

Serum Potassium Concentrations in Older Hypertensive Patients Receiving Enalapril

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The angiotensin converting enzyme inhibitors (ACEI) represent an important advance in the treatment of mild to moderate hypertension. The use of enalapril, the long-acting ACEI with once-a-day dosing, in the geriatric population has been limited, however. Hyperkalemia secondary to enalapril is a potential concern, especially in the presence of renal impairment or potassium supplementation, both of which may occur in the older hypertensive patient.¹

The purpose of the study reported here was to determine the effect of enalapril on serum potassium concentrations in older hypertensive patients receiving hydrochlorothiazide with either potassium supplementation or a potassium-sparing diuretic.

METHODS

A computer listing of the hypertensive patients who attended a family medicine clinic during the period from September of 1986 through March of 1987 was obtained. Charts were selected for review if the following audit criteria were met: (1) the patient was over 60 years of age, (2) the patient was receiving combination therapy with enalapril and hydrochlorothiazide and either potassium supplementation or a potassium-sparing diuretic, (3) the patient was not receiving other drug therapy that might alter serum potassium concentrations, and (4) at least two potassium concentrations had been determined both before and following a minimum of one month of enalapril therapy.

The following data were collected: patient age, sex, and weight; enalapril dosage and duration; hydrochlorothiazide dosage and duration; method of potassium supplementation; and serum potassium and creatinine concentrations before and during enalapril therapy. Serum potassium concentrations were compared using the two-tailed *t* test for paired observations.

RESULTS

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A total of 23 charts met the audit criteria. The mean (\pm standard deviation) patient age and weight were 68.0 (± 5.9) years and 63.2 (± 9.8) kg, respectively, with 11 male and 12 female patients included in the analysis. Serum potassium concentrations increased by a mean of 0.35, 0.73, 0.35, and 0.33 mEq/L in patients receiving 25 mg of hydrochlorothiazide and 50 mg of triamterene (70 percent bioavailability), 50 mg of hydrochlorothiazide and 75 mg of triamterene (100 percent bioavailability), 50 mg of hydrochlorothiazide and 5 mg of amiloride, and potassium chloride, respectively. Only one patient's serum potassium concentrations increased into the hyperkalemic range.

COMMENT

The development of hyperkalemia secondary to ACEI therapy is an important concern. Burnakis and Mioduch² have reported five patients (mean age, 67.8 years) in whom the serum potassium concentrations increased from 3.88 ± 0.41 to 4.84 ± 0.45 mEq/L when captopril was added to a potassium-sparing diuretic or potassium supplement. In a retrospective study of 20 patients by Schuna et al,³ however, the addition of captopril did not result in a significant increase in serum potassium concentrations.

In the present study of 23 patients, serum potassium concentrations were not significantly increased by the addition of enalapril. In the five patients with reduced cre-

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FLEXERIL®

(CYCLOBENZAPRINE HCl/MSD)

Note: FLEXERIL has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

Contraindications: Hypersensitivity to the drug. Concomitant use of monoamine oxidase inhibitors or within 14 days after their discontinuation. Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure. Hyperthyroidism.

Warnings: Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short-term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see **Warnings**, below, and **Adverse Reactions**). FLEXERIL may interact with monoamine oxidase (MAO) inhibitors. Hyperpyretic crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs. Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Precautions: *General:* Because of its atropine-like action, FLEXERIL should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients: FLEXERIL may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions: FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats treated with FLEXERIL for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipofusin. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks at lower doses, the change was not seen until after 26 weeks. Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine neither adversely affected the reproductive performance or fertility of male or female rats, nor demonstrated mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

*Pregnancy: Pregnancy Category B—*Reproduction studies have been performed in rats, mice and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to FLEXERIL. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when FLEXERIL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of FLEXERIL in children below the age of 15 have not been established.

Adverse Reactions: The following list of adverse reactions is based on the experience in 473 patients treated with FLEXERIL in controlled clinical studies, 7607 patients in the post-marketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with FLEXERIL were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies	Surveillance Program
drowsiness	39%	16%
dry mouth	27%	7%
dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

Incidence Less Than 1 in 100: The following adverse reactions have been reported at an incidence of less than 1 in 100—*Body as a Whole:* Syncope; facial edema; malaise. *Cardiovascular:* Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension. *Digestive:* Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis. *Musculoskeletal:* Local weakness. *Nervous System and Psychiatric:* Ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; abnormal thinking and dreaming; hallucinations; excitement; paresthesia. *Skin:* Sweating; skin rash; urticaria. *Special Senses:* Ageusia; tinnitus. *Urogenital:* Urinary frequency and/or retention.

Causal Relationship Unknown: Other reactions reported rarely for FLEXERIL under circumstances where a causal relationship could not be established or reported for other tricyclic drugs are listed to serve as alerting information to physicians: *Body as a Whole:* Chest pain; edema. *Cardiovascular:* Hypertension; myocardial infarction; heart block; stroke. *Digestive:* Paralytic ileus; tongue discoloration; stomatitis; parotid swelling. *Endocrine:* Inappropriate ADH syndrome. *Hematic and Lymphatic:* Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia. *Metabolic, Nutritional, and Immune:* Elevation and lowering of blood sugar levels; weight gain or loss. *Musculoskeletal:* Myalgia. *Nervous System and Psychiatric:* Decreased or increased libido; abnormal gait; delusions; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms. *Respiratory:* Dyspnea. *Skin:* Pruritus; photosensitization; alopecia. *Urogenital:* Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

Drug Abuse and Dependence: Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when FLEXERIL is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

Overdosage: The acute oral LD₅₀ of FLEXERIL is approximately 338 and 425 mg/kg in mice and rats, respectively.

Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis, followed by gastric lavage. After gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function must be instituted if there is any evidence of dysrhythmia. Maintenance of an open airway, adequate fluid intake, and regulation of body temperature are necessary. The intravenous administration of 1 to 3 mg of physostigmine salicylate is reported to reverse symptoms of poisoning by atropine and other drugs with anticholinergic activity. Physostigmine may be helpful in the treatment of cyclobenzaprine overdose. Because physostigmine is rapidly metabolized, its dosage should be repeated as required, particularly if life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dosage. Because physostigmine itself may be toxic, it is not recommended for routine use.

How Supplied: Tablets containing 10 mg cyclobenzaprine HCl, in bottles of 100, unit dose packages of 100, and BACK-PACK® unit-of-use package of 30.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486



SERUM POTASSIUM AND ENALAPRIL

atropine clearances, however, serum potassium concentrations did increase to a greater degree. Until further studies in the elderly are completed, hyperkalemia remains a significant concern, and serum potassium concentrations should be monitored carefully when enalapril is added to an antihypertensive regimen that includes either a potassium-sparing diuretic or a potassium supplement.

References

1. Vasotec package insert. West Point, Pa, Merck, Sharpe & Dohme Laboratories, December 1985
2. Burnakis TG, Mioduch HJ: Combined therapy with captopril and potassium supplementation. Arch Intern Med 1984; 144:2371-2372
3. Schuna AA, Schmidt GR, Pitterle ME: Serum potassium concentrations after initiation of captopril therapy. Clin Pharm 1986; 5: 920-923