

CLINICAL CAPSULES

Chronic Idiopathic Cough

Chronic idiopathic cough may be a distinct clinical entity with an as-yet unidentified cause, a retrospective study suggests.

Of 100 patients referred for chronic cough, 42 had a primary diagnosis of chronic idiopathic cough (CIC). Compared with patients who had other diagnoses, such as postnasal drip, gastroesophageal reflux, and asthma, these patients had a longer median duration of cough (72 vs. 24 months) and were significantly more likely to have had an upper respiratory tract infection as the initial trigger of the cough

(48% vs. 24%), Rubaiyat A. Haque, M.B., and colleagues at the Imperial College of London reported.

Furthermore, the CIC patients had significantly greater cough sensitivity, as measured by median log concentrations of capsaicin required to induce five coughs (-0.009 vs. 0.592), the investigators noted (Chest 2005;127:1710-3).

The study population represents patients who had been difficult to diagnose. Therefore, CIC is overrepresented in the sample; CIC patients actually make up a very small subgroup among chronic

coughers, the investigators noted. However, the findings suggest a pattern—defined by upper respiratory tract infection history, long cough history, and heightened cough sensitivity—that indicates a distinct clinical entity of CIC, which may be a variation of “postviral cough,” they concluded.

Contaminated Basil

Contaminated fresh basil was the cause of nearly 300 recent cases of cyclosporiasis in Florida, according to the U.S. Food and Drug Administration.

The FDA is conducting a trace-back investigation to locate the source of the

basil. The Florida Department of Health reported 293 laboratory-confirmed cases in 32 Florida counties, including several clusters and numerous sporadic cases.

The gastrointestinal infection results from ingestion of the Cyclospora parasite and is associated with watery diarrhea and frequent, explosive bowel movements. Loss of appetite, substantial weight loss, stomach cramps, nausea, vomiting, muscle aches, low-grade fever, and fatigue can also occur, usually within a week of consuming the contaminated food. The symptoms can last for a month or more if untreated.

Tonsillopharyngitis Rx

The optimal dose of azithromycin for the treatment of group A streptococcal tonsillopharyngitis in adults is 500 mg/day for 3 days, a metaanalysis of randomized controlled trials suggests.

A total of 19 trials involving 4,626 patients were included in the analysis. The trials compared various 10-day drugs and two different azithromycin doses and treatment durations, Janet R. Casey, M.D., and Michael E. Pichichero, M.D., of the University of Rochester Medical Center (N.Y.), reported.

In the adult trials, a 30-mg/kg dose of azithromycin (over 3 or 5 days) was comparable to the 10-day drugs (odds ratio 0.86). The 5-day Z Pak (500 mg/day) course of azithromycin approved in the United States was inferior to the 10-day drugs (OR 0.41), but a 3-day course approved outside the United States with the same total dose showed a slight trend toward superiority over the 10-day medications (OR 1.87) (Clin. Infect. Dis. 2005;40:1748-55).

Shorter-course, higher-dose treatment with azithromycin is associated with better bacterial cure rates, and, because longer treatment regimens appear to be associated with poor treatment compliance and thus with treatment failures, it is the preferred approach for treatment of patients with GAS tonsillopharyngitis, the investigators concluded.

Coccidiomycosis Cases

A significant increase in coccidiomycosis cases in Arizona between 1998 and 2001 is attributable to climatic factors, an investigation revealed.

In 1998 there were 33 cases of the disease, also known as valley fever, per 100,000 population; in 2001 there were 43 cases per 100,000 population. The disease has previously been linked to soil disruption, construction, and even earthquakes. In this study, certain climatic and environmental factors (particularly hot and dry conditions) were strongly associated with outbreaks, Benjamin J. Park, M.D., of the Centers for Disease Control and Prevention, Atlanta, and his colleagues reported.

Known risk factors for infection were not significantly more prevalent during the high- vs. low-incidence periods, the investigators noted (J. Infect. Dis. 2005;191:1981-7).

The findings could help public health officials predict seasonal outbreaks of the disease, which is associated with considerable morbidity and a substantial public health burden and allow for the use of appropriate preventive measures, they concluded.

—Sharon Worcester

before use of such preparations with AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

Non-steroidal Anti-inflammatory Drugs — In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when AVALIDE and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Irbesartan-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the irbesartan-hydrochlorothiazide combination. Irbesartan-hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan-hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC_{0-24hours}, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses of 500 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC_{0-24hours}, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters)

(See WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

Nursing Mothers

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of AVALIDE 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.

ADVERSE REACTIONS

Irbesartan-hydrochlorothiazide

AVALIDE (irbesartan-hydrochlorothiazide) Tablets has been evaluated for safety in 898 patients treated for essential hypertension. In clinical trials with AVALIDE, no adverse experiences peculiar to this combination drug product have been observed. Adverse experiences have been limited to those that were reported previously with irbesartan and/or hydrochlorothiazide (HCTZ). The overall incidence of adverse experiences reported with the combination was comparable to placebo. In general, treatment with AVALIDE was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of AVALIDE therapy due to clinical adverse experiences was required in only 3.6%. This incidence was significantly less (p=0.023) than the 6.8% of patients treated with placebo who discontinued therapy.

In these double-blind controlled clinical trials, the following adverse experiences reported with AVALIDE occurred in B1% of patients, and more often on the irbesartan-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Irbesartan/HCTZ (n=898) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
Body as a Whole				
Chest Pain	2	1	2	2
Fatigue	7	3	4	3
Influenza	3	1	2	2
Cardiovascular				
Edema	3	3	2	2
Tachycardia	1	0	1	1
Gastrointestinal				
Abdominal Pain	2	1	2	2
Dyspepsia/heartburn	2	1	0	2
Nausea/vomiting	3	0	2	0
Immunology				
Allergy	1	0	1	1

(continued)

	Irbesartan/HCTZ (n=898) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
Musculoskeletal				
Musculoskeletal Pain	7	5	6	10
Nervous System				
Dizziness	8	4	6	5
Dizziness Orthostatic	1	0	1	1
Renal/Genitourinary				
Abnormality Urination	2	1	1	2

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness, and muscle cramp.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Irbesartan

Other adverse experiences that have been reported with irbesartan, without regard to causality are listed below:

Body as a Whole: fever, chills, orthostatic effects, facial edema, upper extremity edema
Cardiovascular: flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, hypotension, syncope, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis
Dermatologic: pruritus, dermatitis, ecchymosis, erythema face, urticaria
Endocrine/Metabolic/Electrolyte Imbalances: sexual dysfunction, libido change, gout
Gastrointestinal: diarrhea, constipation, gastroenteritis, flatulence, abdominal distention
Musculoskeletal/Connective Tissue: musculoskeletal trauma, extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness
Nervous System: anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident
Renal/Genitourinary: prostate disorder
Respiratory: cough, upper respiratory infection, epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing
Special Senses: vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation
Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions
Metabolic: hyperglycemia, glycosuria, hyperuricemia
Musculoskeletal: muscle spasm
Nervous System/Psychiatric: restlessness
Renal: renal failure, renal dysfunction, interstitial nephritis
Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis
Special Senses: transient blurred vision, xanthopsia

Post-Marketing Experience

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue). Hyperkalemia has been rarely reported.

Very rare cases of jaundice have been reported with irbesartan.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with AVALIDE alone. No patient discontinued taking AVALIDE due to increased BUN. One patient discontinued taking AVALIDE due to a minor increase in serum creatinine.

Hemoglobin: Mean decreases of approximately 0.2 g/dL occurred in patients treated with AVALIDE alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with AVALIDE alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes: (See PRECAUTIONS.)

OVERDOSAGE

Irbesartan

No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

Consult package insert before prescribing AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

Distributed by:
 Bristol-Myers Squibb Sanofi-Synthelabo Partnership
 New York, NY 10016

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