VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

A Publication of the Department of Pharmacy

June 2000 *Volume 7, Number 2*

In This Issue...

Changes to Formulary	1
Updated Policies and Procedures	2
Revised Equianalgesic Oral Dosing Chart	2
Clopidogrel Safety Update	2
ADR Reporting : Drugs of Current Interest	3
Donepezil	3
Patients' Perceptions about Substitution of a Reference Drug while in Hospital	6

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

This and other Drug and Therapeutics Newsletters are available on our website at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. **Donepezil 5mg, 10mg tabs (Aricept®)**
- symptomatic treatment of mild to moderate Alzheimer disease
- Cost: $4.59/5mg or 10mg hs
- See page 3 for review

2. **Carboprost 250 mcg/mL vial (Hemabate®)**
- Prostaglandin F_{2alpha} , abortifacient
- To replace Dinoprost (Prostin F2 Alpha®)
- Cost: $27.91/250 mcg vial

3. **Flagystatin® vaginal cream**
- Metronidazole-Nystatin vaginal cream
- To replace Sultrin® vaginal cream
- Cost: $22.32/55g tube

Deletions

The following items have been deleted due to minimal to no usage over the past 3 years or discontinuation by the manufacturer.

1. **Cisapride tablets/solution (Prepulsid®)**
- Discontinued by manufacturer
- Remaining stock will be dispensed until Aug 7/00
- Alternative: metoclopramide, domperidone

2. **Gentian Violet 1% solution**

3. **P&S® Liquid Phenol** (phenol lotion)

4. **Sebulex® shampoo** (salicylic acid/sulphur)

5. **Levodopa-benserazide caps (Prolopa®)**
- Alternative: levodopa-carbidopa (Sinemet®)

6. **Methysergide 2mg tablets (Sansert®)**

7. **E-Pilo® eye drops** (epinephrine-pilocarpine)

8. **Epifrin® eye drops** (epinephrine)

9. **Tolmetin tablets (Tolectin®)**
- Alternatives: diclofenac, ibuprofen, naproxen , sulindac

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
Find us on the Web at **www.vhpharmsci.com**

10. Sodium Fluoride tablets
- Alternative: sodium fluoride gel

11. Poly vi sol® drops
- Alternative: Infantol® drops)

12. Dinoprost injection (Prostin F2 Alpha®)
- Discontinued by manufacturer
- Alternative: Carboprost (Hemabate®)

13. Triple sulfa vaginal cream (Sultrin®)
- Discontinued by manufacturer
- Alternative: Flagystatin® vaginal cream

14. Methohexital injection (Brietal®)
- Discontinued by manufacturer
- Alternative: Thiopental (Pentothal®)

15. Beef-Pork Insulins
- Discontinued by manufacturer
- Alternatives: Human or pure pork insulins

16. Bretylium injection (Bretylate®)
- Discontinued by manufacturer

Updated Policies/Procedures

1. Prescription Interpretation Policy

- All prescriptions requesting "Ciprofloxacin 500 mg IV" will be automatically changed to "Ciprofloxacin 400 mg IV" at the same dosage interval.

2. Revised Drug Administration Policies

The following changes will be added to the next Parenteral Drug Therapy Manual (PDTM) update (June/July 2000):

- **Propofol tubing and administration sets** must be **changed every 12 hours.**

- **Chlorpromazine** may be administered **subcutaneously** on **any nursing unit.**

- **Oxytocin** may be **diluted as 10-40 units in 500-1000 mL IV fluid** and **infused over 2-3 hours** for termination of pregnancy or management of uterine atony following abortion.

- The Equianalgesic Dosing Chart for Management of Acute or Chronic Pain (Appendix XI of PDTM) has been updated to include oxycodone and propoxyphene. Table 1 lists the oral narcotic dosage equivalents.

Table 1. Oral Narcotic Dosage Equivalents

Drug	PO Dosage Equivalent
Morphine Codeine Hydromorphone Oxycodone	20-30 mg 200 mg 4 mg 15-20 mg
Anileridine Meperidine*	75 mg 300 mg
Methadone** Propoxyphene HCl*	2-3 mg 260-390 mg

*not recommended for chronic pain management
** Methadone dose equivalence is for chronic dosing

Adverse Drug Reaction Alert

Clopidogrel (Plavix®) Safety Update
Karen Shalansky, Pharm.D.

Clopidogrel, an antiplatelet drug, was recently added to VHHSC formulary as an alternative to ticlopidine in patients who cannot tolerate or have failed ASA for the prevention of stroke or other vascular events. Early studies suggested that clopidogrel may have a more favourable safety profile compared to ticlopidine, especially with respect to the incidence of thrombotic thrombocytopenic purpura (TTP).[1]

Nine cases of TTP were reported with ticlopidine in a large retrospective study of 43,322 stent procedures, giving an incidence of 1 case per 4814 patients treated.[2] Other studies have reported a frequency as high as 1 in 1600 treated patients.[3] On the other hand, there were no cases of TTP reported in a large prospective trial of 19,185 patients with previous stroke, MI or peripheral vascular disease treated with clopidogrel or aspirin.[1] There was one case of severe agranulocytosis in the clopidogrel phase reported in this trial.[4]

A pre-publication article has just been released describing the development of 11 cases of TTP with clopidogrel.[5] The patients were identified by active surveillance of blood banks, hematologists

and a surveillance program by the manufacturers of clopidogrel over a two year period. Ten of the 11 patients had received clopidogrel for 14 days or less before the onset of TTP and one patient had discontinued the drug 3 weeks before the onset of this syndrome. All patients required between 1 to 30 plasma exchanges (median 8) with resolution of symptoms occurring in 10 patients. One patient died and 2 patients had relapses while off clopidogrel.

While there is almost a 10-year history with the use of ticlopidine, clopidogrel has a cumulative post-marketing experience of less than 2 years.[2] Accordingly, prescribers should be aware that clopidogrel is not without potential hematologic toxicities.

References

1. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. Lancet 1996;348:1329-39.
2. Steinhubl SR et al. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. JAMA 1999;281:806-10.
3. Bennett CL et al. Thrombotic thrombocytopenic purpura after stenting and ticlopidine. Lancet 1998;352:1036-7.
4. Green D. CAPRIE trial correspondence. Lancet 1997;349:354-5 (letter).
5. Bennett CL et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. NEJM 2000; June 15 (in press).

Adverse Drug Reaction (ADR) Reporting: Drugs of Current Interest

The February issue of this D&T Newsletter described 41 suspected ADRs reported at VHHSC during 1999. This data was forwarded to the Canadian ADR Monitoring Program in Ottawa for further analysis. This group has developed a set of criteria to stimulate reporting for a select group of marketed drugs in order to identify drug safety signals. The maintenance of this list (Table 2) facilitates regular monitoring and constitutes one element of post-approval assessment activities. Criteria for inclusion of drugs on the "Drugs of Current Interest" list are as follows:

- Recently marketed drugs (< 2 years), with limited post-marketing experience and potential safety concern from pre-market review;
- Marketed drugs for which there are emerging safety concerns, new serious adverse drug reactions that are unlabelled in the product monograph ;
- The first marketed drug of a new pharmacological/chemical class of medication

Please alert a pharmacist if you suspect an ADR for assessment and documentation.

Table 2. Drugs of Current Interest, May 2000

Abacavir (Ziagen®)	Naratriptan (Amerge®)
Alteplase (Activase® rt-PA)	Nefazodone (Serzone®)
Bupropion (Zyban®, Wellbutrin® SR)	Nevirapine (Viramune®)
Celecoxib (Celebrex®)	Oseltamivir (Tamiflu®)
Cisapride (Prepulsid®)	Pramipexole (Mirapex®)
Clopidogrel (Plavix®)	Ritonavir (Norvir®)
Delavirdine (Rescriptor®)	Rofecoxib (Vioxx®)
Factor VII-recombinant, activated (NiaStase®)	Ropinirole (Requip®)
Hypericum perforatum (St. John's Wort)	Saquinavir (Invirase®)
Indinavir (Crixivan®)	Sildenafil (Viagra®)
Melanoma theraccine (Melacine®)	Terbinafine (Lamisil®)
Mefloquine (Lariam®)	Ticlopidine (Ticlid®)
	Trastuzumab (Herceptin®)
	Trovofloxacin (Trovan®)
	Zanamivir (Relenza®)
	Zolmitriptan (Zomig®)

New Drug/Drug Products

Donepezil (Aricept®)

Dr. B Lynn Beattie, Geriatric Medicine, Dr. Martha Donnelly, Geriatric Psychiatry, Dr. Alan Low, Pharmaceutical Sciences CSU

Donepezil is an acetylcholinesterase inhibitor recommended for symptomatic treatment of mild to moderate Alzheimer's disease (AD).[1-4] Double-blind, randomized, controlled trials (RCT) in more than 500 patients with mild to moderate AD have found that donepezil slightly improves a measure of cognitive function and a clinician's global assessment of general and behavioral function.[1,3,4]

Pharmacology/Pharmacokinetics

Donepezil is the first of a new class of piperidine-based, non-competitive, reversible acetylcholinesterase inhibitors. In patients with AD, cognitive impairment is associated with a reduction in acetylcholine in the brain.[5,6] By preventing acetylcholine metabolism, donepezil increases the concentration of acetylcholine in brain synapses which allows for increased stimulation of muscarinic receptors.[5] Donepezil has high selectivity for acetylcholinesterase in the central nervous system, with little peripheral activity.[6]

Donepezil is well absorbed, with a bioavailability of 100% that is unaffected by food. It is extensively metabolized by the cytochrome p450 isoenzymes (CYP) 2D6 and 3A4. Drugs affecting these isoenzymes can affect the metabolism of donepezil. However, data regarding drug-drug interactions with donepezil is very limited.

Indication
Donepezil is indicated for patients with mild to moderate AD (MMSE > 10). To establish the diagnosis, the patient should have a clinical course of at least 6 to 12 months of insidious onset of progressive impairment in memory and other cognitive functions significantly severe to interfere with function.[7] The diagnosis and work-up should be consistent with the Canadian Consensus Conference Guidelines for diagnosis of AD.[8]

The NINCDS ADRDA criteria[9] recognize that *definite* AD is diagnosed by biopsy/autopsy and the best clinical diagnosis is *probable* AD. It is also clear, that particularly in old people, *possible* AD is common. In this situation the diagnosis is suggestive of AD however:

- The onset of the syndrome is atypical, eg. with language problems (aphasia) more prominent than memory (new learning) difficulty, or there are soft signs of parkinsonism in the face of an insidious progressive dementia. In the latter case the Lewy Body Variant (LBV) of AD is suggested.
- There are clinical or radiological features suggestive of co-morbid diagnosis such as CT evidence of focal infarction but the overall clinical syndrome is consistent with the AD diagnosis.

Donepezil therapy may be considered in both of these scenarios.

Dose and Onset of Effect
The initial dose of donepezil is 5mg at bedtime; after 4 to 6 weeks the dose can be increased to 10 mg. If insomnia becomes a problem, the medication can be given earlier in the day. The half-life of donepezil is 3 days and steady-state plasma concentrations are reached in 2 weeks. Effects of the drug are measurable as early as 3 weeks and definitely by 6 to 12 weeks.

After initiation of the medication, follow-up should occur in 4 to 6 weeks to ascertain tolerance and to consider an increase in dosage to 10mg. Further follow-up to evaluate effectiveness is recommended at 12 weeks, at 6 months, then every 6 months thereafter.

Duration of Therapy
Optimal duration of therapy is unknown. An open-label study evaluating the efficacy of donepezil beyond 6 months of treatment found improvements in cognitive performance and global functions were sustained for almost 2 years (92 weeks) beyond the original 12 week treatment protocol.[2] There is some indication that individuals on long-term therapy continue to decline but their overall capacity appears better than those on placebo. At follow-up evaluation, there should be assessment of cognition, function and behavior compared with baseline. If there is improvement, therapy should be continued. If there is essentially no change from baseline, it may still be reasonable to continue the therapy. If there is decline which is consistent over two or three follow-up periods, the drug may be discontinued. When the deterioration is such that the effectiveness of the medication appears to be absent, the drug may be withdrawn with the proviso that if the overall capacity of the individual deteriorates, the drug may be reinstated to see if baseline is restored. A decision to restart the drug should be made within three weeks of discontinuation if the patient appears to worsen. Again, this process is difficult to evaluate since a review of findings for individuals on treatment who are restarted after a washout period, suggests that these individuals may lose part of their treatment effect.

Adverse Effects
The main adverse effects are cholinergic including nausea, vomiting, diarrhea, insomnia and muscle cramps. These symptoms may disappear with continued use or respond to a dose reduction to 7.5 or 5mg daily.

In some circumstances, the literature suggests that there may be adverse effects with more drastic changes in behavior, seemingly unpredictable, and requiring discontinuation of donepezil.[10-12] Bouman et al reported a case of severe violent behavior within 5 days of initiating donepezil 5mg daily.[10] Personal communication with these authors revealed that the manufacturer had recorded 5% of patients with agitation and 1% with physical aggression. Two cases of nightmares have also been reported which resolved by administering the drug earlier in the day instead of at bedtime.[13]

The Bureau of Drug Surveillance (Canadian ADR Monitoring Program) received 106 suspected adverse reactions from donepezil, 67 of which were expected and 39 which were not expected.[12] Thirty-six ADRs were considered serious. Three

patients died: 1 of a massive CVA 2 weeks after starting donepezil; 1 had weakness and somnolence after 1 dose of donepezil and died 2 days later; and 1 received donepezil, had an episode of syncope whereupon donepezil was discontinued but the individual died 2 months later. Other complications included convulsions (4), aggressive reaction (1), confusion (2), delirium (1), delusion (1), manic reaction (1) and other reactions (93). Some of the reactions may be associated with chronic illnesses such as seizures and confusion which may be part of the disease syndrome itself. Eight reports included concomitant drugs which could potentially interact with donepezil via the CYP 2D6 or 3A4 enzyme systems: diltiazem, fluoxetine, paroxetine and sertraline.

Adjunct Medications

Concern for potential drug-drug interactions is critical since older persons particularly may have co-morbidities. Additionally, a number of other products may be sought in hope/desperation leading to potential possibilities of drug-drug interactions.

Vitamin E has been studied in one double-blind RCT at a dose of 2000 IU daily over 2 years.[14] Although the primary analysis was negative, the study suggested that the treatment group had delayed functional deterioration (time to death, institutionalization, loss of ability to perform ADLs or severe dementia). Vitamin E is reasonably safe and may be used as an adjunct at doses up to 2000 IU daily.

Gingko biloba has been studied in two double-blind RCTs of AD and multi-infarct dementia.[15,16] These studies were highly criticized for scientific merit. Further, there is no standardized gingko preparation in North America. There have also been periodic reports of adverse outcomes (e.g. bleeding into the eye). Use of this preparation is common and advice for its continuation is difficult due to the limited literature and variety of different products available.

Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for individuals with depressive symptoms and dementia. In some cases there may be associated adverse events with drug-drug interactions as suggested above, but the evidence is anecdotal.

Economic Considerations

O'Brien *et al*, using Canadian Study of Health and Aging data, reviewed the economic evaluation of donepezil for the treatment of AD in Canada.[17] The cost-effectiveness was estimated as an adjunct to usual care for AD persons in the mild to moderate stage of the disease (MMSE 10-26). The effectiveness measure for the model was over 5 years with non-severe AD, i.e. MMSE 10 or greater. They concluded that use of donepezil for mild to moderate AD is associated with lower 5-year costs and less time spent with severe AD. The indication for prescribing donepezil continues to be mild to moderate AD. In this model a 5mg dose was used. The VHHSC acquisition cost for donepezil both 5mg and 10mg is $4.59.

Guidelines for donepezil use at VHHSC

1. Using the Canadian Consensus Conference Guidelines for diagnosis of Alzheimer disease[8], primary care physicians may make the diagnosis and consider donepezil per current recommendations:
   a. The patient has mild to moderate *probable* AD (MMSE > 10) (see NINCDS ADRDA criteria[9] discussed under indication)
   b. MMSE, 3MS or equivalent is recorded
   c. Functional impairment due to cognitive impairment is recorded
   d. Behavioral symptoms are recorded

   At VHHSC, before donepezil therapy is initiated by a primary care physician, a specialist physician (neurologist, psychiatrist, geriatrician) must provide a second opinion for the treatment plan.

2. Follow-up at 4 weeks, 3 months, and then every 6 months is undertaken evaluating cognition, function and behavior. At 4 to 6 weeks, the dose can be increased to 10mg if there are no untoward side effects. The most common side effects are gastrointestinal (nausea, vomiting, diarrhea), muscle cramps and insomnia. Evaluation of efficacy can be rated in terms of a five point scale: marked worsening, some worsening, stable, some improvement, marked improvement particularly for function and behavior.

   At 3 months and then every 6 months, an MMSE or 3MS should be repeated. In view of the natural history of AD, "stable" is a potential goal for effectiveness. It is anticipated that the

follow-up will be made by the primary care physician in consultation with formal and informal caregivers as well as in consultation with the specialist as required.

3. Continue follow-up every 6 months and note improvement, stabilization, or deterioration.

4. If the dementia is severe (MMSE < 10) and/or deterioration due to dementia is to the point that omission of the medication makes no difference in cognition, function and behavior, then the drug may be discontinued. Since the half-life is 3 days, it is likely that the drug can be discontinued abruptly. If within 2 to 3 weeks, there is deterioration of cognition, function or behavior the medication may be restarted. The decision to discontinue treatment must be made in conjunction with the patient and those closest to him or her.

References

1. Rogers SL et al. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter randomized, double-blind controlled clinical trial. Dementia 1996;7:293-303.
2. Rogers SL et al. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicenter open-label study. Eur Neuropsychopharmacol 1998;8:67-75.
3. Rogers SL et al. A 24-week double-blind, placebo controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136-45.
4. Rogers SL et al. Donepezil improves cognition and global function in Alzheimer Disease: a 15 week, double blind, placebo controlled study. Arch Intern Med 1998;138:1021-31.
5. Barner EL et al. Donepezil use in Alzheimer Disease. Ann Pharmacother 1998;32:70-7.
6. Anon. Donepezil (Aricept®) for Alzheimer's Disease. Med Lett Drugs Ther 1997;39:53-4.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM IV) 4th ed. Wahington; The Association. 1994.
8. Patterson CJS et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. Can Med Assoc J 1999;160 (Suppl 12):S1-15.
9. McKhann G et al. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-44.
10. Bouman WP et al. Violent behavior associated with donepezil. Am J Psychiatry 1998;155:1626.
11. Wengel SP et al. Behavioral complications associated with donepezil. Am J Psychiatry 1998;155:1632.
12. Springuel P. Donepezil: suspected adverse reactions. Can Med Assoc J 1998;159:81.
13. Ross JS et al. Aricept®-induced nightmares in Alzheimer's disease: 2 case reports. J Amer Geriatr Soc 1999;46:119-20.
14. Sano M et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. NEJM 1997;336:1216-22.
15. LeBars PL et al. A placebo-controlled double-blind, randomized trial of an extract of Gingko biloba for dementia. JAMA 1997;278:1327-32.
16. Kanowski S et al. Proof of efficacy of the gingko biloba special extract Egb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996;29:47-56.
17. O'Brien BJ et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Amer Geriatr Soc 1999;47:570-8.

Abstract

(Can J Hosp Pharm 2000;53:86-91)

Patients' Perceptions about Substitution of a Reference Drug while in Hospital: Focus on H_2-Receptor Antagonists

N Jolly Gill, Luciana Frighetto, Carlo Marra, Peter Jewesson, Pharmaceutical Sciences CSU, Vancouver General Hospital

Objective: To assess patients' perceptions about substitution of a reference drug (H_2-receptor antagonist) with a formulary alternative while in the hospital.
Methods: This study consisted of standardized patient interviews conducted over a 6-week period. Eligible, consenting patients admitted to Vancouver General Hospital who were given a prescription for an H_2-receptor antagonist were interviewed to determine patient characteristics, history of H_2-receptor antagonist use, and understanding and opinion of reference-based pricing.
Results: Forty-one (46%) of the 89 eligible patients consented to participate. Twenty-eight (68%) of the participants were receiving ranitidine at the time of admission to hospital, and 12 of the remaining 13 were converted to ranitidine from another H_2-receptor antagonist (cimetidine) at the time of admission. Eighteen patients (44%) were aware of the reference-based pricing policy, but 4 (10%) were only familiar with the program's name. Of the 12 patients for whom therapy was converted from cimetidine to ranitidine, only 5 (42%) appeared to be aware that their H_2-receptor antagonist had been changed, and 7 (58%) claimed to feel the same or better while taking ranitidine in hospital. After participants were notified of the conversion by the investigator, the median satisfaction rating of the conversion from one H_2-receptor antagonist to another was 5 (range 1 to 5; maximum score 10). In addition, 7 (58%) stated no particular preference for either H_2-receptor antagonist. On discharge, 36 (88%) of the patients resumed taking the H_2-receptor antagonist that they had been using before admission.
Conclusion: Despite the influence of the reference-based pricing policy on use of H_2-receptor antagonists in the community, more than half of interviewed patients were taking ranitidine before admission to this hospital. Of those converted from cimetidine to ranitidine during their hospital stay, none identified any problems associated with the change. Once discharged from the hospital, most patients resumed their previous H_2-receptor antagonist therapy.