

Isotretinoin Use May Increase the Risk for IBD

BY SHERRY BOSCHERT

SAN DIEGO — Isotretinoin use was associated with a 68% increased risk for subsequent development of inflammatory bowel disease, particularly ulcerative colitis, in a retrospective case-control study of 30,021 patients.

The odds ratio of 1.68 for inflammatory bowel disease (IBD) in isotretinoin users compared with nonusers had a

95% confidence interval (CI) of 0.98-2.86. Dr. Seth Crockett and his associates reported in a poster presentation at the annual meeting of the American College of Gastroenterology.

The findings add to ongoing controversy that IBD risk with isotretinoin may have been a factor in the decision by Roche to pull the best-known brand of isotretinoin, Accutane, off the market in June 2009.

The current study examined a large administrative claims database with records on 55 million patients from more than 70 U.S. health plans. The investigators compared 8,189 patients with at least 12 months of continuous health plan enrollment and diagnoses of ulcerative colitis, Crohn's disease, or indeterminate IBD with three non-IBD control patients per IBD patient, matched by age, gender, and geographic region. They looked at

exposure to isotretinoin in the 21,832 control patients during the first 12 months of health plan enrollment.

Results pointed to a possible dose-response effect: The risk for IBD increased with the number of isotretinoin prescriptions. Having four or more isotretinoin prescriptions was associated with an odds ratio of 2.67 for development of IBD (CI, 1.32-5.41), reported Dr. Crockett of the University of North Carolina, Chapel Hill.

Subgroup analyses showed a strong association between isotretinoin use and ulcerative colitis (odds ratio, 4.36; CI, 1.98-9.66) but no association between isotretinoin exposure and Crohn's disease (odds ratio, 0.68).

"The flip side of all this is that there are patients who desperately need isotretinoin," Dr. Stephen P. Stone commented in an interview. "Those of us who care for people with acne and are

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aware of the physical and psychosocial aspects of it find it an indispensable drug," said Dr. Stone, chair of the American Academy of Dermatology's task force on retinoids and professor at Southern Illinois University, Carbondale. The drug also is helpful for less common problems such as cutaneous lupus that do not respond to other treatments, he added.

The possible association between isotretinoin and IBD has long been included in label warnings, but it drew increased interest after a 2006 study by gastroenterologists at the University of Chicago. That study looked at all 85 cases of IBD in isotretinoin users reported to the Food and Drug Administration in 1997-2002 and graded the strength of causality using the Naranjo adverse drug reaction probability scale. Mean scores suggested that the oral retinoid was a "probable" cause of IBD (Am. J. Gastroenterol. 2006;101:1569-73). Some dermatologic experts criticized the study's methodology, saying that a one-point adjustment for accuracy in the probability ratings would downgrade the mean score to "possible."

A separate study by gastroenterologists at the University of Manitoba, Winnipeg, found no significant association between isotretinoin use and IBD. Using a large government database and drug registry, they found that 1.2% of patients with IBD and 1.1% of matched patients without IBD used isotretinoin before IBD diagnosis, an insignificant difference (Am. J. Gastroenterol. 2009;104:2774-8). ■

Disclosures: Dr. Crockett and his associates reported having no conflicts of interest related to their study. Dr. Stone reported no conflicts of interest.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and was not significantly different from that seen in placebo-treated patients (about 1%). The most common side effects were headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are presented in Table 3.

Table 3: Incidence (%) of Dose-Related Adverse Effects with Amlodipine at Doses of 2.5 mg, 5.0 mg, and 10.0 mg or Placebo

Adverse Event	Amlodipine 2.5 mg n=275 %	Amlodipine 5.0 mg n=296 %	Amlodipine 10.0 mg n=268 %	Placebo n=520 %
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1% in placebo-controlled clinical trials are presented in Table 4.

Table 4: Incidence (%) of Adverse Effects Not Clearly Dose Related but Reported at an Incidence of >1% in Placebo-Controlled Clinical Trials

Adverse Event	Amlodipine n=1730 %	Placebo n=1250 %
Headache	7.3	07.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; **Central and Peripheral Nervous System:** hypoesthesia, neuropathic peripheral, paresthesia, tremor, vertigo; **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia; **General:** allergic reaction, asthenia, back pain, hot flashes, malaise, pain, rigors, weight gain, weight decrease; **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia; **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **Respiratory System:** dyspnea, epistaxis; **Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular; **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **Urinary System:** micturition frequency, micturition disorder, nocturia; **Autonomic Nervous System:** dry mouth, sweating increased; **Metabolic and Nutritional:** hyperglycemia, thirst; **Hemopoietic:** leukopenia, purpura, thrombocytopenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine.

Telmisartan

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine

Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

DRUG INTERACTIONS

Drug Interactions with TWYNSTA Tablets

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with TWYNSTA tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of TWYNSTA tablets, as described below.

Drug Interactions with Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized

by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Drug Interactions with Amlodipine

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, Maalox®, sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions.

Nursing Mothers

Telmisartan

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Amlodipine

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered.

Pediatric Use

Safety and effectiveness of TWYNSTA in pediatric patients have not been established.

Geriatric Use

TWYNSTA Tablets

Of the total number of 3282 hypertensive patients receiving a telmisartan/amlodipine combination in clinical studies, 605 (18%) patients were 65 years of age or older and of these, 88 (3%) patients were 75 years and older. No overall differences in efficacy or safety of TWYNSTA tablets were observed in this patient population.

Telmisartan

Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in patients 75 years of age and older.

Hepatic Insufficiency

Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients.

Race

The magnitude of blood pressure lowering in black patients approached that observed in non-black patients but the number of black patients was limited (237 of 1461 patients).

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

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