
Communications

Treatment of Urinary Tract Infection With Cephalexin

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Although cephalexin is not generally regarded as the drug of first choice for urinary tract infections, several investigators¹⁻⁴ have used it successfully for the treatment of these conditions, giving 1 g daily in divided doses. Because of the efficacy of the drug in these studies, the low incidence of adverse reactions, and the high urine levels achieved with the 500 mg oral dose, an evaluation of cephalexin comparing the dose schedules of 500 mg twice daily and 250 mg four times daily in a double-blind study was undertaken.

Methods

Male and female patients over the age of 15 years presenting with symptomatic urinary tract infections were enrolled if they were otherwise in reasonably good health. Pregnant patients were excluded, as were those with known renal or hepatic impairment, those with a concomitant infection, and those who had received successful antibacterial therapy within the preceding four days.

Patients were admitted to the study after giving their consent (parental consent was obtained for patients under 18 years of age) and after urine cul-

tures had shown the presence of 10^5 colony-forming units per milliliter of an organism shown to be susceptible to cephalexin.

A second urine culture was obtained between the 2nd and 4th days of treatment and another one 5 to 9 days after treatment was completed. Whenever possible, a follow-up culture was obtained four to six weeks after the end of treatment.

All patients were treated with cephalexin, 1 g daily for at least seven days. The patients were randomly allocated by a computer-generated random number table to a treatment schedule of 250 mg four times a day or 500 mg twice a day. To maintain the double-blind technique, all patients received capsules four times a day: those allocated to the schedule of 500 mg of cephalexin taken twice a day also received alternate doses of placebo capsules of identical appearance. No attempt was made to assess patient compliance with the treatment schedule.

Any adverse reactions that were spontaneously volunteered or elicited in response to nonspecific questions were recorded, and an attempt was made to establish whether they were drug related.

Results

One hundred eighty-four patients were admitted to the study. There were 32 male patients and 152

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Brief Summary

Enduronyl[®] Methyclothiazide and Deserpidine

Oral thiazide-rauwolfia therapy for hypertension.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indications: ENDURONYL (methyclothiazide and deserpidine) is indicated in the treatment of mild to moderately severe hypertension (see boxed warning). In many cases ENDURONYL alone produces an adequate reduction of blood pressure. In resistant or unusually severe cases ENDURONYL also may be supplemented by more potent antihypertensive agents. When administered with ENDURONYL, more potent agents can be given at reduced dosage to minimize undesirable side effects.

Contraindications: Methyclothiazide is contraindicated in patients with renal decompensation and in those who are hypersensitive to this or other sulfonamide-derived drugs.

Deserpidine is contraindicated in patients with known hypersensitivity, mental depression especially with suicidal tendencies, active peptic ulcer, and ulcerative colitis. It is also contraindicated in patients receiving electroconvulsive therapy.

Warnings: METHYCLOTHIAZIDE — Methyclothiazide shares with other thiazides the propensity to deplete potassium reserves to an unpredictable degree.

Thiazides should be used with caution in patients with renal disease or significant impairment of renal function, since azotemia may be precipitated and cumulative drug effects may occur.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

DESERPIDINE — Extreme caution should be exercised in treating patients with a history of mental depression. Discontinue the drug at the first sign of despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide.

Usage in Pregnancy and Lactation: METHYCLOTHIAZIDE — Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Thiazides appear in breast milk. If use of the drug is deemed essential, the patient should stop nursing.

DESERPIDINE — The safety of deserpidine for use during pregnancy or lactation has not been established; therefore, it should be used in pregnant women or in women of childbearing potential only when in the judgment of the physician its use is deemed essential to the welfare of the patient. Increased respiratory secretions, nasal congestion, cyanosis, and anorexia may occur in infants born to rauwolfia alkaloid-treated mothers, since these preparations are known to cross the placental barrier to enter the fetal circulation and appear in cord blood. They also are secreted by nursing mothers into breast milk.

Reproductive and teratology studies in rats reduced the mating index and neonatal survival indices; the no effect dosage has not been established.

Precautions: Periodic determinations of serum electrolytes should be performed at appropriate intervals for the purpose of detecting possible electrolyte imbalances such as hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when a patient is vomiting excessively or receiving parenteral fluids. All patients should be observed for other clinical signs of electrolyte imbalances such as dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any other potent diuretic, especially when brisk diuresis occurs, severe cirrhosis is present, or when corticosteroids or ACTH are given concomitantly. Interference with the adequate oral intake of electrolytes will also contribute to the possible development of hypokalemia. Potassium depletion, even of a mild degree, resulting from thiazide use, may sensitize a patient to the effects of cardiac glycosides such as digitalis.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening.

In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Thiazides have been reported, on rare occasions, to have elevated serum calcium to hypercalcemic levels. The serum calcium levels have returned to normal when the medication has been stopped. This phenomenon may be related to the ability of the thiazide diuretics to lower the amount of calcium excreted in the urine.

Because rauwolfia preparations increase gastrointestinal motility and secretion, this drug should be used cautiously in patients with a history of peptic ulcer, ulcerative colitis, or gallstones, where biliary colic may be precipitated.

Caution should be exercised when treating hypertensive patients with renal insufficiency since they adjust poorly to lowered blood pressure levels.

Use deserpidine cautiously with digitalis and quinidine since cardiac arrhythmias have occurred with rauwolfia preparations.

Preoperative withdrawal of deserpidine does not assure that circulatory instability will not occur. It is important that the anesthesiologist be aware of the patient's drug intake and consider this in the overall management, since hypotension has occurred in patients receiving rauwolfia preparations. Anticholinergic and/or adrenergic drugs (metaraminol, norepinephrine) have been employed to treat adverse vagocirculatory effects.

Adverse Reactions: METHYCLOTHIAZIDE — **GASTROINTESTINAL SYSTEM REACTIONS:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

CENTRAL NERVOUS SYSTEM REACTIONS: Dizziness, vertigo, paresthesias, headache, xanthopsia.

HEMATOLOGIC REACTIONS: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

DERMATOLOGIC / HYPERSENSITIVITY REACTIONS: Purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis), and erythema multiforme.

CARDIOVASCULAR REACTION: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates, or narcotics.

OTHER: Hyperglycemia, glycosuria, hypercalcemia, hyperuricemia, muscle spasm, weakness, restlessness.

There have been isolated reports that certain nonedematous individuals developed severe fluid and electrolyte derangements after only brief exposure to normal doses of thiazide and non-thiazide diuretics. The condition is usually manifested as severe dilutional hyponatremia, hypokalemia, and hypochloremia. It has been reported to be due to inappropriately increased ADH secretion and appears to be idiosyncratic. Potassium replacement is apparently the most important therapy in the treatment of this syndrome along with removal of the offending drug.

Whenever adverse reactions are severe, treatment should be discontinued.

DESERPIDINE — The following adverse reactions have been reported with rauwolfia preparations. These reactions are usually reversible and disappear when the drug is discontinued.

GASTROINTESTINAL: Including hypersecretion, anorexia, diarrhea, nausea, and vomiting.

CARDIOVASCULAR: Including angina-like symptoms, arrhythmias (particularly when used concurrently with digitalis or quinidine), and bradycardia.

CENTRAL NERVOUS SYSTEM: Including drowsiness, depression, nervousness, paradoxical anxiety, nightmares, extrapyramidal tract symptoms, CNS sensitization manifested by dull sensorium, and deafness.

DERMATOLOGIC — HYPERSENSITIVITY: Including pruritus, rash, and asthma in asthmatic patients.

OPHTHALMOLOGIC: Including glaucoma, uveitis, optic atrophy, and conjunctival injection.

HEMATOLOGIC: Thrombocytopenic purpura.

MISCELLANEOUS: Nasal congestion, weight gain, impotence or decreased libido, dysuria, dyspnea, muscular aches, dryness of mouth, dizziness, and headache.

Overdosage: Symptoms of thiazide overdosage include electrolyte imbalance and signs of potassium deficiency such as confusion, dizziness, muscular weakness, and gastrointestinal disturbances. General supportive measures including replacement of fluids and electrolytes may be indicated in treatment of overdosage.

An overdosage of deserpidine is characterized by flushing of the skin, conjunctival injection and pupillary constriction. Sedation ranging from drowsiness to coma may occur. Hypotension, hypothermia, central respiratory depression and bradycardia may develop in cases of severe overdosage. Treatment consists of the careful evacuation of stomach contents followed by the usual procedures for the symptomatic management of CNS depressant overdosage. If severe hypotension occurs it should be treated with a direct acting vasopressor such as norepinephrine bitartrate injection.

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female patients. One hundred seventy-eight patients were diagnosed as having "cystitis" or "urinary tract infection," and six had asymptomatic bacteriuria. *Escherichia coli* was the most common pathogen (113 patients) followed by *Proteus mirabilis* (27 patients). Single pathogens were isolated from 166 patients, 82 of whom received the twice-a-day schedule, and 84 of whom received the four-times-a-day schedule. Multiple pathogens were isolated from six patients on the twice-a-day schedule and three patients on the four-times-a-day schedule. There were no significant differences in the patient populations from the four centers or for the two treatment schedules; thus, it was reasonable to combine the results from the four centers.

Nine of the 184 patients failed to meet the criteria for complete evaluation of efficacy: In four patients, one or more urine cultures were not obtained at the specified time. Three patients were infected with organisms resistant to cephalixin or inadequately identified (including one patient with asymptomatic bacteriuria), and two patients required additional therapy that made them ineligible for the study. Of the remaining 175 patients, 88 received 500 mg cephalixin twice a day and 87 received 250 mg cephalixin four times a day.

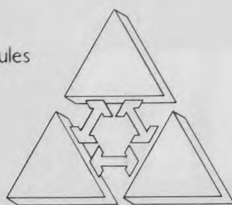
A satisfactory symptomatic response defined as disappearance or improvement of the signs and symptoms of the infection with no recurrence five to nine days post-therapy was seen in 81 (94 percent) of the 88 evaluable patients on the twice-a-day schedule and 78 (93 percent) of the 87 patients on the four-times-a-day schedule. Five patients were asymptomatic on admission to the study and so were unable to provide symptomatic evaluation. Eleven patients, five on the twice-a-day schedule, and five on the four-times-a-day schedule, were asymptomatic on admission to the study and so were unable to provide symptomatic evaluation. Eleven patients, five on the twice-a-day schedule, and five on the four-times-a-day schedule, were asymptomatic on admission to the study and so were unable to provide symptomatic evaluation.

Bacteriologic cure, defined as elimination of the original pathogen from all the follow-up cultures, was achieved in 82 (93 percent) of the 88 patients on the twice-a-day schedule and 79 (91 percent) of the 87 patients on the four-times-a-day schedule. The six patients who received the twice-a-day schedule and in whom the organisms were not eradicated had uncomplicated cystitis; the infecting organisms were *E coli* (3), *P mirabilis* (2), and *Proteus sp* (1). Six patients who received the

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Imodium[®] Capsules

(loperamide HCl)



In diarrhea: Fast direct action Relieves cramping Reduces stool frequency

BRIEF SUMMARY

Before prescribing, please consult complete prescribing information, a summary of which follows:

INDICATIONS

IMODIUM is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. IMODIUM is also indicated for reducing the volume of discharge from ileostomies.

CONTRAINDICATIONS

IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS

Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., enteroinvasive *E. coli*, *Salmonella*, *Shigella*, and in pseudomembranous colitis associated with broad-spectrum antibiotics.

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS

In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence: Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis: In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy: Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established. Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS

The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported: Abdominal pain, distention or discomfort; Constipation; Drowsiness or dizziness; Dry mouth; Nausea and vomiting; Tiredness.

Hypersensitivity reactions (including skin rash), however, have been reported with IMODIUM use.

OVERDOSAGE

Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. Clinical trials have demonstrated that a slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed into the systemic circulation by as much as ninefold. If vomiting occurs spontaneously upon ingestion, a slurry of 100 gms of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gms of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.

In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. In studies designed to examine the potential for side effects, intentional ingestion of up to 60 mg of loperamide hydrochloride in a single dose to healthy subjects resulted in no significant adverse effects.

HOW SUPPLIED

IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "JANSSEN" imprinted on one segment and "IMODIUM" on the other segment. IMODIUM capsules are supplied in bottles of 100 and 500 and in blister packs of 10 x 10 capsules.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium and is manufactured by Ortho Pharmaceutical Corporation, Raritan, New Jersey, December 1982. U.S. Patent 3,714,159.

world leader in anti-diarrheal research



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four-times-a-day schedule and in whom the organisms were not eliminated had uncomplicated cystitis, and all were infected with *E. coli*. Two other patients on the four-times-a-day schedule had complicated cystitis and were infected with *P. mirabilis*.

Follow-up urine cultures, taken four to six weeks after therapy ended, were obtained from 68 patients. Thirty-one of 32 patients who had received the twice-a-day schedule had sterile urine; one patient had become reinfected with a new pathogen. In the group that had received the four-times-a-day schedule, 35 of 36 patients had sterile urine, and one patient had a pathogen present at less than 10^5 colonies per milliliter.

Adverse reactions were reported by seven (8 percent) patients who received the twice-a-day schedule. Four had vaginitis, one had genital moniliasis, one had a rash, and one complained of nausea. In the group that received the four-times-a-day schedule, one patient had genital moniliasis, and one had diarrhea. None of the patients stopped taking the cephalixin because of the adverse reaction.

Based on the results of this study, it can be concluded that cephalixin, 1 g daily, is an effective treatment for urinary tract infections caused by the common uropathogens, and that the drug is equally effective given twice a day or four times a day.

References

1. Lima MCC, Marson O, Albuquerque EMR: Cephalixin in urinary infection: A possible regimen. *Invest Med Int* 6(suppl 1):30, 1979
2. Charlton CAC, O'Grady F, MacSherry A, Sutcliffe M: Use of cephalixin for the initial treatment of patients with persistent or recurrent urinary tract infection. *Postgrad Med J* 46(suppl):30, 1970
3. Fairley KF: Cephalixin in recurrent urinary tract infection. *Postgrad Med J* 46(suppl):24, 1970
4. Montgomery WG, Cox CE: Cephalixin: Clinical and laboratory studies with 500 mg twice daily dosage in urinary infection. *Int J Clin Pharmacol Ther Toxicol* 4:212, 1971