Drug Monitor

Anticoagulants: OK for Elders with AF?

Should an elderly patient with atrial fibrillation (AF) who has had a previous episode of upper gastrointestinal (GI) tract bleeding receive an anticoagulant to prevent stroke? What about an older patient with AF and high blood pressure or a history of falls?

Such patients are less likely than others at risk for stroke to be given prophylactic warfarin sodium by their primary care physicians—and that's unfortunate, say a pair of Canadian investigators from the University of Ottawa and the University of Toronto. They charge that the possibility of major bleeding has frightened many clinicians away from prescribing anticoagulants for older patients who could benefit greatly from such therapy.

In order to develop an approach for appropriate anticoagulant use in elders with AF, the researchers reviewed medical literature published between 1966 and 2002. They looked for any evidence that certain risk factors actually increased bleeding complications associated with anticoagulant therapy taken for stroke prevention.

Their conclusion? Not all purported risk factors should influence treatment decisions in the same way. For instance, studies show that, since we now routinely test for and treat *Helicobacter pylori* infection in patients with upper GI bleeding unrelated to the use of nonsteroidal anti-inflammatory drugs, these patients aren't at increased risk for subsequent GI bleeding episodes.

Similarly, neither a predisposition to falling nor old age alone should preclude prophylactic anticoagulant therapy, the researchers say. One study determined that, even when taking anticoagulants, patients with AF who have an average level of stroke risk (5% per year) have such a small chance of developing a subdural hematoma from a fall that it would take 300 falls in a year to nullify the benefits derived from anticoagulant therapy. In addition, though advanced age may raise the risk of anticoagulant-related bleeding slightly, the researchers point out that, of all age groups, patients older than 65 are at highest risk for stroke from AF.

Considering the multiple studies that have revealed older people with AF to be the least likely to receive anticoagulant therapy, the researchers say that many clinicians may be overly concerned about the possible negative effects of this treatment. This concern, they say, may be causing clinicians to underemphasize its potential benefits in discussions with patients. The researchers recommend, therefore, that clinicians first consider the level of stroke risk in an elderly patient with AF—and then factor in bleeding risk. They also emphasize that some contraindications to anticoagulant therapy, such as hypertension, can be resolved with clinical intervention.

Source: *Arch Intern Med.* 2003; 163:1580–1586.

Relieving Chronically Pruritic Burn Wounds

Even after their wounds have healed, up to 80% of burn patients experience continued itching—which can be disabling and last for months or even years. Because the main mechanisms behind this phenomenon are thought to involve both increased histamine release from wound mast cells and heightened sensitivity of sensory nerves (leading to chronic inflammation), current treatment focuses primarily on oral antihistamines, moisturizers, and sedatives. But researchers from Brigham and Women's Hospital in Boston, MA say topical doxepin, a tricyclic antidepressant with potent antihistamine properties, is a better choice.

They tested this treatment in a randomized, three-month study of 31 outpatients with chronic pruritus four to 12 months postburn. Patients were included if their wounds were healed and didn't exceed 20% of their total body surface. Additionally, all patients were taking oral antihistamines and using skin moisturizers with unsatisfactory results. After an initial assessment of the degree of burn itch and erythema (rated on a 0 to 10 itch scale and a 0 to 3 erythema scale, with 10 and 3, respectively, representing the most severe symptoms), all patients

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were assigned randomly to receive either "standard care" (dose-adjusted oral antihistamine therapy) or treatment with a 5% doxepin topical cream, applied four times daily. All patients continued to use a skin moisturizer.

The doxepin cream was superior to standard care in controlling postburn itching. Itching disappeared in 75% of patients using doxepin, compared with 20% of those taking oral antihistamines. Erythema also diminished significantly with doxepin therapy.

The use of a topical tricyclic antidepressant compound is a recognized treatment for itch, the researchers say. They suggest that in chronically pruritic burn wounds, such compounds actually may alter the wound by reducing the number of mast cells. Doxepin is known to be the safest member of this drug class, with somnolence being the most common adverse effect. In this study, only 10% of the patients using the doxepin cream reported somnolence, compared to 50% of the patients receiving oral antihistamines.

Source: *Wounds.* 2003;15: 195–200.

Finasteride and Prostate Cancer Development

It's been proposed that finasteride—which inhibits 5alpha-reductase, the enzyme that converts testosterone into the more potent androgen dihydrotestosterone—might be useful in preventing or delaying the occurrence of prostate cancer. But though results from the multicenter, randomized Prostate Cancer Prevention Trial support this hypothesis, not all the news is good. In this trial, finasteride was associated with a small, absolute increase in the risk of high-grade tumors and a greater incidence of adverse sexual effects.

The researchers randomly assigned 18,882 men, who were 55 years of age or older and had a normal digital rectal examination and a prostate specific antigen level of 3 ng/mL or lower, to receive either finasteride 5 mg/day or placebo. After seven years, prostate cancer was diagnosed in 803 (18.4%) of the 4,368 men included from the finasteride group in the final analysis, compared with 1,147 (24.4%) of the 4,692 men included from the placebo group—a 24.8% reduction in relative risk.

At the same time, however, rates of high-grade tumors (defined as those with Gleason scores between 7 and 10) were slightly higher in the finasteride group than in the placebo group: 6.4% versus 5.1%. The researchers say it's possible that finasteride induces high-grade tumors by reducing the level of intracellular dihydrotestosterone in the prostate. Alternatively, finasteride could be inhibiting low-grade tumors selectively. Long-term follow-up of the study patients and further laboratory research are needed to get to the truth.

The researchers note that the rate of cancer detection among placebo patients was unexpectedly high, given the 16.7% lifetime risk predicted for the type of low risk patients this study enrolled. They say that this elevated rate may indicate overdiagnosis of disease in the study.

The incidence of adverse sexual effects (such as reduced volume of ejaculate, erectile dysfunction, loss of libido, gynecomastia, and breast cancer) was higher with finasteride than with placebo, while the incidence of urinary symptoms (including benign prostatic hyperplasia, increased urgency or frequency, incontinence, retention, need for transurethral resection of the prostate, prostatitis, and infection) was lower. All of these trade-offs must be considered carefully in the context of the patient's individual needs and goals, say the researchers, before any decisions about finasteride chemopreventive therapy can be made. ●

Source: *N Engl J Med.* 2003; 349:215–224.