

New Anticancer Drugs Can Trigger Hypertension

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Several new and effective anticancer drugs have produced the unexpected and potentially serious side effect of hypertension in many patients.

Drugs that work by inhibiting the vascular endothelial growth factor signaling pathway (VSP), such as bevacizumab (Avastin), sunitinib (Sutent), and sorafenib (Nexavar), all have been documented to

trigger hypertension in roughly 10%-40% of patients, in many cases leading to grade 3 hypertension, with blood pressure rising over 180/110 mm Hg, Dr. Michael L. Maitland said at a symposium on cardiovascular disease in cancer patients, sponsored by the University of Texas M.D. Anderson Cancer Center, Houston. In some cases patients also developed heart failure, which was severe in some instances.

Although the magnitude of the problem of hypertension that is triggered by these

drugs remains poorly understood, several rules for their safe use have emerged:

- ▶ Candidates for VSP inhibitor therapy should have a pretreatment risk assessment.
- ▶ The blood pressure goal for patients on a VSP inhibitor is a maximum of 140/90 mm Hg.
- ▶ Blood pressure should be measured accurately, early, and often in patients on one of these drugs.
- ▶ If hypertension develops, it should be promptly treated.

If a patient's blood pressure spikes, the treatment with the VSP inhibitor should be immediately stopped until his or her pressure can be normalized, said Dr. Maitland, an oncologist and pharmacologist at the University of Chicago.

Not enough is currently known about VSP inhibitor-triggered hypertension to guide a rational management approach. Consensus management recommendations are being written, Dr. Maitland said in an interview. Until these guidelines are issued, "treat it like conventional hypertension," using agents such as ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and β -blockers, he said.

"Aggressive treatment of blood pressure may substantially minimize the cardiotoxicity" of new anticancer drugs, including sunitinib and imatinib, another anticancer drug that's been implicated in causing heart damage, Dr. Aarif Y. Khakoo, a cardiologist at M.D. Anderson Cancer Center in Houston, said in a separate talk at the meeting, which also was sponsored by the American College of Cardiology and the Society of Geriatric Cardiology. "If caught early, the sunitinib toxicity may be reversible," Dr. Khakoo added.

The consequences of a profound spike in blood pressure and possibly other physiological changes caused by drugs like sunitinib have been documented in results from recent studies. A review of 75 patients with metastatic GI stromal tumors treated with sunitinib for a median of 34 weeks showed that 35 (47%) eventually became hypertensive (compared with a 6% prevalence of hypertension at baseline), with several developing grade 3 hypertension. Eight (11%) of the sunitinib-treated patients had a cardiovascular event, including six with heart failure (8%) and one with a myocardial infarction. Of the 65 sunitinib-treated patients who underwent LVEF monitoring, 13 (20%) had their left ventricular ejection fraction fall below 50% (Lancet 2007;370:2011-9).

A multivariate analysis of the outcomes identified a history of coronary artery disease as the only significant independent predictor of a cardiovascular event in the sunitinib recipients. Patients with this history were about 40-fold more likely to have a cardiovascular event.

In most patients, the declines in left ventricular function rapidly reversed once treatment with sunitinib stopped, said Dr. Ming Hui Chen, a cardiologist at Brigham and Women's Hospital in Boston and a collaborator on this sunitinib study.

In a second review of 224 patients who were treated with sunitinib at M.D. Anderson Cancer Center, 6 patients (3%) developed significant heart failure within 4-44 days after treatment began, according to a recent report from Dr. Khakoo and his associates (Cancer 2008;112:2500-6). Three patients developed New York Heart Association class IV failure, two had class III heart failure, and the sixth patient developed class II heart failure. One patient died because of this adverse effect, which was linked to sunitinib treatment. All six patients also had increased blood pressure, and the effect of the drug did not fully resolve when treatment stopped. ■

BRIEF SUMMARY: For full prescribing information, see package insert.

Transderm Scop®
scopolamine 1.5 mg
Transdermal Therapeutic System
Programmed to deliver *in-vivo* approximately
1.0 mg of scopolamine over 3 days

INDICATIONS AND USAGE

Transderm Scop is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch should be applied only to skin in the postauricular area.

CONTRAINDICATIONS

Transderm Scop is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma.

WARNINGS

Glaucoma therapy in patients with chronic open-angle (wide-angle) glaucoma should be monitored and may need to be adjusted during Transderm Scop use, as the mydriatic effect of scopolamine may cause an increase in intraocular pressure.

Transderm Scop should not be used in children and should be used with caution in the elderly. See PRECAUTIONS.

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Rarely, idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine. The most serious of these that have been reported are: acute toxic psychosis, including confusion, agitation, rambling speech, hallucinations, paranoid behaviors, and delusions.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scop should be used with caution in the elderly or in individuals with impaired liver or kidney functions because of the increased likelihood of CNS effects.

Caution should be exercised in patients with a history of seizures or psychosis, since scopolamine can potentially aggravate both disorders.

Skin burns have been reported at the patch site in several patients wearing an aluminumized transdermal system during a Magnetic Resonance Imaging scan (MRI). Because Transderm Scop contains aluminum, it is recommended to remove the system before undergoing an MRI.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch. In addition, it is important that used patches be disposed of properly to avoid contact with children or pets.

Patients should be advised to remove the patch immediately and promptly contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain and reddening of the eyes, accompanied by dilated pupils). Patients should also be instructed to remove the patch if they develop any difficulties in urinating.

Patients who expect to participate in underwater sports should be cautioned regarding the potentially disorienting effects of scopolamine. A patient brochure is available.

Drug Interactions

The absorption of oral medications may be decreased during the concurrent use of scopolamine because of decreased gastric motility and delayed gastric emptying.

Scopolamine should be used with care in patients taking other drugs that are capable of causing CNS effects such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties; e.g., other belladonna alkaloids, antihistamines (including meclizine), tricyclic antidepressants, and muscle relaxants.

Laboratory Test Interactions

Scopolamine will interfere with the gastric secretion test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been completed to evaluate the carcinogenic potential of scopolamine. The mutagenic potential of scopolamine has not been evaluated. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. Maternal body weights were reduced in the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system).

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in rats. Scopolamine hydrobromide has been shown to have a marginal embryotoxic effect in rabbits when administered by daily intravenous injection at doses producing plasma levels approximately 100 times the level achieved in humans using a transdermal system. During a clinical study among women undergoing cesarean section treated with Transderm Scop in conjunction with epidural anesthesia and opiate analgesia, no evidence of CNS depression was found in the newborns. There are no other adequate and well-controlled studies in pregnant women. Other than in the adjunctive use for delivery by cesarean section, Transderm Scop should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because scopolamine is excreted in human milk, caution should be exercised when Transderm Scop is administered to a nursing woman.

Labor and Delivery

Scopolamine administered parenterally at higher doses than the dose delivered by Transderm Scop does not increase the duration of labor, nor does it affect uterine contractions. Scopolamine does cross the placenta.

Pediatric Use

The safety and effectiveness of Transderm Scop in children has not been established. Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scop should not be used in children because it is not known

whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE DRUG EXPERIENCES

The adverse reactions for Transderm Scop are provided separately for patients with motion sickness and with post-operative nausea and vomiting.

Motion Sickness: In motion sickness clinical studies of Transderm Scop, the most frequent adverse reaction was dryness of the mouth. This occurred in about two thirds of patients on drug. A less frequent adverse drug reaction was drowsiness, which occurred in less than one sixth of patients on drug. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, was also observed.

Post-operative Nausea and Vomiting: In a total of five clinical studies in which Transderm Scop was administered perioperatively to a total of 461 patients and safety was assessed, dry mouth was the most frequently reported adverse drug experience, which occurred in approximately 29% of patients on drug. Dizziness was reported by approximately 12% of patients on drug.

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of Transderm Scop, the following are spontaneously reported adverse events from postmarketing experience. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of Transderm Scop in their causation cannot be reliably determined: acute angle-closure (narrow-angle) glaucoma; confusion; difficulty urinating; dry, itchy, or conjunctival injection of eyes; restlessness; hallucinations; memory disturbances; rashes and erythema; and transient changes in heart rate.

Drug Withdrawal/Post-Removal Symptoms: Symptoms such as dizziness, nausea, vomiting, and headache occur following abrupt discontinuation of antimuscarinics. Similar symptoms, including disturbances of equilibrium, have been reported in some patients following discontinuation of use of the Transderm Scop system. These symptoms usually do not appear until 24 hours or more after the patch has been removed. Some symptoms may be related to adaptation from a motion environment to a motion-free environment. More serious symptoms including muscle weakness, bradycardia and hypotension may occur following discontinuation of Transderm Scop.

OVERDOSAGE

Because strategies for the management of drug overdose continually evolve, it is strongly recommended that a poison control center be contacted to obtain up-to-date information regarding the management of Transderm Scop patch overdose. The prescriber should be mindful that antidotes used routinely in the past may no longer be considered optimal treatment. For example, physostigmine, used more or less routinely in the past, is seldom recommended for the routine management of anticholinergic syndromes.

Until up-to-date authoritative advice is obtained, routine supportive measures should be directed to maintaining adequate respiratory and cardiac function.

The signs and symptoms of anticholinergic toxicity include: lethargy, somnolence, coma, confusion, agitation, hallucinations, convulsion, visual disturbance, dry flushed skin, dry mouth, decreased bowel sounds, urinary retention, tachycardia, hypertension, and supraventricular arrhythmias.

Most cases of toxicity involving the use of the product will resolve with simple removal of the patch. Serious symptomatic cases of Overdosage involving multiple patch applications and/or ingestion may be managed by initially ensuring the patient has an adequate airway, and supporting respiration and circulation. This should be rapidly followed by removal of all patches from the skin and the mouth. If there is evidence of patch ingestion, gastric lavage, endoscopic removal of swallowed patches, or administration of activated charcoal should be considered, as indicated by the clinical situation. In any case where there is serious Overdosage or signs of evolving acute toxicity, continuous monitoring of vital signs and ECG, establishment of intravenous access, and administration of oxygen are all recommended.

The symptoms of overdose/toxicity due to scopolamine should be carefully distinguished from the occasionally observed syndrome of withdrawal (see Drug Withdrawal/Post Removal Symptoms). Although mental confusion and dizziness may be observed with both acute toxicity and withdrawal, other characteristic findings differ: tachyarrhythmias, dry skin, and decreased bowel sounds suggest anticholinergic toxicity, while bradycardia, headache, nausea and abdominal cramps, and sweating suggest postremoval withdrawal. Obtaining a careful history is crucial to making the correct diagnosis.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: To prevent the nausea and vomiting associated with motion sickness, one Transderm Scop patch (programmed to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post-operative nausea and vomiting, the patch should be applied the evening before scheduled surgery. To minimize exposure of the newborn baby to the drug, apply the patch one hour prior to cesarean section. Only one patch should be worn at any time. Do not cut the patch.

Handling: After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, the hands and the application site should be washed thoroughly with soap and water and dried. (A patient brochure is available).

Continuation of Therapy: Should the patch become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. For motion sickness, if therapy is required for longer than 3 days, the first patch should be removed and a fresh one placed on the hairless area behind the other ear. For perioperative use, the patch should be kept in place for 24 hours following surgery at which time it should be removed and discarded.

Rx ONLY

Mfd by: ALZA Corporation
Mountain View, CA 94043
Distributed by: Novartis Consumer Health, Inc.
Parsippany, NJ 07054-0622
©2006-2008
42013C
Printed in U.S.A.
(Rev. 2/06) PRF-32008A