VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

Changes to Formulary

Additions

1. Clarithromycin 250mg, 500mg tablets (Biaxin®)
- macrolide antibiotic
- restricted for management of Helicobacter pylori associated peptic ulcer disease and for prophylaxis of Mycobacterium Avium Complex (MAC) infections
- cost: refer to treatment guidelines for H. pylori infections, page 4

2. Olanzapine 5mg, 7.5mg, 10mg tablets (Zyprexa®)
- atypical antipsychotic agent pharmacologically and structurally similar to clozapine
- cost: refer to page 2 for review

3. Tacrolimus (FK506) 1mg, 5mg capsules, 5mg/mL ampoule (Prograf®)
- immunosuppressive agent indicated for prophylaxis of organ rejection in patients receiving solid organ transplants.
- may also be used in bone marrow transplant recipients who develop cyclosporine-resistant/intolerant graft-versus-host disease
- replaces cyclosporine in regimens

4. Baclofen intrathecal 0.05mg/mL, 2mg/mL ampoule (Lioresal®)
- intrathecal infusion for treatment of spasticity that is intractable to oral baclofen and other antispasticity drugs

Deletions

1. Methocarbamol injection 100mg/mL (Robaxin®)
- no usage in past 3 years

2. Pentagastrin injection 0.25mcg/mL (Peptavlon®)
- no usage in past 3 years

3. Pepsin solution 3.3mg/mL (Fermentol®)
- no usage in past 3 years

4. Triamcinolone diacetate 25mg/mL, 40mg/mL (Aristocort® intralesional)
- alternative: triamcinolone acetonide 10mg/mL, 40mg/mL (Kenalog®)

5. Pentazocine 50mg tabs, 50mg/mL injection (Talwin®) (effective Sept 1, 1997)
- minimal usage in past 3 years
- alternatives: morphine, anileridine

6. Flucloxacillin 250mg capsules (Fluclox®)
- discontinued by manufacturer

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Updated Policies & Procedures

Revised Drug Administration Policies

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

- Table 1 illustrates the recommended dosages of Vitamin K for the treatment of warfarin-induced hypoprothrombinemia:

Table 1: Vitamin K Dosage Guidelines for Warfarin- induced Hypoprothrombinemia

INR	Recommendation
< 6 and no bleeding	No vitamin K. Hold warfarin until INR in therapeutic range.
6-9 and no bleeding	Hold warfarin until INR in therapeutic range. May give vitamin K 1-2mg SC or slow IV. May repeat in 24 hours.
> 9 and no bleeding	Vitamin K 3-5mg SC or slow IV. May repeat in 6 hours.
Serious bleed	Vitamin K 10mg SC or slow IV. May repeat in 6 hours. Supplement with fresh frozen plasma as required.

- The Operating Room (OR) has been added as a critical care area
- Octreotide may be given by subcutaneous (SC) infusion for palliation of intractable vomiting
- Methotrimeprazine may be administered by SC injection on any nursing unit
- Diltiazem parenteral may be administered in any critical care area and may also be prescribed for the prevention of arterial spasm
- Amrinone may be prescribed for augmentation of myocardial contraction for assessment of myocardial contractile reserve with imaging

New Drugs/Drug Products

Olanzapine: Atypical Antipsychotic

Karen Shalansky, Pharm.D.
Reviewed by Dr. R. Lam , Psychiatry
and A. Runikis, B.Sc. (Pharm)

Olanzapine is a new atypical antipsychotic drug indicated for acute and maintenance treatment of schizophrenia and related psychotic disorders in which positive (hallucinations, delusions, hostility) and/or negative (blunted affect, emotional and social withdrawal)[1] symptoms are prominent. Olanzapine represents an alternative to conventional neuroleptic therapy (e.g. haloperidol), with the advantage of causing fewer extrapyramidal symptoms (EPS).

Comparable Formulary Agents

Clozapine and risperidone are two atypical antipsychotics available on formulary at VHHSC. Olanzapine is structurally and pharmacologically related to clozapine. It has affinity for various neurotransmitter binding sites including serotonin type 2 (5-HT2) and dopamine receptors. Although there have been no head-to-head trials, clinical effects of olanzapine appear similar to those of clozapine in schizophrenic patients in improving both positive and negative symptoms. As opposed to clozapine, olanzapine has never been studied in patients with refractory schizophrenia.

Compared to haloperidol, olanzapine produces similar decreases in positive symptoms of schizophrenia, but is superior in reducing negative symptoms.[2,3] As well, it is associated with a lower incidence of EPS, especially dystonic reactions, and elevation of serum prolactin levels.

Pharmacokinetics

Olanzapine is 93% bound to plasma proteins and is eliminated extensively by

first pass metabolism in the liver.[4] The half-

Treatment of Helicobacter pylori in association with Peptic Ulcer Disease

Dr. K. Shalansky, C. Hughes, Dr. P. Loewen, Pharmacy
Reviewed by Dr. D. Carr, Dr. E. Yoshida, Gastroenterology

It is now accepted that the majority of peptic ulcers occur secondary to either H. pylori infection or non-steroidal anti-inflammatory drugs (NSAIDs).[1] H. pylori is a gram negative bacillus which colonizes the human gastric mucosa.[2] The percentage of peptic ulcers associated with H. pylori infection is as follows[3]:

Gastric ulcers (GU): ~ 70%
Duodenal ulcers (DU): > 95%

Indications for anti-H. Pylori Therapy

All patients with a documented DU or GU associated with H. pylori infection should receive antimicrobial therapy. The presence of H. pylori can be determined by endoscopy with biopsy or non-invasively through serologic antibody testing or breath tests for urea.[1,3] For practical purposes, in patients with an uncomplicated DU, empiric antibiotic therapy without H. pylori testing has been advocated due to the high association with this organism.[3,4]

Treatment Strategies for H. pylori

According to the consensus guidelines, two regimens are currently recommended for eradication of H. pylori (Table 3).[3,5] Both regimens are effective with one week of therapy. The addition of omeprazole in the quadruple regimen enhances symptom relief and improves eradication by ~ 5%.

Quadruple therapy is considered the "gold standard" regimen, however, patient compliance may be hindered by its complexity. Triple therapy offers a simpler BID regimen, albeit slightly less efficacious and more expensive. Dual therapy with omeprazole plus amoxicillin 1g BID or clarithromycin 500mg TID x 2 weeks are not recommended due to lower success rates of 50-80%.

Adverse effects (primarily metallic taste, nausea and diarrhea) result in ~ 5% patient withdrawal. Clarithromycin inhibits the Cyp 3A enzyme system which can result in toxic levels of cyclosporine, theophylline, cisapride, and non-sedating antihistamines (terfenadine, astemizole).

Table 3: Eradication of H. pylori infection: regimens and costs

Recommended Regimens (x 7 days)	Success Rate	Cost/7 days[1]
QUADRUPLE THERAPY	94-98%	$44.61
Bismuth Subsalicylate 30mL (or ii tablets) QID		$12.13
Metronidazole 250mg QID		$0.56
Tetracycline 500mg QID		$1.12
Omeprazole 20mg BID		$30.80
TRIPLE THERAPY	86-91%	$72.76 or $74.70
Metronidazole 500mg BID (or Amoxicillin 1g BID)		$0.56 ($2.40)
Clarithromycin 500mg BID		$41.40
Omeprazole 20mg BID		$30.80

[1] based on VHHSC acquisition cost

Follow-up

Once cure has been achieved, reinfection rates are less than 0.5%.[3] Eradication of H. pylori should be confirmed 4 weeks after completion of antibiotic treatment for complicated, large or refractory ulcers. Antisecretory therapy should be continued until H. pylori cure has been confirmed in these cases. Once ulcer healing is complete and H. pylori eradicated, maintenance antisecretory therapy (e.g. ranitidine 150mg HS) is only warranted in high risk patients where recurrence of bleeding may cause death.[3]

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Pre-printed H.pylori eradication orders are now available from printing for all wards.

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life is approximately 27 hours (range 21 to 54 hours) with steady-state concentrations reached in about 1 week.[4]

Adverse Effects

The more common adverse effects include postural hypotension, dizziness, somnolence, dry mouth and akathesia. Less common side effects are constipation, weight gain (average 2.8 kg), transient elevations of hepatic transaminases, syncope (0.6%), and seizures (0.9%).[4,5]

The potential advantage of olanzapine over clozapine is that it does not appear to cause severe neutropenia or agranulocytosis and so does not require as close monitoring of blood counts. Although there are no reports in the literature, there has been one case of olanzapine-related agranulocytosis which occurred at VH-UBC site and 2 cases of exacerbation of agranulocytosis by olanzapine reported to the BC Drug and Poison Information Centre (DPIC) from Riverview Hospital.

Dose and Cost

Olanzapine is initiated at 5-10mg/day, with gradual 5mg weekly adjustments to a maximum daily dose of 20mg. The target range is usually 10-15mg daily. Orthostasis, dizziness and weight gain may be minimized with a lower starting dose of 5mg/day and more gradual upward titration. Refer to Table 2 for cost comparison of atypical antipsychotic agents.

Place in Therapy

Table 2. Cost comparison of atypical antipsychotics

Drug	Comparable Upper Range Dose and Cost[1]
Risperidone	8mg/day = $7.64/day
Clozapine	450mg/day = $17.00/day
Olanzapine	15mg/day = $10.14/day

[1] based on VHHSC acquisition cost

Olanzapine has been approved by Pharmacare for patients who have failed one typical antipsychotic agent (e.g. haloperidol) or who develop intolerable adverse effects to these agents. In contrast, clozapine is indicated in patients who are refractory to typical antipsychotics (at least 2 chemically unrelated drugs) or who have intolerable EPS. More direct and long-term safety comparisons with clozapine are required to determine the exact role of olanzapine in therapy.

Conclusions

Olanzapine, an atypical antipsychotic agent, is pharmacologically and structurally similar to the formulary drug clozapine. Although there are no head-to-head comparisons, the clinical effects of both agents appear to be similar in schizophrenic patients. Both agents improve positive and negative symptoms and are associated with a lower incidence of EPS compared to haloperidol. The potential advantage of olanzapine over clozapine appears to be its side effect profile. Initial reports suggest that olanzapine use is not associated with the development of severe neutropenia or agranulocytosis as has been described with clozapine. Unfortunately, local reports suggest that this complication may not be unique to clozapine.

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Drug Interaction: Phenytoin and Folic Acid

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Reviewed by Dr. P. Loewen, Dr. K. Shalansky, Pharmacy and Dr. M. Jones, Neurology

The interaction between phenytoin and folic acid is commonly cited in major drug interaction texts.[1,2,3] However, the interaction is more complex than it may initially appear. The most commonly cited effect is that of decreased serum phenytoin concentrations when folic acid is taken concurrently.[1,2] It has also been shown that phenytoin can decrease folate concentrations in patients.[4] This drug-nutrient interaction is dual and interdependent.[5] While some clinicians advocate avoiding this drug combination, others theorize a benefit of supplementing all phenytoin treated patients with folic acid. Is there a common ground?

Effects of Folate on Phenytoin

There are few controlled studies of the effect of folic acid supplementation on phenytoin pharmacokinetics. Those that have been published come to conflicting conclusions.[6] Some trials have demonstrated decreases in serum phenytoin concentrations to varying degrees after 1-2 weeks of combined therapy.[6,7] Doses of folic acid ranged from 5-30mg/day. Other trials have not shown a decrease in serum phenytoin levels after 1mg or 5mg per day of folic acid.[8]

Decreased phenytoin concentrations may be due to an increase in the metabolism of phenytoin by folic acid. An increase in the parahydroxylated metabolite of phenytoin in the urine, corresponding to a decrease in serum phenytoin concentration, has been observed with the initiation of folic acid.[9,10] Analysis of the kinetics of this interaction suggests that folic acid supplementation causes an increase in the affinity of the enzyme complex for phenytoin resulting a decrease in the Michaelis-Menten rate constant (K_m) with no effect on the maximum rate of metabolism (V_{max}).[11]

Folic acid may decrease phenytoin concentrations to varying degrees. Scattered reports of loss of seizure control are not supported by controlled trials.

Conversely, a retrospective analysis of this interaction concluded that there was no change in K_m, but an increase in V_{max}.[12] Both findings support the suggestion that the interaction is highly patient specific.

Clinically, while some authors report a loss of seizure control when folic acid is added to phenytoin therapy[7,13-15], a review of eight large controlled studies, mostly double blind, showed no significant difference in mean seizure frequency with combination therapy[6].

Effects of Phenytoin on Folate

The prevalence of subnormal serum folate concentrations in patients receiving chronic phenytoin therapy ranges from 27-91%.[4] Progression to megaloblastic anemia occurs in <1% of patients.[16] The development of subnormal folate concentrations in epileptic patients on anticonvulsant therapy is not consistently related to phenytoin dose, duration of therapy or serum concentrations[6], although such relationships have been suggested[8,17-19]. The mechanism by which phenytoin causes a decrease in folate concentrations is not understood. Possible hypotheses include: 1) malabsorption of dietary folate due to pH changes caused by phenytoin[20], 2) malabsorption of dietary folate due to inhibition of intestinal enzymes by phenytoin[21], 3) phenytoin-induced impairment of folate transport into tissue[22], and 4) phenytoin-induction of liver enzymes which are dependent on folate as a cofactor[23].

Phenytoin can cause decreased serum folate concentrations, although megaloblastic anemia is rare.

Controversy surrounds the question of neurological and psychiatric implications of a folate deficiency resulting from long-term phenytoin

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therapy. No controlled study has found anysignificant change in mentation associated with phenytoin therapy in folate-deficient epileptic patient populations.[24-27]

Conclusions

The phenytoin-folic acid interaction has yet to be fully elucidated. While folic acid may decrease serum phenytoin concentrations to varying degrees, folic acid levels may also decrease during phenytoin therapy. From the literature, it appears that the majority of patients are not affectedsignificantly by these interactions. Controlled trials have not shown a significant increase in seizure activity when folic acid is added to phenytoin therapy, and megaloblastic anemia occurs rarely.

In conclusion, phenytoin therapy should not preclude the use of folic acid in patients in whom folic acid is deemed necessary. Of note, it is currently recommended that all women of childbearing age consume folic acid 0.4mg/day to prevent neural tube defects in offspring.[28] It would therefore be prudent to provide folic acid to all women ofchildbearing age who are receiving phenytoin. If folic acid supplementation is initiated in a patientstabilized on a regimen of phenytoin, serum phenytoin levels should be re-evaluated in 1-4 weeks to assess the impact of this interaction.

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