

Idiopathic Anaphylaxis

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ABSTRACT

Anaphylaxis is an acute, life threatening event that can progress extremely rapidly. External allergens as causations have been identified over the last century. The most recently identified type of anaphylaxis is not caused by any external allergen and has been termed Idiopathic Anaphylaxis (IA). Two major types are Generalized or Angioedema with airway obstruction. IA is also classified by frequency of episodes and response to therapy. Therapy consists of acute emergency therapy and induction of remissions using prednisone, beta agonists, and H₁ blockers. Control and remission are usually induced. IA occurs at all ages, and pediatric and geriatric IA are often special problems, as is a psychogenic form where no true reactions occur. Although appropriate management of IA, in general, has a good prognosis, several problems exist. Among these are failure to accept IA as an entity or in an individual case by physicians and patients. A different problem occurs when the recommended treatment is used and there is control of IA, but only with persisting high doses of prednisone. This is corticosteroid dependent IA. The lack of defined mechanisms that will lead to improved therapies and wider acceptance of IA as an entity remains a major problem. Undifferentiated Somatoform IA is a serious management problem for physicians. (Allergy and Asthma Proc 20:311-315, 1999)

Anaphylaxis is a generalized allergic reaction and a medical emergency that can result in death within minutes. A classification of anaphylaxis is shown in Table I.

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HISTORICAL ASPECTS

IgE mediated anaphylaxis was first documented in 2641 B.C., when King Menses was stung to death by a wasp or hornet according to hieroglyphics.¹ The first scientific description of anaphylaxis was in dogs, secondary to an allergic reaction to toxin from a sea anemone.² As allergenic substances became available, such as horse serum used as an antitoxin, reports of anaphylaxis occurred, and penicillin was identified as a major problem in the mid 20th century. Thus, the allergen had to be available for anaphylaxis to that agent to be described.

Idiopathic Anaphylaxis (IA) was first described in 1978.³ A point to consider is that anaphylaxis to hymenoptera stings was first apparent in 2641 B.C., but correlation of food anaphylaxis was not defined until early in the 20th century and was initially termed food "poisoning."⁴ Thus, food anaphylaxis (like hymenoptera anaphylaxis) probably existed for thousands of years. Similarly, it can be postulated that IA did not have its onset in the last quarter of this century, but occurred for thousands of years without recognition of what the disease was. Unfortunately, the diagnosis is frequently missed even at the present time.

CLASSIFICATION OF IA

As increasing numbers of cases of IA were seen, it became possible to classify the cases in terms of major clinical presentation, i.e., Generalized (G) or life threatening Angioedema (A). Further, the frequency of episodes were classified as frequent (F) or infrequent (I). The current classification of IA is shown in Table II.

TREATMENT OF IA

As increasing numbers of cases of IA were seen, both acute and preventative treatment regimens were designed and used. These were initially based on regimens used to prevent radiographic contrast media reactions⁵ and are shown in Figure 1. These treatment regimens were shown to be effective.^{6,7} The outcome of these treatment regimens is diagrammed in Figure 2.

In general, the outcome of treatment of IA has a good prognosis. Most patients are off prednisone within 1 year of

TABLE I

Classification of Anaphylaxis

Type	Mechanism	Examples of Causes
IgE mediated anaphylaxis	Antigen reacts with IgE antibody on mast cells	Foods, insect venoms, drugs, foreign serum, latex, allergen injections
Anaphylactoid	A. Opiates B. Radiographic contrast media	A. Direct stimulation of mast cells B. Mechanism unknown
Exercise induced	Uncertain	Running causes anaphylaxis
Food and exercise induced	Uncertain	A specific food plus exercise results in anaphylaxis
Idiopathic anaphylaxis (IA)	Uncertain	Sudden spontaneous onset of generalized anaphylaxis or life threatening angioedema
Undifferentiated somatoform IA (USIA)	Psychogenic	Patient describes symptoms of IA but these are never objectively documented

TABLE II

Classifying Idiopathic Anaphylaxis (IA)

Disease	Symptoms
Generalized (G)	Urticaria or angioedema with bronchospasm, hypotension, syncope
Angioedema (A)	Angioedema with upper airway compromise (laryngeal, pharyngeal, tongue)
Frequency of episodes	More than 6 times per year: frequent (F) Less than 6 times per year: infrequent (I)
Summary of diagnoses	IA-G-F, IA-A-F, IA-G-I, IA-A-I

Variations of IA Diagnoses

Corticosteroid dependent IA (CSD-IA)	Applied when a patient is controlled by prednisone, but has recurrent episodes of IA below a threshold dose of prednisone
Malignant IA (M-IA)	Applied when a patient requires high doses of prednisone to control IA. The doses of prednisone were arbitrarily set at 30 mg daily or 60 mg on alternate days, but much higher doses may be required.
IA-Questionable (Q)	Applied for a patient with possible IA where documentation of objective findings are unsuccessful and diagnosis is uncertain.
IA-Variant (V)	Applied when symptoms of IA vary from classic IA. IA-V may subsequently be classified as IA-A, IA-G, IA-Q, or USIA.
Undifferentiated somatoform IA (USIA)	Symptoms mimic IA but not objective findings are documented, and the symptoms are not responsive to the regimen for IA.

initiation of treatment. This is in contrast to the outcome of patients with severe prednisone dependent asthma.

SPECIAL PROBLEMS IN IA

Undifferentiated Somatoform IA

This diagnosis defines patients who have a psychiatric disease and express this by reporting symptoms that appear to be IA.⁸ The diagnosis is one of exclusion by failure to find objective evidence of documentation of physical findings consistent with IA in Emergency Service ex-

aminations and usually failure to respond to the regimen for IA. The prognosis is poor as the concept of psychiatric disease is rejected by the patient and sometimes by the personal physician. These patients may be treated with excess doses of prednisone with the expected side effects.

Pediatric IA

There is a lower incidence of IA in the pediatric population, but this does occur and is frightening to patients and families.^{9,10} Fortunately, the pediatric IA cases

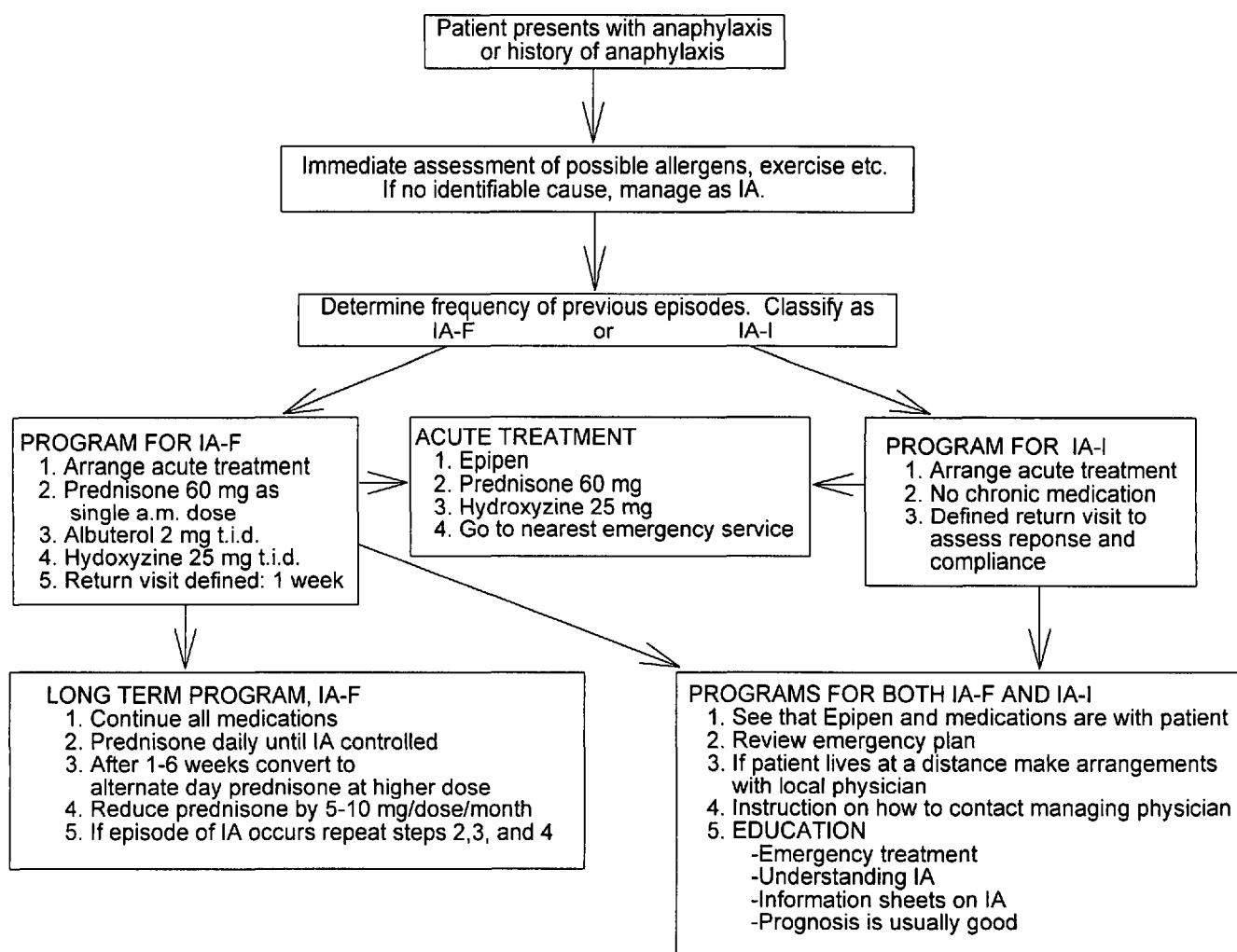


Figure 1. Algorithm for the management of idiopathic anaphylaxis. From Patterson R, Harris KE. Classification of idiopathic anaphylaxis (IA) and an algorithm for the management of IA. In Patterson R. (Ed.) *Idiopathic Anaphylaxis*. Providence, RI: Oceanside Publications, 22, 1997.

respond to the same regimen developed for adult cases of IA, with appropriate adjustment of doses for body weight.

Fatalities from IA

Fatalities have been reported¹¹ and it is very likely that far more fatalities have occurred than have been reported because of failure to describe the disease for decades (or centuries as described in the introductory statements) and failure to make the diagnosis even at the present time.

Corticosteroid Dependent IA

This refers to patients whose prednisone dosage cannot be lowered below a certain threshold. Zaditen (ketotifen), a mast cell stabilizer not available in the U.S., is helpful in many such cases.¹²

Patient Education

Patients with IA, and at times the referring physician, may not accept the diagnosis and lack of an external allergen as a triggering event. Further, the use of prednisone

alarms some patients and their personal physicians. For these reasons we published a book on IA, from which we receive no royalties, so that a comprehensive source of information was available to patients and their physicians.¹³

Potential Mechanisms of IA

These have been discussed in detail by Grammer.¹⁴ The explanation for IA reactions is unknown, and it may be decades before the mechanisms are established for IA-G and IA-A. These two types of IA may differ in the mechanisms responsible. Possible mechanisms to be considered are as follows. An autoimmune mechanism such as IgG antibodies against IgE fixed to mast cells or IgG antibodies against the IgE receptor on mast cells are both possible mechanisms. The action of histamine releasing factors is another mechanism to be studied. A major problem in evaluating mechanisms is that patients with IA-F must have treatment started immediately to prevent fatalities, and the mechanism responsible for IA may be altered by the IA therapeutic regimen.

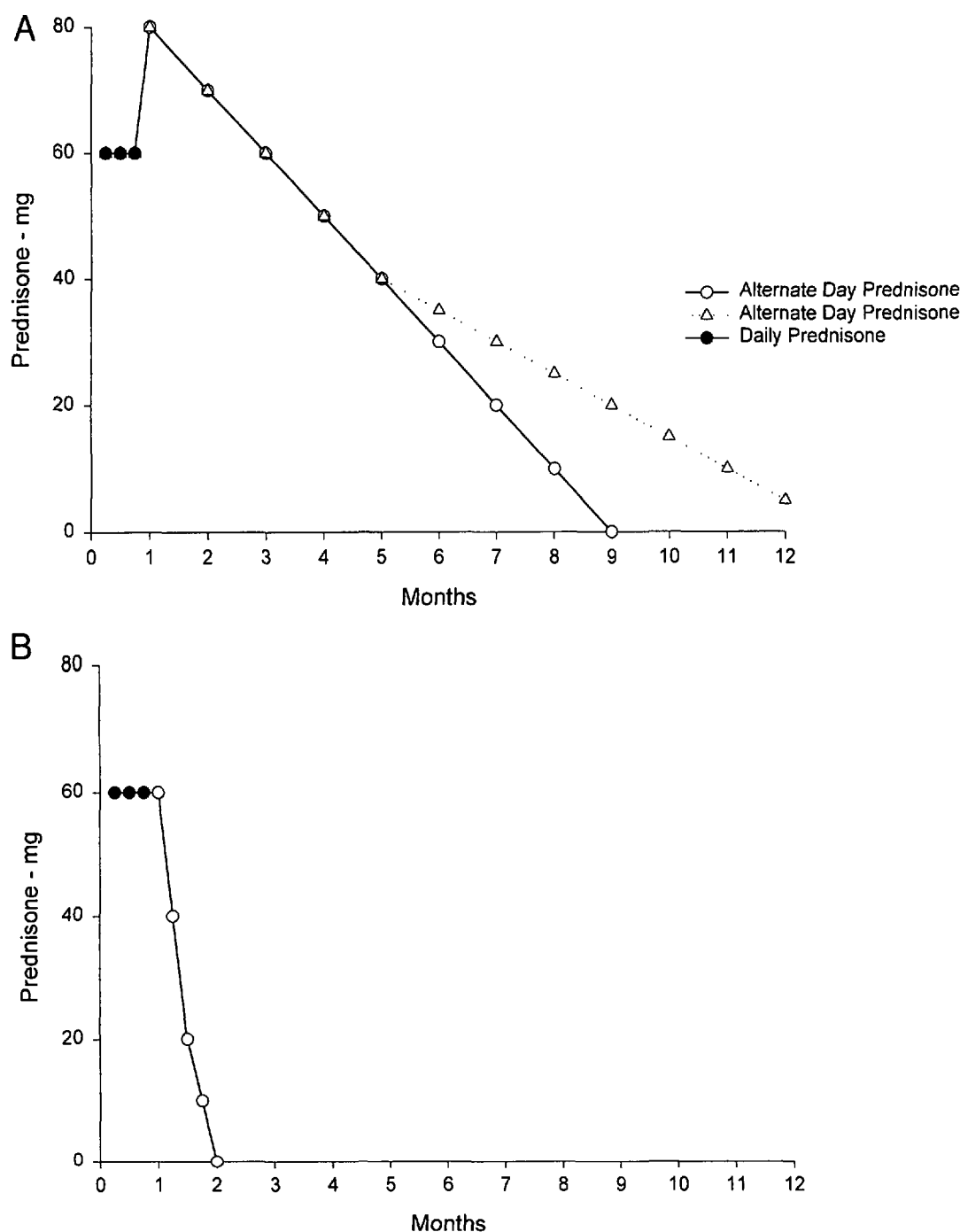


Figure 2. Two outcomes of therapy for IA-G-F. A. Daily prednisone is converted to alternate day prednisone, reduced, and discontinued. The rate of prednisone reduction depends upon the history, experience, and judgment of the physician. B. Prednisone does not control episodes and no objective evidence of IA is documented. Rapid reduction and discontinuation of prednisone is carried out as the patient has undifferentiated somatoform IA. From: Patterson R, Harris KE. Patterns of response to management of idiopathic anaphylaxis and ketotifen in management of idiopathic anaphylaxis. In Patterson R. (ed.) *Idiopathic Anaphylaxis*. Providence, RI: Oceanside Publications, 35, 1997.

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In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondritis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY** in full Prescribing Information.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, light-headedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See **PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.**)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dysnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS and ADVERSE REACTIONS.**)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome), vasculitis, arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, anemia, including hemolytic and aplastic, thrombocytopenia, including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.**)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.**)

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General:

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance ≤ 80 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION** in full Prescribing Information.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See **WARNINGS and Drug Interactions.**)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately. (See **Drug Interactions and ADVERSE REACTIONS.**)

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS and ADVERSE REACTIONS.**)

Information for Patients:

Patients should be advised:

- to drink fluids liberally.
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See **WARNINGS and ADVERSE REACTIONS.**)
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded.
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS and ADVERSE REACTIONS.**)
- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs.
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician. (See **PRECAUTIONS: General and Drug Interactions.**)
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.
- that if therapy with oral levofloxacin is initiated, then (1) antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution should be taken at least two hours before or two hours after levofloxacin administration. (See **Drug Interactions**); and (2) oral levofloxacin can be taken without regard to meals.

Drug Interactions:

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Injection: There are no data concerning an interaction of Intravenous quinolones with oral antacids, sucralfate, multivitamins, Videx®, (Didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

LEVAQUIN Tablets: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx®, (Didanosine) chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

Theophylline: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See **WARNINGS and PRECAUTIONS: General.**)

Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S-warfarin was detected in a clinical study involving healthy volunteers. No significant change in prothrombin time was noted in the presence of levofloxacin. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, since some quinolones have been reported to enhance the effects of oral anticoagulant warfarin or its derivatives in the patient population, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{1/2}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{1/2}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and CL_e were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See **WARNINGS and PRECAUTIONS: General.**)

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years; the highest dose was 2 or 10 times the recommended human dose based on surface area or body weight, respectively.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/JU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day (2124 mg/m²), corresponding to 3.0 or 18 times the recommended maximum human dose based on surface area or body weight, respectively, and intravenous doses as high as 100 mg/kg/day (590 mg/m²), corresponding to 1.0 or 5 times the recommended maximum human dose based on surface area or body weight, respectively.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day (4779 mg/m²), which corresponds to 14 or 82 times the recommended maximum human dose based on surface area or body weight, respectively, or at intravenous doses as high as 160 mg/kg/day (944 mg/m²) corresponding to 2.7 or 16 times the recommended maximum human dose based on surface area or body weight, respectively. Doses equivalent to 26 or 81 times the recommended maximum human dose of levofloxacin (based on surface area or body weight, respectively) caused decreased fetal body weight and increased fetal mortality in rats when administered orally at 810 mg/kg/day (8910 mg/m²). No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day (550 mg/m²) which corresponds to 1.6 or 5.0 times the recommended maximum human dose based on surface area or body weight, respectively, or when dosed intravenously as high as 25 mg/kg/day (275 mg/m²) corresponding to 0.8 or 2.5 times the maximum recommended human dose based on surface area or body weight, respectively.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

Nursing Mothers:

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS.**)

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving levofloxacin therapy, 3.4% discontinued levofloxacin therapy due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin: nausea 1.3%, diarrhea 1.1%, vaginitis 0.7%, pruritus 0.5%, abdominal pain 0.4%, dizziness 0.4%, flatulence 0.4%, rash 0.4%, dyspepsia 0.3%, genital moniliasis 0.3%, insomnia 0.3%, taste perversion 0.2%, vomiting 0.2%, anorexia 0.1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, fungal infection 0.1%, headache 0.1%, increased sweating 0.1%, leukorrhea 0.1%, malaise 0.1%, nervousness 0.1%, sleep disorders 0.1%, tremor 0.1%, urticaria 0.1%.

In clinical trials, the following events occurred in >3% of patients regardless of drug relationship:

nausea 7.1%, headache 6.4%, diarrhea 5.6%, injection site reaction 5.6%, insomnia 4.0%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

constipation 2.9%, dizziness 2.9%, injection site pain 2.7%, abdominal pain 2.6%, dyspepsia 2.5%, vomiting 2.2%, rash 1.7%, flatulence 1.6%, vaginitis 1.6%, injection site inflammation 1.5%, pruritus 1.5%, fatigue 1.3%, back pain 1.2%, pain 1.2%, chest pain 1.1%, pharyngitis 1.1%, rhinitis 1.1%, taste perversion 1.0%.

In clinical trials, the following events occurred in 0.5 to less than 1% of patients, regardless of drug relationship: anorexia, anxiety, arthralgia, coughing, dry mouth, dyspnea, ear disorder (not otherwise specified), edema, fever, fungal infection, genital pruritus, increased sweating, skin disorder, somnolence.

In clinical trials, the following events, of potential medical importance, occurred at a rate of less than 0.5% regardless of drug relationship: abnormal coordination, abnormal dreaming, abnormal hepatic function, abnormal platelets, abnormal renal function, abnormal vision, acute renal failure, aggravated diabetes mellitus, aggressive reaction, agitation, anemia, angina pectoris, ARDS, arrhythmia, arthritis, arthrosis, asthenia, asthma, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, carcinoma, cerebrovascular disorder, cholelithiasis, circulatory failure, coma, confusion, conjunctivitis, convulsions (seizures), coronary thrombosis, dehydration, delirium, depression, diplopia, dysphagia, ejaculation failure, embolism (blood clot), emotional lability, epistaxis, erythema nodosum, face edema, gastroenteritis, genital moniliasis, G.I. hemorrhage, granulocytopenia, haematoma, haemoptysis, hallucination, heart block, hepatic coma, hyperglycemia, hyperkalemia, hyperkinesia, hypertension, hypertonia, hypoaesthesia, hypoglycemia, hypokalemia, hypotension, hypoxia, impaired concentration, impotence, increased LDH, involuntary muscle contractions, jaundice, leukocytosis, leukopenia, lymphadenopathy, malaise, manic reaction, mental deficiency, muscle weakness, myalgia, myocardial infarction, nervousness, palpitation, paracetitis, parosmia, paralysis, paranoia, parosmia, pleuritis, pleural effusion, postural hypotension, pseudomembranous colitis, purpura, respiratory insufficiency, rhabdomyolysis, rigors, skin exfoliation, skin ulceration, sleep disorders, speech disorder, stupor, subdermal chest pain, supraventricular tachycardia, syncope, synovitis, tachycardia, tendinitis, thrombocytopenia, tinnitus, tongue edema, tremor, urticaria, ventricular fibrillation, vertigo, weight decrease, WBC abnormal (not otherwise specified), withdrawal syndrome.

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Crystalluria and cylindruria have been reported with other quinolones.

The following laboratory abnormalities appeared in 2.1 to 2.3% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Blood Chemistry: decreased glucose

Hematology: decreased lymphocytes

Post-Marketing Adverse Reactions:

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, Stevens-Johnson Syndrome, tendon rupture, vasodilation.

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