Pediatric Pharmacotherapy

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THERAPY REVIEW: WARFARIN (COUMADIN®)

Warfarin (Coumadin®)

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Formulary Update

Although not common in pediatric patients, warfarin therapy is used to prevent complications from established blood clots or prevent clot formation. Warfarin interferes with the hepatic synthesis of vitamin K-dependent clotting factors, resulting in depletion of factors VII, IX, X and II (prothrombin). It also interferes with the activity of proteins C and S, coagulation inhibitors. Warfarin will have no effect on an established thrombus, but may prevent further extension of a formed clot or prevent secondary thromboembolic complications (1,2). Prophylactic warfarin therapy may be a part of the management of children with underlying hypercoagulable states (such as antithrombin III deficiency), prosthetic cardiac valves, and renal disease. It may also be used to prevent clot formation in patients with central venous catheters, such as patients receiving long-term parenteral nutrition (3). Two recent surveys in Great Britain and Canada have attempted to quantify the number and types of children receiving anticoagulant therapy (4,5). In both surveys, the primary population treated were children with congenital heart disease. This is also the most frequent indication for use within our institution. Warfarin therapy has been recommended for prophylaxis in children with mechanical prosthetic cardiac since the 1970's (6). It has been found to be as effective in preventing thrombosis as dipyridamole or aspirin in this patient population (7-10).

Pharmacokinetics

The pharmacokinetic and pharmacodynamic characteristics of warfarin have been determined in adults (1,2) but not in children. Oral absorption is rapid and complete (100% bioavailability). Warfarin is highly protein bound, primarily to albumin. It is metabolized by the hepatic cytochrome P450 enzyme system to inactive metabolites which are excreted in the urine and bile.2 The elimination half-life is approximately 36 to 42 hours in adults. Due to the need for depletion of existing clotting factors, peak effect is not seen until 1 to 3 days after starting treatment. The duration of action (time until clotting factors are replenished after discontinuing therapy) is typically 2 to 5 days.

Dosing

To provide continuous anticoagulation, patients should begin treatment with heparin. Warfarin therapy should be added during heparin administration for a period of 3 to 6 days to allow for depletion of existing vitamin K- dependent factors. A loading dose is not necessary, but has been used in some treatment protocols. If a loading dose of warfarin is desired, 0.2 mg/kg/day (to a maximum of 10 mg) may be given for 2 to 3 days (5,11).

Standardized maintenance doses for pediatric patients have not been well established due to the high degree of interpatient variability observed (11). In the few studies reporting maintenance doses, a range of 0.05 to 0.34 mg/kg/day has been used (4-9). It has been suggested that younger children require higher doses based on weight. Andrew and colleagues found that children < 1 year of age required an average of 0.32 + 0.05 mg/kg/day. The effective dose decreased throughout childhood to an average of 0.09 + 0.01 mg/kg/day in children ages 11-18 years.5 Bradley et al found an average effective dose of 0.16 mg/kg/day in children with prosthetic cardiac valves (7).

Monitoring

Traditionally, measurement of the PT has been the standard for warfarin monitoring. Due to variations among the commercial thromboplastin reagents used in laboratory analysis, the INR (international normalized ratio) has been adopted to standardize these values (1,12). The INR value incorporates the specific sensitivity of the reagent used. The equation used to determine INR is:

INR = [(Patient PT)/(Normal PT)] * ISI

where ISI is the international sensitivity index, a value provided by the reagent manufacturer. The University of Virginia clinical lab provides both PT and INR values.

The American College of Chest Physicians has recommended a therapeutic INR range for adults of 2.0- 3.0, except for patients with mechanical cardiac valves who should have an INR of 2.5-3.5.1 The appropriate INR value in children is less well established. In a survey of current practice in Great Britain, Evans and colleagues (4) found that most clinicians used a target INR range of 2.6-3.8 for children with heart disease and a slightly lower range of 2.1-3.3 for treating children with established venous thrombosis. Clinicians at Toronto's Hospital for Sick Children used an INR range of 2.0-3.0 initially, but later found that a lower target of 1.3-1.8 was as effective and resulted in no bleeding complications (5).

Adverse Effects

The primary complication associated with warfarin therapy is excessive anticoagulation. This may be reversed with the administration of vitamin K or replacement of clotting factors with exogenous blood products (1,2)

In addition, skin necrosis may occur early in therapy. This is thought to be due to a paradoxical thrombosis of small vessels associated with the rapid fall in protein C seen at the initiation of therapy. Rare adverse effects include: alopecia, urticaria, dermatitis, fever, nausea, diarrhea, cramping, cholestatic hepatic injury, hypersensitivity reactions, and "purple toe syndrome," the result of systemic cholesterol microembolization (2).

Drug Interactions

Drug interactions in patients receiving warfarin while hospitalized may increase length of stay and add as much as $1,000 to hospital costs per patient (13). Interactions may be divided into two groups: those which increase the anticoagulant effect of warfarin and those that reduce its effect (1,2).

Increased effect due to inhibition of metabolism

- amiodarone
- chloramphenicol
- cimetidine
- co-trimoxazole (Bactrim)
- ifosfamide
- lovastatin
- metronidazole
- omeprazole
- propafenone
- quinidine
- quinine
- sulfinpyrazone

Increased effect due to displacement from albumin

- bumetanide
- chloral hydrate (+/-)
- furosemide
- nalidixic acid

Increased effect due to interference with vitamin K

- aminoglycosides
- mineral oil
- tetracylines
- vitamin E

Increased effect due to potential for increased bleeding

- NSAIDS (ibuprofen, ketorolac, etc.)
- salicylates

Increased effect due to unknown/multiple mechanisms

- acetaminophen
- alcohol
- allopurinol
- androgens
- chlorpropamide
- clofibrate
- corticosteroids (+/-)
- cyclophosphamide
- dextrothyroxine
- diazoxide
- disulfiram
- erythromycin
- fluconazole
- gemfibrozil
- glucagon
- hydantoins (phenytoin)
- influenza vaccine
- ketoconazole
- mefenamic acid
- methylphenidate (Ritalin)
- miconazole
- moricizine (+/-)
- pentoxyfylline
- propoxyphene
- quinolones (Cipro, etc)
- sulfaonamides
- tamoxifen
- thioamines
- tolbutamide
- thyroid hormones

Decreased effect due to reduced bioavailability

- antacids
- cholestyramine
- sucralfate
- enteral feedings*

Decreased effect due to induction of metabolism

- aminoglutethimide
- barbiturates
- carbamazepine
- etretinate
- glutethimide
- rifampin

Decreased effect due to unknown/multiple mechanisms

- antihistamines
- dicloxacillin
- ethanol
- ethchlorvynol
- estrogens
- griseofulvin
- nafcillin
- oral contraceptives**
- spironolactone
- thiazide diuretics
- thiopurines
- trazodone

- (+/-) May increase or decrease PT and INR
- * Warfarin should be administered 1 hour before or 2 hours after an enteral feeding. Tubing should be flushed with water before and after dose administration.14
- ** Young women of child-bearing age should be informed of the potential for warfarin to induce serious birth defects or fetal hemorrhage. Appropriate counseling regarding alternative birth control options may be necessary.

Patient Education

The importance of taking warfarin on a routine basis should be emphasized. In the analysis by Stewart and colleagues, noncompliance with warfarin therapy was shown to be the primary factor responsible for the thromboembolic complications found in children with prosthetic cardiac valves (8).

Patients and their parents should be aware of the need to report any unusual bleeding or bruising. The use of any medications, including those purchased without a prescription should be discussed with a health care professional. Dietary restrictions are rarely necessary; the maintenance of a steady diet is of greater importance. Foods high in vitamin K, such as green vegetables, should be eaten in moderation.

Written instructions for patients and their parents are available through MIS. Copies can also be obtained from the pharmacy.

Product Information

Coumadin® is the most frequently used warfarin product. It is available in 1, 2, 2.5, 5, 7.5, and 10 mg tablets. The tablets are scored.2 Warfarin is also available as Panwarfin®

and Sofarin®, but the therapeutic equivalency of these products has not been established. Brand interchange is not recommended (1). UVa pharmacies currently stock the Coumadin® brand.

Editor's Note: Although warfarin has been available since the 1940's, it still does not have an FDA-approved indication for pediatric use!

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FDA Update

Good news! The FDA has ruled that all current and future new drug applications (NDA) must contain information on pediatric use, effective January 12, 1995. Manufacturers have until December 1996 to comply with these new regulations which also require that all currently marketed products carry information regarding potential use in children. If a drug is routinely used in children, but has not received an FDA-approved indication for pediatric use, a supplementary NDA will be required. A special pediatric subcommittee has been established to track the implementation of the new regulations and support the testing of new drugs in pediatrics. Label requirements for non-prescription drugs will be reviewed at a meeting to be held this month.

Serevent® (salmeterol) inhalers have been associated with 28 reports of patient death stemming from overuse. This long-acting beta-agonist is targeted for maintenance treatment in asthmatics. It is designed for twice daily administration. If given in more frequent repeated doses to treat an acute attack, drug accumulation may result in arrhythmias. The FDA has recommended relabeling to highlight this warning. Serevent® is on formulary at UVa. Evaluate the potential for overuse carefully when considering treatment with this agent.

Pharmacology Literature Review

Dornase (DNase) Review

Dornase alpha (recombinant human DNase) is used to reduce the elasticity and adhesiveness of the sputum in patients with cystic fibrosis (CF). The numerous clinical trials performed prior to and during the FDA-approval process are described in this review. Bryson HM et al. Dornase alpha. *Drugs 1994;48(6):894-906.*

Drug Metabolism in CF

Using caffeine as a marker, the level of xanthine oxidase activity was determined in 12 children with cystic fibrosis and in matched controls. Xanthine oxidase activity was significantly elevated in the CF group, demonstrating the potential for more rapid biotransformation of drugs via the cytochrome P450 mixed-function enzyme system in that population. Hamelin BA et al. Caffeine metabolism in cystic fibrosis: enhanced xanthine oxidase activity. *Clin Pharmacol Ther 1994;56:521-9.*

G-CSF Review

This review focuses on the use of G-CSF in patients receiving cancer chemotherapy, but also discusses its role in the treatment of patients with chronic neutropenia. Efficacy, adverse effects, and dosing considerations are presented. Frampton JE et al. Filgrastim: A

review of its pharmacologic properties and therapeutic efficacy in neutropenia. *Drugs 1994;48(5):731-60.*

Management of Hypertension

The current drug classes available to treat children with hypertension are presented with dosing guidelines, adverse effects, and drug interactions. A brief discussion of the treatment of hypertensive emergencies is included. Miller K. Pharmacological management of hypertension in pediatric patients. *Drugs 1994;48(6):868-87.*

Morphine Use in Neonates

The results of a drug-utilization evaluation (DUE) in 50- bed NICU are reported. During a 6 month period, 285 orders for morphine were written, with an average dose of 0.1+0.02 mg/kg. The most frequently cited indication for use was agitation. Seven adverse reactions were reported, six cases of apnea/oxygen desaturation and one case of hypotension. As a result of the DUE, improvements were made in nursing documentation to clarify patient response. Tholl DA et al. Morphine use and adverse effects in a neonatal intensive care unit. *Am J Hosp Pharm 1994;51:2801-3.*

Pharmacokinetics of Cardiovascular Drugs

A very thorough review of our current knowledge of the disposition of the catecholamines and related inotropic agents in children is presented. This in-depth analysis of the multitude of dopamine/dobutamine kinetic studies is an excellent reference tool. Steinberg C et al. Pharmacokinetics of cardiovascular drugs in children: Inotropes and vasopressors. *Clin Pharmacokinet 1994;27(5):345-67.*

Steroids in Asthma

In an effort to confirm clinical experience, five studies involving a total of 141 patients (both children and adults) were analyzed to demonstrate the benefit of chronic inhaled steroid therapy in patients with mild asthma. Using improvement in peak expiratory flow rate as the objective endpoint, this therapy was shown to be effective. Hatoum HT et al. Meta-analysis of controlled trials of drug therapy in mild chronic asthma: The role of inhaled corticosteroids. A*nn Pharmacother 1994;28:1285-9.*

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee on 12/16/94:

1. Amlodipine (Norvasc®) was added to the formulary. This is a dihydroperidine calcium channel blocker similar to nifedipine, but with a much longer half-life (approx. 50 hrs in adults). At this time, there are no data on its use in children.
2. A request for the addition of CMVIG to the formulary was turned down. This preparation will be available through an investigational protocol. Contact Dr. Jim Bergin, Director of the Heart Transplantation Program for more information.
3. A request to add fluvastatin was also turned down. This agent is a HMG-CoA reductase inhibitor similar to lovastatin and pravastatin. These drugs are used to treat primary hypercholesterolemia which does not respond to dietary restrictions. Fluvastatin offered no significant benefit compared to the other agents in this class.
4. Lomofloxacin was removed from the formulary due to the apparent increased incidence of CNS adverse reactions (seizures) and phototoxicity compared to other quinolones, such as ciprofloxacin.
5. The results of the vancomycin drug utilization evaluation (DUE)were discussed, as well as the restrictions to be placed on vancomycin use. These actions have been taken in response to the emergence of vancomycin-resistant bacterial strains.

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