Electrocardiographic changes in acute cholecystitis

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The syndrome of abdominal fullness and nausea, diaphoresis, chest pain, and ECG changes long has been associated with impending myocardial infarction. For a few patients, however, a working diagnosis of coronary ischemia is seen to be inaccurate on further testing, including stress testing and cardiac catheterization. Acute cholecystitis may cause a clinical picture similar to that of cardiac ischemia. The ECG changes that may occur in acute cholecystitis, the possible basis for these changes, and their clinical implications are discussed in this article.

Myocardial ischemia is the most likely diagnosis when the symptom complex includes chest pain, nausea, diaphoresis, and abdominal fullness associated with ECG changes. Occasionally, this clinical picture does not prove to represent cardiac ischemia. Serial cardiac enzyme determinations, stress testing, and coronary angiography may all have negative findings for a coronary event. Therefore, other causes for this clinical presentation have been studied. The two main areas of concentration have been extracardiac disease and its influence on coronary blood flow and extracardiac effects on the electric activity recorded on the ECG. Acute cholecystitis is one disease that has a clinical presentation similar to myocardial ischemia.

Historical review

In 1947, Breitwieser¹ performed a retrospective study of ECG changes associated with gallbladder disease. Of 621 patients who had undergone cholecystectomy, 66 had undergone electrocardiography in the year prior to surgery. Thirty of these 66 patients were available for postoperative electrocardiography. Seventeen patients who had had presurgical ECG changes reverted to normal ECG patterns. This study, although inconclusive, was one of the first to indicate that noncardiac disease might have an influence on the ECG. However, the author did not identify the extent of preexisting coronary disease, nor did she discuss the possible mechanisms for this phenomenon.

Research on the gallbladder and its influence on the ECG was continued in 1955 by Glotzer and Barcham.² In their study, 20 cholecystectomy candidates were selected to have preinduction, postinduction, and intraoperative (while traction was applied to the gallbladder) electrocardiography. Thirteen of the 20 patients had ST segment changes following induction of anesthesia; eight of these had further changes following traction on the gallbladder. These authors proposed that traction on the gallbladder might have stimulated the vagus nerve, thus causing the ECG changes.

In 1982, Terradellas and associates³ studied ST segment elevation associated with bacterial shock in seven patients. In one patient, the bacteria originated from the gallbladder. However, all episodes of ST segment elevation were attributed to ischemia induced by dopamine.

During the past two decades, several European reports on ECG changes associated with acute cholecystitis have been published. The findings of these studies have supported a neuronal-induced phenomenon rather than preexisting cardiac disease or an electrolyte imbalance as the contributing factors to these changes.⁴

Proposed mechanisms

Because the ECG changes in cholecystitis most commonly involve the ST segment, it has been thought that the disease must influence cardiac blood flow. Because elevated cholesterol levels are associated both with gallbladder disease and coronary artery disease, it seems logical that both conditions might coexist. That is, acute cholecystitis might cause a patient to seek medical attention, and the underlying coronary disease would be found on further examination.

However, this theory does not explain ST segment changes in persons without preexisting coronary artery disease. Glotzer and Barcham² proposed that because of the common innervation of the cardiac plexus and gallbladder by the vagus nerve, stimulation of the vagus nerve through irritation of the gallbladder induced cardiac ischemia. This phenomenon either could worsen preexisting disease or could induce ischemia.

Alkalotic inducement of ischemia also may play

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Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

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Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.
Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*, and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum. Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction. Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination. Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- E. coli DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae Point Mutation Assay (Negative)
- Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Microsome Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 10 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus of ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSE ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). The events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.1%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, restlessness, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY: (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema multiforme, nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).
SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of light), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.
RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, ystygismus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria; vaginal candidiasis and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro[®] (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in unit dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

*Due to susceptible strains of indicated pathogens. See indicated organisms in Prescribing Information.

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Figure. Electrocardiogram of 66-year-old woman with chest pain, nausea, and diaphoresis. Note inverted T-wave in lead 3 and sinus bradycardia. Subsequent cardiac evaluation revealed

absence of cardiac disease while gallbladder ultrasonography revealed multiple cholelithiasis.

a role in ST segment changes. Alkalosis is known to cause constriction of the capillaries in the heart and may lead to ischemia. The anxious, uncomfortable patient may hyperventilate, thus causing an alkalotic state, which may be aggravated by accompanying nausea and vomiting.²

Evaluation

The ECG changes associated with cholecystitis never should prevent evaluation of a patient for coronary artery disease. Yet, this phenomenon may have clinical significance in the following situations: (1) Noninvasive ultrasonography of the gallbladder may play a role in the evaluation of the patient with recurrent clinical symptoms that suggest cardiac ischemia. Once it has been proved that a patient does not have coronary artery disease, evaluation for gallbladder disease may prevent repeated negative findings on cardiac testing; (2) patients who have ST segment changes during episodes of acute cholecystitis may be found to be at higher risk of coronary vasospastic disease, and their condition should be followed accordingly; and (3) ST segment changes associated with acute cholecystitis may help to identify patients who are at risk of having cardiac dysrhythmias or ischemia

develop during abdominal surgery that involves structures innervated by the vagus nerve.

Conclusions

Perhaps future studies may demonstrate the influence of other intra-abdominal diseases on coronary blood flow and ECG changes. For now, however, awareness of the effect of cholecystitis on the heart may lead clinicians to evaluate patients presenting with abdominal fullness and nausea, diaphoresis, and chest pain and ECG changes more thoroughly.

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