

TCDD Exposure Triples Risk of Graves' Disease

VITALS

Major Finding: Graves' disease was diagnosed in 54 of 23,939 veterans exposed to Agent Orange and 148 of 200,109 nonexposed veterans (OR 3.05).

Data Source: Electronic database analysis of veterans born between 1925 and 1953.

Disclosures: Study was funded by the Department of Veteran's Affairs. Dr. Varanasi had no other disclosures.

BY MIRIAM E. TUCKER

BOSTON — Vietnam veterans exposed to Agent Orange were found to have a threefold increased risk of Graves' disease in an analysis of electronic medical records of more than 200,000 vets who served during the Vietnam era.

The herbicide Agent Orange was sprayed over South Vietnam between

1962 and 1971, ultimately covering nearly 20% of the country's surface. Much of the concern over its use stemmed from the dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) it was contaminated with during production. Its persistent toxicity in biological tissue has been known for 35 years, Dr. Ajay Varanasi said at the annual meeting of the American Association of Clinical Endocrinologists.

Evidence of thyroid tissue damage arising from TCDD has been observed in animals and humans, said Dr. Varanasi of the State University of New York at Buffalo and the VA Western New York Health Care System.

The study included Department of Veterans Affairs electronic medical records data from 224,048 veterans born between 1925 and 1953 who were followed in upstate New York. Of those, 23,939 were classified as having been exposed to Agent Orange. Only about 10% of veterans from the Vietnam era actually set foot in Vietnam, but it can be assumed that nearly all who did were exposed to Agent Orange, he noted.

The exposed group did not differ significantly from the 200,109 nonexposed veterans in terms of age (average 62 years), race (1/5 were African American), smoking history (more than 90% were smokers), and sex (92% of the exposed and 89% of the nonexposed were men).

Diabetes, however, was significantly more common among the exposed, 24% vs. 14%. The substantial increase in type 2 diabetes among Vietnam veterans has been described previously and is well recognized, he noted.

Graves' disease was diagnosed in 54 exposed and 148 nonexposed vets, for an odds ratio (OR) of 3.05. Hypothyroidism was significantly more prevalent in the nonexposed group, with 7,273 receiving the diagnosis vs. 740 exposed veterans (OR 0.85). There were no significant differences in the rates of thyroid cancer (OR 1.16) or thyroid nodules (OR 1.14).

In a multivariate analysis, Agent Orange exposure was independently associated with an increased risk of Graves' disease (OR 2.76), whereas smoking history (OR 1.42), diabetes (OR 1.05), and race (OR 1.22 for African American vs. other) were not, Dr. Varanasi reported.

Recent literature indicates that TCDD can have both immune-suppressing and immune-promoting effects in humans. The dioxin may play a role in normal immune responses as well (Trends Immunol. 2009;30:447-54).

Data also suggest that TCDD exposure can promote Th17-cell differentiation and expansion. In one study, the proportion of peripheral Th17 cells in patients with autoimmune thyroid disease was higher than in controls, and the proportion of these cells in patients with intractable Graves' disease was higher than in patients with Graves' that was in remission (Thyroid 2009;19:495-501).

An increased prevalence of combined thyroid disorders—thyrotoxicosis, goiter, hypothyroidism, and thyroid adenoma—was seen in accidentally exposed German workers (Occup. Environ. Med. 1994;51:479-86). However, other studies of TCDD and thyroid function have produced less-consistent findings (Occup. Environ. Med. 1999;56:270-6).

"Our finding of an increased prevalence of Graves' disease in Vietnam veterans potentially exposed to TCDD warrants further investigation," Dr. Varanasi concluded. ■



(colchicine, USP) tablets

COLCRYS® (colchicine, USP) tablets for oral use

Brief Summary of full Prescribing Information

The following is a brief summary only. Please see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

COLCRYS® (colchicine, USP) tablets are indicated for prophylaxis and the treatment of gout flares.

Prophylaxis of Gout Flares: COLCRYS is indicated for prophylaxis of gout flares.

Treatment of Gout Flares: COLCRYS is indicated for treatment of acute gout flares when taken at the first sign of a flare.

Familial Mediterranean fever (FMF): COLCRYS is indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).

CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

WARNINGS AND PRECAUTIONS

Fatal Overdose: Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. COLCRYS should be kept out of the reach of children.

Blood Dyscrasias: Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported with colchicine used in therapeutic doses.

Drug Interactions: Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and strong CYP3A4 inhibitors. If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicine may need to be reduced or interrupted [see DRUG INTERACTIONS]. Use of COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors is contraindicated in patients with renal or hepatic impairment [see CONTRAINDICATIONS].

Monitor for toxicity and if present consider temporary interruption or discontinuation of COLCRYS.

Neuromuscular Toxicity: Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine with COLCRYS may potentiate the development of myopathy [see DRUG INTERACTIONS]. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

ADVERSE REACTIONS

Prophylaxis of Gout Flares: The most commonly reported adverse reaction in clinical trials of colchicine for the prophylaxis of gout was diarrhea.

Treatment of Gout Flares: The most common adverse reactions reported in the clinical trial with COLCRYS for treatment of gout flares were diarrhea (23%) and pharyngolaryngeal pain (3%).

FMF: Gastrointestinal tract adverse effects are the most frequent side effects in patients initiating COLCRYS, usually presenting within 24 hours, and occurring in up to 20% of patients given therapeutic doses. Typical symptoms include cramping, nausea, diarrhea, abdominal pain, and vomiting. These events should be viewed as dose-limiting if severe as they can herald the onset of more significant toxicity.

DRUG INTERACTIONS

COLCRYS is a substrate of the efflux transporter P-glycoprotein (P-gp). Of the cytochrome P450 enzymes tested, CYP3A4 was mainly involved in the metabolism of colchicine. If COLCRYS is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicine are likely. Fatal drug interactions have been reported. Physicians should ensure that patients are suitable candidates for treatment with COLCRYS and remain alert for signs and symptoms of toxicities related to increased colchicine exposure as a result of a drug interaction. Signs and symptoms of COLCRYS toxicity should be evaluated promptly and, if toxicity is suspected, COLCRYS should be discontinued immediately. See full Prescribing Information for a complete list of reported potential interactions.

USE IN SPECIFIC POPULATIONS

- In the presence of mild to moderate renal or hepatic impairment, adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare, and FMF but patients should be monitored closely.
- In patients with severe renal impairment for prophylaxis of gout flares the starting dose should be 0.3 mg/day, for gout flares no dose adjustment is required but a treatment course should be repeated no more than once every 2 weeks. In FMF patients, start with 0.3 mg/day and any increase in dose should be done with close monitoring.
- In patients with severe hepatic impairment, a dose reduction may be needed in prophylaxis of gout flares and FMF patients; while a dose reduction may not be needed in gout flares, a treatment course should be repeated no more than once every 2 weeks.
- For patients undergoing dialysis, the total recommended dose for prophylaxis of gout flares should be 0.3 mg given twice a week with close monitoring. For treatment of gout flares, the total recommended dose should be reduced to 0.6 mg (1 tablet) x 1 dose and the treatment course should not be repeated more than once every two weeks. For FMF patients the starting dose should be 0.3 mg per day and dosing can be increased with close monitoring.
- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: Caution should be exercised when administered to a nursing woman.
- Geriatric Use: The recommended dose of colchicine should be based on renal function.

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