

# Interactions with warfarin

Beware of bruising and major bleeds

■ by Philip S. Wells, MD

Warfarin is the most commonly used oral anticoagulant in North America. Its efficacy is well established in patients with atrial fibrillation, prosthetic heart valves and venous thromboembolism.<sup>1,2,3</sup> The wide range of response, however, and the frequency of major bleeds — 0.6-3.7% per year — rank it as an important cause of mortality,<sup>4</sup> and mandate careful monitoring.

Because cytochrome P450 2C9 (CYP2C9) is the main enzyme that terminates warfarin's effect, any drug, food, herb or natural product that affects CYP2C9 activity may increase or decrease anticoagulation. Warfarin lowers vitamin K levels, reducing active clotting factors II, VII, IX and X. So genetics, concomitant illness, compliance, exercise and vitamin K ingestion play a role as well. Remember the 7 As — anti-infectives, anti-fungals, antidepressants, anti-lipids, antiarrhythmics, anti-inflammatories/analgesics, and all others. NSAIDs and COX-2 inhibitors will increase the bleeding risk up to 12-fold.<sup>5</sup> Of course, concomitant use of antiplatelets and other anticoagulants raises the risk of bleeds. SSRIs may do this by causing serotonin depletion in platelets.<sup>6</sup> Amiodarone, fluorouracil, omeprazole and ciprofloxacin are other meds of particular concern.<sup>7</sup>

## When disease strikes

### FEVER

- increases clearance of vitamin K-dependent coagulation factors
- possibly decreases warfarin clearance, by reducing cytochrome P450-mediated metabolism
- net effect — potentiation

### DIARRHEA

- enhances response to warfarin

### LIVER DYSFUNCTION

- exaggerates response

### THYROID DISORDERS

- hyperthyroidism — increases sensitivity to warfarin
- hypothyroidism — decreases

### CANCER

- anticoagulation is challenging
- nausea, vomiting and anorexia due to chemotherapy — can alter absorption of warfarin and decrease vitamin K stores
- multiple drug interactions — capecitabine, fluorouracil, gemcitabine, paclitaxel, tamoxifen, gefitinib, trastuzumab, levamisole, interferon

### CONGESTIVE HEART FAILURE

- acute exacerbation heightens response to warfarin

### RENAL DYSFUNCTION

- significance unclear
- patients on chronic hemodialysis are at high risk of major bleeds

## Physiologic influences

### GENETICS - LOWER DOSE NEEDED FOR INDIVIDUALS WITH:

- CYP2C9 allelic variants \*2 and \*3
- polymorphisms of VKORC1 — 1173C > T and 1639G > A

### EXERCISE

- may decrease anticoagulation and require dose escalation

### COMPLIANCE

- for each 10% increase in skipped dose, there was a 14% increase in the odds of under-anticoagulation

## Management of interaction

- most important — don't absolutely forgo drugs known to interact with warfarin, if they're clinically indicated; do carefully manage their use
- consider alternative meds — e.g. rabeprazole instead of omeprazole; acetaminophen (max dose < 4 gm per day) rather than NSAIDs<sup>7</sup>
- measure international normalized ratio (INR) more frequently
- when starting meds with high potential for interaction — check INR 2x/week
- if changing dose of a drug — monitor INR frequently, even after drug is stopped
- cancer, thyroid dysfunction, decompensated heart failure — order frequent INR, monitor carefully
- NSAIDs, COX-2 inhibitors, SSRIs — consider using a proton pump inhibitor

## The 7 A's

Drugs that potentiate warfarin's effect (as measured by INR)

### ANTIBIOTICS — MAINLY MACROLIDES AND QUINOLONES

- ciprofloxacin, trimethoprim-sulfamethoxazole, erythromycin, isoniazid, metronidazole, amoxicillin-clavulanate, azithromycin, clarithromycin, levofloxacin, lopinavir, tetracycline

### ANTIFUNGALS — AZOLES

- fluconazole, metronidazole, miconazole oral gel or vaginal, voriconazole, itraconazole

### ANTIDEPRESSANTS

- fluvoxamine, sertraline, citalopram, other SSRIs

### ANTILIPIDS

- fenofibrate, fluvastatin, simvastatin

### ANTIARRHYTHMICS

- amiodarone, clofibrate, diltiazem, propafenone, propranolol, sulfapyrazone, quinidine, ropinirole

### ANTI-INFLAMMATORIES AND ANALGESICS

- NSAIDs and COX-2 inhibitors — phenylbutazone, piroxicam, celecoxib, rofecoxib
- opioids — dextropropoxyphene, tramadol
- acetaminophen, ASA
- interferon

### ALL OTHERS

- gastric acid inhibitors — cimetidine, omeprazole
- anabolic steroids
- leukotriene inhibitors — zileuton
- chemotherapy — fluorouracil, paclitaxel, tamoxifen
- urinary incontinence drugs — tolterodine
- CNS drugs — entacapone, phenytoin, choral hydrate
- anti-alcoholism drug — disulfiram

## Drugs that inhibit warfarin's effect

### ANTIBIOTICS

- griseofulvin, nafcillin, ribavirin, rifampin, dicloxacillin

### ANTILIPIDS

- cholestyramine

### ALL OTHERS

- barbiturates, carbamazepine, chlordiazepoxide

- immunosuppressants — mesalamine, azathioprine
- chemotherapy — mercaptopurine, aprepitant
- endothelin modulator — bosentan
- ulcer medication — sucralfate
- influenza vaccine
- chelation therapy
- estrogen receptor modulator — raloxifene

## Foods

### POTENTIATION OF WARFARIN

- chondroitin/glucosamine supplements
- fish oil
- mango, papaya
- grapefruit juice

### INHIBITION OF WARFARIN

- foods or enteral feeds with high vitamin K content
  - liver, broccoli, Brussels sprouts, cabbage
  - rocket or arugula salad (*Eruca sativa*), kale, spinach, Swiss chard, watercress
  - squash, mung beans, mushrooms
  - soybeans, rapeseed oil
- large amounts of avocado
- soy milk, sushi containing seaweed
- multivitamins with vitamin K
- high protein, low carbohydrate diet

## Herbal supplements

### POTENTIATION OF WARFARIN

- boldo-fenugreek, guilinggao, ginkgo biloba
- danshen (*Salvia miltiorrhiza*), dong quai (*Angelica sinensis*), Chinese wolfberry (*Lycium barbarum* and *L. chinense*), PC-SPES (an 8-herb anticancer formula)

### INHIBITION OF WARFARIN

- ginseng, St. John's wort

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