

May 1998

Volume 5, Number 2

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## Changes to Formulary

### Additions

All formulary changes and policy/procedure updates have been approved by the Medical & Academic Advisory Council (MAAC) (Feb-Apr 1998)

#### 1. Fluticasone 25mcg, 125mcg metered dose inhaler (MDI) (Flovent®)

- steroid inhaler which is twice as potent as beclomethasone
- refer to page 2 for interchange policy: fluticasone 125mcg for beclomethasone 250mcg (Becloforte®)

#### 2. Tolcapone 100mg, 200mg tablets (Tasmar®)

- adjunctive therapy for Parkinson's disease
- refer to page 3 for review

#### 3. Fexofenadine 60mg tablet (Allegra®)

- non-sedating histamine (H<sub>1</sub>) antagonist brought on formulary to replace terfenadine (Seldane®)
- refer to page 5 for review

#### 4. Interleukin-2 injection (Proleukin®)

- restricted to BMT/leukemia patients for treatment of select patients with acute myelogenous leukemia (AML) as per protocol

#### 5. Ropivacaine injection (Naropin®)

- amide-type local anesthetic
- compared to bupivacaine, ropivacaine may cause a lower incidence of CNS and cardiac toxicity at higher dosages
- restricted to anesthesia and the acute pain service (APS) for the following:
  - ⇒ where a large volume of long-acting local anesthetic would be required and result in doses above the maximum safe dose of bupivacaine
  - ⇒ when large volumes of local anesthetic may be required for block efficacy and a risk of absorption from a nearby vascular plexus exists, e.g. axillary catheter infusions, > 6 intercostal blocks, lumbosacral blocks and intrapleural catheter infusions
  - ⇒ when epidural infusion rates with bupivacaine are unacceptably high and result in side effects and/or in the event of tachyphylaxis to bupivacaine

#### EDITORIAL STAFF:

Karen Shalansky, Pharm.D.  
Peter Loewen, Pharm.D.  
Rubina Sunderji, Pharm.D.  
Peter Jewesson, Ph.D.

Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU-Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email [kshalans@vanhosp.bc.ca](mailto:kshalans@vanhosp.bc.ca)  
Find us on the Web at [www.vhpharmsci.com](http://www.vhpharmsci.com)

## Deletions

### 1. Beclomethasone 250mcg (80 dose) MDI (Beclforte®)

- 80 dose inhalers have been discontinued by the manufacturer
- alternative: fluticasone 125mcg MDI

### 2. Terfenadine 60mg tablets (Seldane®)

- alternative: fexofenadine 60mg

## Updated Policies/Procedures

### 1. Fluticasone-Becloforte® Interchange

Beclomethasone 250mcg 80 dose MDIs have been discontinued by the manufacturer, leaving only the 200 dose MDI available at a substantially higher cost (Table 1).

Drug	Strength	VHHSC Acquisition Cost
Beclomethasone - Beclvent® MDI - Beclforte®	50mcg 250mcg	\$5.65/200 dose \$71.05/200 dose
Fluticasone MDI - Flovent®	25mcg 125mcg	\$13.20/120 dose \$18.00/60 dose
Budesonide - Pulmicort® turbuhaler	200mcg	\$23.00/100 dose

Fluticasone is comparable to beclomethasone MDI at a 2:1 potency ratio.<sup>1</sup> In adults, at fluticasone dosages up to 500mcg/day (1000mcg beclomethasone), adverse systemic effects are minimal.<sup>2</sup> Fluticasone has been reported to be less systemically absorbed compared to beclomethasone<sup>3</sup>, although the clinical significance of this is unknown. Both adrenal suppression and osteoporosis have been reported in children receiving high doses.<sup>4</sup>

Commencing May 18/98, all beclomethasone 250mcg orders will be automatically interchanged to fluticasone 125mcg (same puffs per day), unless "do not substitute" is written on the beclomethasone prescription. In this case, either the patient's own supply or a newly purchased Becloforte® 200 dose MDI will be used. Note that beclomethasone 50mcg (Beclvent®)

MDIs are not part of this interchange policy due to their continued lower purchase price.

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### 2. Clinical Clerks' Prescribing (MSI-3, MSI-4)

Due to changes in the Faculty of Medicine curriculum and the addition of MSI-3s to patient care areas, the logistics of drug prescribing by clinical clerks has been revised. Effective June 1, 1998, the following are the medication prescribing privileges for all clinical clerks:

- all prescriptions for medications written by clinical clerks must be preceded by a verbal interaction with a resident or more senior medical personnel; and
- a written prescription from a clinical clerk will be considered similar to a verbal order taken by a nurse in that the signature of the clerk must be accompanied by the printed name of the resident or more senior personnel. As well, the clinical clerk must write "cc" after their name.

The clinical clerk will be contacted by a pharmacist to clarify the prescription if there is no senior name after their signature.

In addition to the MAAC, this policy has been approved by the Faculty of Medicine.

### 3. Vitamin K in TPN

Effective April 13, 1998, at the VGH site only, the vitamin K protocol for existing and new TPN orders will be changed from 10mg twice weekly (Mon, Thur) to 10mg once a week (Mon). Non-protocol vitamin K orders may be prescribed as per specific requirements of the patient.

#### 4. Administration of Medication by Nuclear Technologists

Upon a written prescription, a nuclear technologist may administer the following medications: adenosine, aminophylline, amrinone, captopril, dipyridamole, dobutamine, furosemide and ranitidine.

Nuclear technologists may administer the following medications without a written prescription: sincalide (Kinevac®), potassium perchlorate, stannous pyrophosphate and vitamin B<sub>12</sub>.

During administration of these drugs, a physician must be immediately available in the event of a complication. Full resuscitative equipment must also be readily available.

#### 5. Digoxin Immune Fab (Digibind®)

The Drug and Poison Information Centre (DPIC) must approve the use of Digibind prior to administration. At VHHSC, DPIC may be informed after drug administration for the following situations:

- serum digoxin level > 12.8 nmol/L in an acute ingestion OR
- serum potassium > 5mmol/L in an acute ingestion OR
- acute ingestion of > 10mg in an adult OR
- potentially life-threatening cardiotoxicity

#### 6. Aminoglycoside and Vancomycin Serum Concentration Monitoring

Aminoglycosides (gentamicin/tobramycin) and vancomycin serum concentrations will be determined by the laboratory at the following times:

- Monday-Friday: 0930, 1130, 1500 hours
- Sat, Sun, RAD, STAT: 1100 hours

Amikacin serum levels will be reported by 1500 hours 7 days per week.

Pharmacists will continue to interpret and report on these drug concentrations on a 7 day per week basis.

## New Drugs/Drug Products

### TOLCAPONE (Tasmar®)

Nilooofar Alikashani, Pharmacy Resident  
Alan Low, Pharm.D.

Tolcapone has been recently added to formulary as an adjunct to levodopa therapy to treat the signs and symptoms of idiopathic Parkinson's disease.

#### Pharmacology

Motor symptoms of Parkinson's disease are largely due to the loss of dopaminergic D<sub>2</sub> receptor stimulation and relative excess cholinergic activity that results. The strategy for drug therapy is to increase dopaminergic activity in the brain with or without a concomitant reduction in cholinergic activity. Levodopa is the mainstay of drug therapy for Parkinson's disease, most often in combination with a dopa decarboxylase inhibitor (DDI), such as carbidopa (Sinemet®) or benserazide (Prolopa®). The DDIs are co-administered with levodopa to reduce peripheral conversion of levodopa to dopamine. Unfortunately, Parkinson's disease continues to progress despite therapy. Moreover, long-term complications of drug therapy begin to be seen three to five years after the onset of levodopa therapy. Patients develop motor response fluctuations such as the "wearing-off" effect and the "on/off" effect.

Tolcapone is a selective and reversible catechol-o-methyl-transferase (COMT) inhibitor.<sup>1-5</sup> COMT metabolizes levodopa to an inactive metabolite 3-methoxy-4-hydroxy-L-phenylalanine or 3-o-methyldopa (3-OMD). 3-OMD has a long half-life of fifteen hours compared to levodopa which has a half-life of one hour. During long-term levodopa therapy, 3-OMD can accumulate. In fact, high plasma levels of 3-OMD are suspected of contributing to the "wearing-off" phenomenon.<sup>6</sup> Furthermore, 3-OMD competes with levodopa for the transport across the blood brain barrier as both agents use the same saturable carrier system.<sup>1,6</sup> The use of tolcapone as an adjunct to levodopa/DDI preparations allows improved entry of levodopa into the brain. Tolcapone also

sustains levodopa plasma levels better than levodopa/DDI alone, thereby maintaining constant dopaminergic stimulation in the brain.<sup>1,2</sup> Tolcapone alters the pharmacokinetics of levodopa by decreasing its metabolism resulting in an increased half-life and area-under-the curve. An increased incidence of levodopa adverse reactions may be observed with concomitant administration, necessitating a reduction in the daily levodopa dosage.<sup>1-3</sup>

### Studies

Four randomized, double-blind, placebo-controlled trials were undertaken to assess the effects of tolcapone added as an adjunct to levodopa/DDI preparations on the "wearing off" phenomenon.<sup>1-4</sup> All four studies demonstrated that treatment with tolcapone resulted in significantly reduced "off" time an average of 26-48% and increased total "on" time by 21-38% using a dose of 100-200mg TID for 6 weeks to 3 months. As well, the daily dose of levodopa was significantly reduced as was the number of daily doses.

### Adverse Events

Adverse effects are primarily related to levodopa therapy. The most frequent dopamine related adverse events include nausea, vomiting, dyskinesia, orthostatic hypotension and hallucinations.<sup>1-6</sup> The common non-dopamine related adverse events include diarrhea, anorexia, sleep disturbances and discoloration of urine to yellow. Unwanted dopaminergic effects can be best managed by reducing the levodopa dosage.<sup>6</sup>

There have been four cases of neuroleptic malignant syndrome (NMS) which occurred upon reduction or discontinuation of tolcapone.<sup>7</sup> NMS may occur due to a sudden decrease in dopamine. It is characterized by muscle rigidity, elevated temperature and altered consciousness associated with elevated serum creatine phosphokinase, and is potentially life-threatening. If tolcapone is discontinued, an increase in levodopa dose is recommended.

Elevated liver transaminases of eight times the upper normal limit have occurred in 0.3% to 0.7%

of patients in clinical trials.<sup>1,5</sup> Transaminase levels may take as long as 2 months to return to normal after discontinuation of tolcapone. It is recommended that liver function tests (AST, ALT, GGT, bilirubin) be monitored every six weeks for a period of six months.<sup>7</sup>

### Dosage/Cost

Therapy with tolcapone is initiated at 100mg po TID and may be increased to 200 mg TID. The drug should be given with the first dose of the day of levodopa/DDI preparations with subsequent doses taken 6 to 8 hours apart.<sup>1-5</sup>

The VHHSC acquisition cost of tolcapone is \$1.63/100mg tablet and \$2.83/200mg tablet.

### Conclusion

Tolcapone has proven to be an efficacious adjunct to levodopa/DDI preparations for the relief of the "wearing-off" phenomenon experienced after long-term levodopa therapy. As UBC Hospital is the main referral centre for refractory and difficult Parkinson's disease patients, tolcapone has been added to formulary at VHHSC to avoid delay in therapy and to avoid the occurrence of NMS which may potentially occur upon a sudden decrease in the tolcapone dose.

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## Fexofenadine (Allegra®)

Karen Shalansky, Pharm.D.

Fexofenadine is a second generation selective non-sedating histamine (H<sub>1</sub>) antagonist indicated for the relief of symptoms associated with seasonal allergic rhinitis. It is the predominant active metabolite of terfenadine (Seldane®).

### *Pharmacokinetics*

Following a 60mg oral dose, antihistaminic effects occur within one hour, peak at 6 hours and last at least 12 hours.<sup>1</sup> Fexofenadine is only 0.5-1.5% metabolized to an inactive metabolite in the liver via the cytochrome p450 3A4 isoenzyme system (CYP 3A4). It is primarily eliminated unchanged in the feces (80%) and urine (11%) with an elimination half-life of 11-16 hours.

### *Comparison to Non-sedating Antihistamines*

Fexofenadine has been directly compared to cetirizine (Reactine®) in a double-blind, randomized, placebo-controlled trial of 839 patients.<sup>2</sup> Fexofenadine 120mg and 180mg daily, and cetirizine 10mg daily administered for 14 days were similar and superior to placebo for the treatment of seasonal allergic rhinitis. Adverse effects (headache and drowsiness) were similar in all three treatment groups.

### *Potential Advantages over Other Antihistamines*

Two non-sedating antihistamines, terfenadine and astemizole (Hismanal®), have been associated with causing potentially life-threatening arrhythmias, especially when taken with interacting drugs or foods. Similar in effect to quinidine, both drugs have the propensity to block cardiac muscle potassium channels resulting in QT prolongation and cardiac arrhythmias.<sup>3,4</sup> As well, both drugs are metabolized extensively in the liver via CYP-3A4 and drugs which inhibit this system, (e.g. erythromycin, ketoconazole) may produce potentially cardiotoxic concentrations of these drugs.

A 10 year review (1986-1996) of adverse events of non-sedating antihistamines from 17 coun-

tries, using the WHO ADR database, indicated that cetirizine and loratadine (Claritin®) have also been implicated with cardiac rate and rhythm disturbances (primarily ventricular dysrhythmias).<sup>3</sup> Of note, both terfenadine and astemizole have been changed to prescription status in Canada due to their cardiotoxic and drug interaction potential.<sup>5</sup>

In contrast, fexofenadine has not been shown to prolong the QT<sub>c</sub> interval or affect potassium channels, even at higher dosages.<sup>4</sup> As well, due to its minimal metabolism by CYP 3A4, significant drug/food interactions are unlikely; specifically fexofenadine has not been shown to interact with erythromycin or ketoconazole.<sup>1</sup>

### *Adverse Effects*

Most common adverse effects reported include headache (3.1%), nausea (1.3%), drowsiness (1.3%) and fatigue (1.0%). There is not an increase in adverse events with higher doses.<sup>1</sup>

### *Dose/Cost*

Similar to terfenadine, the dosage is 60mg BID, reduced to 60mg daily for creatinine clearances less than 40mL/minute. The cost of fexofenadine is \$0.72/day (60mg BID) which is similar to terfenadine.

### *Conclusions*

Fexofenadine is a safer, non-sedating antihistamine compared to terfenadine due to its lack of cardiotoxic or drug interaction potential. As well, it has a comparable cost and dose to terfenadine. As a result, fexofenadine has been added to formulary and terfenadine has been deleted from the VHHSC formulary.

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## Hypertensive Urgencies : *No Role for Nifedipine*

Marie-France Beauchesne, Pharm.D. Candidate  
Rubina Sunderji, Pharm.D., Karen Shalansky, Pharm.D.  
Reviewed by Dr. A. Fung, Cardiology

The term hypertensive crisis is defined as an elevation of the blood pressure to a degree which is potentially life-threatening and that requires immediate management in order to prevent end-organ damage.<sup>1</sup> This condition has been classified as hypertensive emergencies and hypertensive urgencies. The delineation between these two situations is not based on the extent to which the blood pressure is increased, but by the presence or absence of target organ damage.<sup>2</sup> In hypertensive emergencies, the elevation of blood pressure is accompanied by an acute or ongoing end-organ damage (eg. renal failure, encephalopathy), whereas in hypertensive urgencies, the increase in blood pressure (usually a diastolic blood pressure greater than 110 mmHg) is not associated with any evidence of acute end-organ damage.<sup>1</sup>

### *Management of Hypertensive Urgencies*

While hypertensive emergencies generally require parenteral therapy, the management of hypertensive urgencies is usually satisfactory with oral medication.<sup>3</sup> The goal in the treatment of hypertensive urgencies is to gradually reduce the blood pressure over several hours.<sup>1</sup> Precipitous reductions in blood pressure or reductions to normotensive levels are not desirable since it can cause end-organ hypoperfusion and damage.<sup>2</sup> In the recent past, the most popular agent for the treatment of hypertensive urgencies was short-acting nifedipine, given either sublingually or orally.<sup>2</sup> Several severe side effects, however, have been reported with its use.<sup>4</sup>

### *Adverse effects from short-acting nifedipine*

In a review of serious adverse reactions associated with short-acting nifedipine, 16 published case reports have been described.<sup>4-13</sup> Of these, 12 patients were treated with 10 mg, 2 patients with 30 mg and 2 patients with 20 mg of short-acting nifedipine (per os or sublingual). The age of the patients ranged from 33 to 72 years old. In most cases (12 patients), nifedipine was given to treat

high blood pressure. It was also used for the management of unstable angina in two patients, for pulmonary hypertension in one patient, and for pregnancy-induced hypertension in one patient. The adverse drug reactions were hemiparesis in three patients, loss of consciousness in one patient, one case of fetal distress, and cardiac events in 11 patients (ECG changes (4), syncope and complete heart block (1), myocardial infarction (5), hypotension and sinus arrest (1)). Overall, 14 patients recovered and two died. Both deaths were reported in patients who were given nifedipine for unstable angina.

In a study designed to evaluate the benefit of nifedipine alone and in combination with metoprolol in patients with unstable angina, monotherapy with short-acting nifedipine was associated with an increased risk of nonfatal MI or recurrent angina within the first 48 hours of therapy.<sup>14</sup> This trial was terminated prematurely due to a higher risk of myocardial infarction in patients assigned to nifedipine alone. Another trial evaluating the effect of nifedipine on mortality in patients with acute myocardial infarction was also terminated early because of an excess number of deaths in the nifedipine group.<sup>15</sup> Therefore, short-acting nifedipine should be avoided especially in patients with coronary artery disease.

The 1997 sixth report of the Joint National Committee in detection, evaluation and treatment of high blood pressure does not recommend the use of sublingual nifedipine for the management of hypertensive crisis due to the serious adverse events that have been reported with its use.<sup>16</sup> The use of short-acting nifedipine is no longer considered appropriate because it can cause a rapid unpredictable fall in blood pressure and may precipitate ischemic events.<sup>16,17</sup>

### *What are some alternatives to nifedipine ?*

Oral agents with a relatively fast onset of action can be used for the management of hypertensive urgencies<sup>16</sup> (Table 2). These include captopril (angiotensin-converting enzyme (ACE) in-

hibitor), labetalol (alpha- and beta-adrenergic blocker), atenolol (beta-adrenergic blocker) and clonidine (central alpha-2 agonists). A lower starting dose of these agents should be administered in the elderly, volume-depleted patients, patients on concomitant antihypertensive therapy, and patients with preexisting cerebrovascu-

**Table 2. Oral agents for hypertensive urgencies**

Drug	Captopril (Capoten)	Labetalol (Trandate)	Atenolol (Tenormin)	Clonidine (Catapres)
Dose	6.25-25mg q30min prn po or sl <sup>1</sup>	200-400mg q3-4h prn po	100mg q12-24h prn po	0.1-0.2mg q1h prn po (max .0.8mg)
Onset (minutes)	15-30	30-120	60	30-60
Peak Effect (hours)	1	3-4	12-16	2-4
Duration (hours)	4-6	6-8	24	6-8
Side Effects	Hypotension, acute renal failure	Orthostasis, broncho-spasm, bradycardia	Broncho-spasm, bradycardia	Sedation, dry mouth, dizziness, drowsiness
Comments	Caution if volume depleted or renal failure; avoid in RAS <sup>2</sup>	Longer time to peak effect; avoid in asthma, heart failure or block	gradual and prolonged reduction in BP; avoid as per labetalol	Avoid in patients with altered mental status

<sup>1</sup>No studies have demonstrated the superiority of sublingual captopril over oral administration<sup>18</sup>

<sup>2</sup>RAS= renal artery stenosis (bilateral or unilateral in solitary kidney)

lar or cardiovascular diseases.<sup>2</sup>

Captopril can be effectively used as an alternative to nifedipine<sup>19,20</sup> and has been suggested as a first-line agent for the treatment of hypertensive urgencies.<sup>19</sup> Caution is advised in patients who are volume-depleted as hypotensive episodes may be precipitated<sup>1</sup>. In addition, a sudden severe deterioration of renal function may occur in patients with renal artery stenosis.<sup>1</sup> Labetalol reduces blood pressure in hypertensive crisis without producing a reflex tachycardia or a change in cardiac output, which can be beneficial in patients with coronary artery disease.<sup>1,3</sup> This agent should be avoided in patients with heart failure, bradycardia, second- or third-degree heart block and bronchospastic airway

disease.<sup>18</sup> Since labetalol has a longer onset of action, it is necessary to wait 3 to 4 hours before repeating a second dose in order to avoid excessive hypotension.<sup>18</sup> Similar to labetalol, atenolol has been used for hypertensive urgencies but has a slower onset of action and more prolonged duration.<sup>21,22</sup> Repeat atenolol doses should not be administered for 12-18 hours. Oral loading with clonidine provides a gradual and predictable reduction in blood pressure in hypertensive urgencies.<sup>19, 23</sup> This agent is not recommended in patients with altered mental status because it may produce drowsiness.<sup>1</sup>

For those patients who are unable to take oral medications, parenteral therapy may be used to initially manage hypertensive urgencies (Table 3).

### Conclusion

In conclusion, the use of short-acting sublingual or oral nifedipine is no longer recommended for the treatment of hypertensive urgencies, as it may precipitate serious adverse reactions. Other alternatives have been shown to be efficacious and safer for the management of hypertensive crisis.

**Table 3. Formulary Parenteral Alternatives for the Management of Hypertensive Urgencies**

Drug	Labetalol (Trandate)	Propranolol (Inderal)	Hydralazine (Apresoline)	Methyldopa (Aldomet)
Dose	20-80mg IV q10 min prn	1-3mg IV q4-6h prn	10-20mg IV q4-6h prn	250-500mg IV q6h prn
Onset (mins)	5-10	2-5	5-20	30-60
Peak Effect	5-15 mins	15 mins	10-80 mins	3-6 hours
Duration (hours)	3-6	3-6	2-6	10-16
Comments	Avoid if asthma, heart failure, heart block or bradycardia	As per Labetalol	May cause reflex tachycardia, avoid if CAD <sup>2</sup>	Avoid in patients with altered mental status

<sup>1</sup>Check Parenteral Drug Therapy Manual (PDTM) for administration guidelines and restrictions

<sup>2</sup>CAD = coronary artery disease

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### Parenteral Drug Therapy Manuals (PDTM)

All PDTMs at VHHSC were updated in March 1998. Please contact Dr. Karen Shalansky 875-4839 if you require any information regarding this manual.