

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

<i>Changes to Formulary.....</i>	<i>1</i>
<i>Pharmacists Ordering Drug Levels.....</i>	<i>2</i>
<i>Revised Drug Administration Policies.....</i>	<i>2</i>
<i>Tiotropium.....</i>	<i>2</i>
<i>Bisoprolol.....</i>	<i>4</i>
<i>Pharmacy Residency Accreditation.....</i>	<i>5</i>

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 on the Web at www.vhpharmsci.com

Changes to Formulary

Additions

- 1. Tiotropium 18mcg inhaler (Spiriva®)**
 - Anticholinergic drug indicated for long-term maintenance treatment of chronic obstructive pulmonary disease (COPD)
 - See page 2 for drug review
- 2. Bisoprolol 5mg tablets (Monacor®)**
 - Cardioselective beta-blocker for management of hypertension and heart failure
 - See page 4 for drug review
- 3. Fenofibrate 100mg (Apo-fenofibrate®), 160mg (Lipidil Supra®)**
 - Fibrate antihyperlipidemic agent effective for reducing triglyceride levels and raising HDL-C levels
 - Fenofibrate is available in three formulations (Table 1):

Table 1. Fenofibrate Formulations

Formulation	Marketed Products
Non-micronized	Apo-fenofibrate® 100mg
Micronized (50% increase in bioavailability compared to non-micronized)	Apo-Feno-Micro® 67mg, 200mg Lipidil® 200mg
Microcoated (75% increase in bioavailability compared to non-micronized)	Lipidil Supra® 100mg , 160mg

The Pharmacy will carry only two formulations of fenofibrate: Apo-fenofibrate® 100mg (\$0.36/tablet) and Lipidil Supra® 160mg (\$1.33/tablet). Table 2 illustrates the therapeutic interchange policy for fenofibrate orders.

Table 2. Therapeutic Interchange for Fenofibrate

Ordered As:	Dispense
Apo-feno-micro® 67mg Fenofibrate 100mg Fenofibrate 200mg Lipidil Supra® 100mg	Apo-fenofibrate® 100mg formulation
Fenofibrate 160mg Lipidil Supra® 160mg Lipidil® 200mg	Lipidil Supra® 160mg formulation

Deletions

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Deletions

1. **Pindolol tablets (Visken®)**
 - Alternative: Acebutolol
2. **Gemfibrozil capsules (Lopid®)**
 - Alternative: Fenofibrate

Updated Policies

1. Serum Drug Level Monitoring

Clinical pharmacists have been authorized to order serum concentrations of all measurable drugs including (but not limited to) aminoglycosides (with serum creatinine), carbamazepine, cyclosporine, digoxin, lithium, phenobarbital, phenytoin (with serum albumin), tacrolimus, theophylline, valproic acid, and vancomycin (with serum creatinine).

2. Revised Drug Administration Policies

The on-line and hard copy versions of the Parenteral Drug Therapy Manual (PDTM) have been updated with these new policies:

- Skeletal muscle relaxants (**cisatracurium, pancuronium, rocuronium, succinylcholine**) are restricted to critical care areas.
- The following platelet inhibitors: **abciximab, eptifibatide and tirofiban** may be administered in any critical care area.

New Drugs/Drug Products

1. Tiotropium inhaler (Spiriva®)

Jennifer Haymond B.Sc. (Pharm), Karen Shalansky, Pharm.D.

Tiotropium is a long-acting anticholinergic agent indicated for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).¹

Pharmacology

Tiotropium is a quaternary ammonium muscarinic receptor antagonist demonstrating specificity for the M₃-receptor subtype.¹ The M₃-muscarinic receptor is largely responsible for visceral smooth muscle contraction in response to acetylcholine.¹ By antagonizing the effects of acetylcholine on bronchial smooth muscle, tiotropium reduces bronchospasm. Other proposed benefits of anticholinergic bronchodilators include regulating mucus secretion and inhibiting viral influence on cholinergic tone².

Tiotropium demonstrates a long duration of action of at least 24 hours that can be attributed to its high affinity for and slow dissociation from the M₃-muscarinic receptor¹.

Comparable Formulary Bronchodilator Agents

Ipratropium, a short-acting anticholinergic bronchodilator, and salmeterol and salbutamol, long-acting and short-acting beta₂ (β₂) agonist bronchodilators, respectively, are currently on formulary (Table 3).

Table 3. Comparison of Formulary Bronchodilators for COPD

Drug Name	Mechanism of Action	Time to Onset (minutes)	Duration of Effect (hours)	Typical Dose	VH Acquisition Cost
Tiotropium (Spiriva®)	Anticholinergic; antagonizes M ₃ -muscarinic receptors	30	24	18 mcg once daily	\$10.50/5 x 18 mcg capsules Inhaler device free
Ipratropium (Atrovent®)	Anticholinergic; non-selective blocker of muscarinic receptors	5-15	4-6	40mcg QID	\$12.79/20mcg inhaler (140-dose inhaler) (nebulizer available)
Salmeterol (Serevent®)	Beta ₂ agonist; ↑ cyclic adenosine monophosphate (cAMP)	10-20	12-18	50mcg BID	\$24.90/25mcg inhaler (120-dose inhaler)
Salbutamol (Ventolin®)	As above	2-5	4-6	200mcg q4-6h	\$2.65/100mcg inhaler (200-dose inhaler) (nebulizer available)

Compared to placebo, tiotropium provides superior bronchodilation and quality of life scores, and fewer exacerbations and hospitalizations in patients with COPD.³ There are two identical randomized, double-blind, parallel group studies directly comparing tiotropium to ipratropium.^{4,5} Results of the two studies were combined after one year.⁴ Patients received either tiotropium 18 mcg daily (n=356) or ipratropium 40mcg qid (n=179).⁴ Tiotropium demonstrated significantly greater improvement in trough FEV₁ and FVC throughout the study. While both groups used lower rescue salbutamol compared to baseline, the reduction was greatest in the tiotropium group (p<0.05 for 40 of the 52 weeks). Tiotropium significantly reduced the proportion of patients with one or greater COPD exacerbations (35% vs. 46%, p=0.014) although the proportion of hospitalized patients was similar (7.3% vs. 11.7%, p=0.11).

Trials comparing tiotropium to salmeterol have been unable to demonstrate significant differences in reducing exacerbation rates or use of rescue salbutamol in patients with moderate to severe COPD.^{6,7} However, tiotropium demonstrated significantly improved FEV₁ over salmeterol at 24 weeks (p<0.01)⁶. This difference may be attributed to a possible tachyphylactic effect with prolonged salmeterol use, resulting in a decrease in salmeterol response.²

Potential Risks

The most commonly reported adverse event for tiotropium in clinical trials is dry mouth.^{4,7} In the 1-year comparative trial of tiotropium and ipratropium, dry mouth was significantly higher in the tiotropium group (12.1% vs. 6.1%, p=0.03).⁴ Dry mouth is usually mild and has led to a 0.3% discontinuation rate.¹

Potential Benefits/Role in COPD Therapy

Tiotropium has demonstrated improvement in reducing exacerbation rates compared with placebo (RR 0.74; 95% CI 0.62-0.89) or ipratropium (RR 0.78; 95% CI 0.63-0.95).⁸ Additionally, tiotropium has demonstrated consistent, significant improvements in reducing exacerbation and hospital admission rates over placebo whereas salmeterol has not.⁸ Once daily administration is also advantageous for compliance purposes and for elderly patients who have difficulty manipulating a metered dose inhaler.

The 2003 guidelines from the Canadian Thoracic Society recommend a long-acting bronchodilator as the second step in therapy if COPD symptoms persist despite reasonable short-acting bronchodilator use (level of evidence: 1A).⁹ Recommended long-acting bronchodilators include tiotropium or a long-acting β_2 agonist. Combination tiotropium and a long-acting β_2 agonist are recommended for patients with persistent moderate to severe symptoms (level of evidence: 3A).

Dose and Cost

The dose of tiotropium is inhalation of one capsule (18mcg) once daily using the supplied handihaler. Tiotropium capsules come in packages of 10 that can be split into two, allowing a 5-day course of tiotropium to be dispensed (\$10.50/5 days). The inhaler itself is provided free of charge to the hospital.

Conclusion

Tiotropium demonstrates superior bronchodilation compared to placebo and ipratropium. Studies have yet to demonstrate significant superiority of tiotropium over salmeterol. Tiotropium is currently recommended in the Canadian COPD Guidelines as an option for patients who are not optimally controlled with short-acting bronchodilators. Ipratropium is still required on formulary due to its availability as a nebulizer for use in acute asthma/COPD exacerbations and as well for initial therapy of mild COPD.

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2. Bisoprolol (Monacor[®])

Karmin Ip B.Sc.(Pharm), Susan Buchkowsky B.Sc.(Pharm), Rubina Sunderji, Pharm.D.

Bisoprolol is a β_1 -adrenergic receptor blocker (cardioselective beta-blocker) indicated for the management of hypertension and heart failure (HF). It does not have intrinsic sympathomimetic activity or membrane stabilizing activity

Clinical Trials

Two randomized placebo-controlled trials evaluating bisoprolol in patients with HF have been published: CIBIS¹ and CIBIS II² (Table 4). In the CIBIS trial¹, patients continued to receive standard therapy with an angiotensin converting enzyme inhibitor (ACEI) (90%) and a diuretic (100%) and were followed for a mean of 1.9 years. The observed difference in mortality in favour of bisoprolol did not reach statistical significance (16.6% vs. 20.9%). The inability to detect a survival difference was attributed to a lower than expected mortality rate used in the power calculation and possible suboptimal dosing of bisoprolol (target 5mg/day).

The CIBIS II trial was designed using a revised estimate of placebo mortality rate from the CIBIS trial and a higher bisoprolol dose (target 10mg/day).² In this larger trial, patients were randomized to placebo or bisoprolol on background therapy with diuretics (98.5%) and ACEI (96%) and were followed for a mean of 1.3 years. The trial was stopped early because the all-cause mortality was significantly less in the bisoprolol group compared to placebo (11.8% vs. 17.3%, $p < 0.0001$, 95% CI 0.54-0.81). The bisoprolol group also had significantly fewer cardiovascular deaths (9% vs 12%, $p=0.004$) and hospital admissions (33% vs. 39% , $p=0.0006$). A subgroup analysis of the CIBIS II trial examining the dose-response of bisoprolol showed a similar reduction in mortality with low, moderate and high doses of the drug.³

In both CIBIS trials, bisoprolol was well tolerated with no significant difference in withdrawal rates due to adverse effects compared to placebo.

Comparison with other Beta-Blockers for HF

Only two other beta-blockers, metoprolol and carvedilol have shown survival benefit in HF in randomized, placebo-controlled trials. Metoprolol is cardioselective whereas carvedilol is a non-selective agent with α_1 , β_1 and β_2 blocking properties (Table 5). The alpha blockade with carvedilol has resulted in a higher incidence of side

Table 4. Studies of Beta-Blockers in Heart Failure

Study (Drug)	Design (N)	Population	Target Dose	Mortality
CIBIS ¹ (Bisoprolol)	R, DB (641)	EF \leq 40% NYHA III-IV	5mg/ day	B:16% P: 20.9% (NS)
CIBIS II ² (Bisoprolol)	R, DB (2547)	EF \leq 35% NYHA III-IV	10mg/ day	B:11.8% P:17.3% ($p < 0.0001$)
MERIT-HF ⁴ (Metoprolol XL)	R, DB (3991)	EF \leq 40% NYHA II-IV	200mg/ day	M:7.3% P:10.8% ($p=0.0062$)
US Carvedilol ⁵ (Carvedilol)	R, DB (1094)	EF \leq 35% NYHA III-IV	50mg BID	C:3.2% P:7.8% ($p < 0.001$)
COPERNI- CUS ⁶ (Carvedilol)	R, DB (2289)	EF \leq 25% NYHA IV	25mg BID	C:11.2% P:16.8% ($p=0.0014$)
COMET ⁷ (Metoprolol vs Carvedilol)	R, DB (3029)	EF $<$ 35% NYHA II-IV	M: 50mg BID C: 25mg BID	M:40% C:34% ($p=0.0017$)

R=Randomized, DB=Double Blind; EF=Ejection Fraction; NYHA=New York Heart Association; B=Bisoprolol; P=Placebo; M=Metoprolol; C=Carvedilol; NS=not significant

effects such as dizziness (32.4% carvedilol vs. 19.2% placebo) in clinical trials.⁸

Similar to bisoprolol, metoprolol and carvedilol have also shown to reduce mortality compared to placebo in HF (Table 4). In a head-to-head trial, carvedilol was significantly superior to regular release metoprolol (COMET).⁷ Of note, the formulation of metoprolol that improved survival in the MERIT-HF trial is a controlled release preparation (metoprolol XL) that is not available in Canada. It is speculated that the controlled release preparations lead to a more pronounced and even beta-blockade over 24 hours in comparison to regular release preparations.⁴ This degree of blockade may be important in protecting the heart from abrupt increases in sympathetic nervous activity which may potentiate ventricular fibrillation and sudden death, and in long-term myocardial performance of the failing heart.⁴

Dose and Cost

The initial dose of bisoprolol is 1.25mg daily gradually increased by 1.25mg every 1-4 weeks to a maximum target dose of 10mg daily for HF.

Table 5. Comparative Properties of Beta Blockers

Drug	β_1 Selective	ISA	Lipid Solubility	Approximate Dose Equivalence	Major Route of Elimination	Once Daily Dosing	Equivalent Daily Cost ^b
Acebutolol	Yes	1+	Low-Mod	200mg	Hepatic, Renal	Yes	\$0.12 (200mg OD)
Atenolol	Yes	-	Low	50mg	Renal	Yes	\$0.11 (50mg OD)
Bisoprolol	Yes	-	Mod	10mg	Hepatic	Yes	\$0.43 (10mg OD)
Carvedilol ^a	No	-	Mod	50mg	Hepatic	No	\$1.71 (25mg BID)
Labetalol	No	-	Mod	200mg	Hepatic	No	\$0.32 (100mg BID)
Metoprolol	Yes	-	Mod	100mg	Hepatic	Yes (SR Preparation)	\$0.08 (50mg BID)
Nadolol	No	-	Low	80mg	Renal	Yes	\$0.36 (80mg OD)
Oxprenolol ^a	No	2+	Mod	80mg	Hepatic	No	\$0.50 (40mg BID)
Pindolol ^a	No	3+	Mod	7.5mg	Hepatic, Renal	Yes	\$0.12 (7.5mg daily)
Propranolol	No	-	High	80mg	Hepatic	Yes (LA Preparation)	\$0.47 (80mg LA daily)
Timolol ^a	No	-	Low	10mg	Hepatic	No	\$0.22 (5mg BID)

^anon-formulary drug at VH

^bVH acquisition cost for formulary drugs

ISA = Intrinsic Sympathomimetic Activity

SR = Sustained Release; LA = Long-Acting

Table 2 illustrates equivalent doses and costs of various beta-blockers including bisoprolol. Both bisoprolol and metoprolol are Pharmacare benefits. Carvedilol 25-50mg bid is the most costly of the three agents and requires a completed special authority form for Pharmacare benefit.

Conclusion

Bisoprolol has been added to formulary for the following reasons:

- Unlike regular release metoprolol, bisoprolol has proven to decrease mortality from HF in a large randomized trial.
- Bisoprolol is preferred over carvedilol due to its lower cost and does not require special authority for Pharmacare benefit.
- Bisoprolol's pharmacokinetic profile allows for once daily dosing and improved patient compliance

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Residency Accreditation Status

The Vancouver Hospital Pharmacy Residency Program was recently awarded full accreditation by the Canadian Hospital Residency Board. Congratulations to Dr. Kerry Wilbur and Dr. Peter Loewen who are the Residency Program co-coordinators and all the other contributors to the residency program.