLS carts and vasopressin has not been added. Epinephrine remains in situ at a standard recommended dose of 1.0mg every 3-5 minutes as indicated.

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Clinical Informatics Comes to VHHSC Pharmaceutical Sciences CSU

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Clinical Informatics has been defined as the developing scientific field that pertains to the storage, retrieval, and optimal use of biomedical information, data, and knowledge to enable clinical problem solving and decision-making.

Pharmacy is an information intensive profession. The health care information explosion combined with an emphasis on evidence-based pharmacotherapy has resulted in a major change in pharmacist roles. Affordable and portable computers combined with advanced information technology now permit useful clinical applications for pharmacists to use in their practice.[1]

To address this technological change, Pharmaceutical Sciences CSU has introduced an Informatics Program coordinated by Dr. Robert Balen. The mandate of this program is to facilitate synergy between practitioners and information technology (IT) resources. A number of initiatives have been completed or are planned including:

- IT Skills Survey: Current IT skills and needs are being assessed to determine the future learning requirements of CSU members.

- Electronic Aggregated Table of Contents (eTOC) Project: Nine core pharmacotherapy journals have been designated as essential literature to the Department. To ensure pharmacists have a timely and efficient method of screening these journals for new advances in pharmacotherapy, eTOC are now delivered by email to our team members within a maximum of 14 days from original publication.

- Personal Digital/Data Assistant Project: Palm devices are being programmed with drug information resources and workload tracking software. These devices are being distributed to select Pharmaceutical Sciences staff members for use in their patient care areas.

- Transition to Online Databases: Online databases are being increasingly utilized to enable timely access to available pharmacotherapy resources. Training has been initiated to promote the informed use of these resources and their application towards the improved care of our patients.

Through these and other initiatives, we expect to further improve our health care professional informatics skills. Stay tuned and keep connected!

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