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Original Research Article

Evaluation of the Effects of Torsemideon Quality of Life in Patients of CHF

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Abstract

Aim: The present study to evaluate the efficacy and tolerability of 8 weeks of torsemide therapy in patients with New York Heart Association (NYHA) Class II (slight limitation of activity; comfortable at rest or with mild exertion) to Class III (marked limitation of activity; comfortable only at rest) CHF whose condition had been stabilized with digitalis or ACE inhibitor treatment.

Methods: Men and women aged 30 to 70 years with NYHA Class II to III CHF stabilized with digitalis or ACE inhibitors were eligible to enter the study.

Results: A total of 120 patients (70 men and 50 women> with a mean age of 61.8* 8.6 years (range, 30 to 70 years) were enrolled in 10 centers. Of these patients, 20 were excluded from the efficacy analysis, 17 having violated protocol (use of prohibited concomitant treatments, poor compliance, NYHA Class IV [any physical activity brings on discomfort, and symptoms also occur at rest; confined to bed or chair]) and 3 having dropped out before the a-month treatment period ended (lost to follow-up [ll, adverse events.

Conclusion: The present study demonstrates that torsemide is well tolerated, effective in treating moderate CHF, and useful when administered with digoxin or ACE inhibitors to reduce the signs and symptoms of CHF.

Keywords: left ventricular dysfunction, loop diuretics, tomemide, congestive heart failure

Introduction

Although several drugs, such as digitalis, angiotensin-converting enzyme (ACE) inhibitors, and vasodilators, are currently used in the management of congestive heart failure (CHF), diuretics are considered first-line therapy. [1-6]

The diuretics most commonly used for treating CHF are the loop diuretics. These compounds reduce excess intravascular and extracellular fluid by increasing salt and water excretion. This relieves symptoms and reduces stress on the heart wall, in turn decreasing oxygen consumption by the ventricle and increasing pumping efficacy. However, the chronic administration of diuretics can induce metabolic and electrolyte abnormalities; potassium depletion commonly occurs in patients treated chronically with loop diuretics, [7,8] and is

often associated with the appearance of malignant ventricular arrhythmias. [9]

Recent studies [10,11] have indicated that torsemide, a high ceiling loop diuretic, has diuretic and natriuretic activity comparable to that of furosemide but with less kaliuretic effect than furosemide. Several studies [12-14]have demonstrated the clinical efficacy and safety of torsemide in the treatment of CHF; however, most studies have a short observational period (4 weeks).

Therefore, we planned the present study to evaluate the efficacy and tolerability of 8 weeks of torsemide therapy in patients with New York Heart Association (NYHA) Class II (slight limitation of activity; comfortable at rest or with mild exertion) to Class III (marked limitation of activity; comfortable only at rest) CHF whose condition had been stabilized with digitalis or ACE inhibitor treatment.

Methods

Men and women aged 30 to 70 years with NYHA Class II to III CHF stabilized with digitalis or ACE inhibitors were eligible to enter the study.

Patients with evidence of active ischemic cardiomyopathy, arrhythmias, bradycardia, valvular heart diease, severe kidney or liver dysfunction, severe pulmonary disease, electrolyte imbalance (serum potassium levels~3.5 mEq/L or serum sodium levels ~135 mEq/L), uncontrolled diabetes mellitus, or alcoholism were excluded from the study. Patients receiving concomitant neurotoxic or nephrotoxic therapy (eg, aminoglycosides, antidepressant drugs, anticonvulsants, lithium, amphetamines, barbiturates), those treated with corticosteroids or spasmolytic and anticholinergic agents, and patients not adhering to a low sodium diet were also excluded.

Finally, women with childbearing potential and those who were breastfeeding were not eligible to participate in the study.

Concomitant therapy with other diuretics or drugs that could affect ventricular function, except established therapy with digoxin or ACE inhibitors, was not permitted during the trial. The protocol was conducted according to the Declaration of Helsinki and its modifications and was approved by the ethics committees of the participating institutions.

Study Design

Eligible patients, after giving written informed consent, were assigned to receive torsemide for 2 months at an initial dose of 10 mg/d, to be taken in the morning. After 14 or 30 days, the dose was decreased to 5 mg ld or increased to 20 mg/d if necessary based on the diuretic effect achieved and the observed pattern of fluid retention. At the baseline visit and monthly thereafter, NYHA class was determined; systolic and diastolic blood pressures, heart rate, and body weight were measured; and blood was collected for determination of serum electrolyte and glucose levels.

Patients also underwent a complete physical examination, including evaluation of peripheral edema by left and right ankle circumference measurements; by signs such as jugular venous distention, pulmonary rales, cyanosis, hepatomegaly, or cardiomegaly; and by symptoms such as nocturnal coughing, nocturia, and dyspnea, the latter assessed by the World

NYHA classification (0 = dyspnea absent; 1 = breathlessness caused by running or walking up an incline; 2 = breathlessness caused by walking on a level road; 3 = the need to stop walking on a level road because of breathlessness; 4 = breathlessness when washing or dressing).

At baseline and at the end of treatment, routine laboratory tests (complete blood count with differential cell count, hemoglobin, hematocrit, platelet count, total and fractioned cholesterol, triglycerides) and 12-lead electrocardiography were performed.All

adverse events experienced during the study were recorded, with date of onset, severity, duration, and any countermeasures specified.

Statistical Analysis

All variables assessed on entry and at succeeding visits (demographic data, history, concomitant diseases and treatments, NYHA classification, severity of signs and symptoms) were submitted to a descriptive analysis, with the number of observations, means, standard deviations, and the minimum and maximum of frequencies reported as appropriate. Descriptive statistics were also computed for all variables at each visit.

For signs and symptoms, frequencies of change compared with baseline values were assessed, with patients classified as recovered, same, or worsened. For NYHA class and dyspnea, patients were classified as improved, unchanged, or worsened. All assessable patients who completed 2 months of treatment were included in the efficacy (per-protocol) analysis.

Results

A total of 120 patients (70 men and 50 women> with a mean age of 61.8 * 8.6 years (range, 30 to 70 years) were enrolled in 10 centers. Of these patients, 20 were excluded from the efficacy analysis, 17 having violated protocol (use of prohibited concomitant treatments, poor compliance, NYHA Class IV [any physical activity brings on discomfort, and symptoms also occur at rest; confined to bed or chair]) and 3 having dropped out before the a-month treatment period ended (lost to follow-up [ll, adverse events [2]) (Table I). Thus the per-protocol sample comprised 100 patients, while 120 patients entered the safety analysis. Baseline characteristics of the two patient populations are shown in Table II.

Efficacy

After 14 days of treatment, the dose of torsemide was reduced to 5 mg fd in 50 patients and increased to 20 mgld in 16 patients; 50 patients continued to receive 10 mg/d. After the first month, only 1 patient required further reduction, from 20 mg/d to 10 mg/d.

Table 1: Baseline characteristics of patients assessable for safety and efficacy analyses.

Characteristics	Efficacy Analysis (N = 120)	Efficacy Analysis (N = 100)
Sex		
Male	70	60
Female	50	40
Age (Y)*	61.8±8.6	61.7±8.8
Body weight (kg)*	74.2±10.4	74.5±10.8
Height (cm)*	166.4±7.8	166.9±7.9
Smokers, n		
No	100	85
Yes	20	15
Medical history, n		
Essential hypertensron	64	60
Myocardial infarction	62	58
Chronic ischemic heart disease	60	55
Atrial fibrillation	20	22
Cardiomyopathy	32	35
Cardiomegaly	80	70
Congenital heart disease	40	30

Concomitant drugs, n (%)	14	14
Analgesic	7	0
Antiarrhythmic, class Ill	6	6
Antiasthmatic	0	4
Antihypertensive	37	35
Antithrombotic	1	1
Beta-blocker	25	22
Calcium channel blocker	17	50
Converting enzyme blocker	20	70
Digitalis		
NYHA Classification, n (%)	80	78
	65	60
Class Il	3	0
Class Ill		
Class IVt		

Table 2: Number (%) of patients included in the efficacy analysis (n = 100) who had signs and symptoms during the study period

	Baseline	Day 14	Day 30	Day 60
Cardiac enlargement	113	110	108	110
Congestive hepatomegaly	54	37	32	30
Cyanosis	6	6	6	6
Jugular vein distention	54	17	10	3
Pulmonary rales	87	34	12	7
Nocturnal coughing	34	18	5	4
Nocturia	66	46	37	35
Peripheral edema	78	48	30	22

Most signs and symptoms improved progressively throughout the study period (Table II).

All patients who received torsemide were included in the safety analysis. Torsemide therapy did not have a negative effect on laboratory findings. In particular, torsemide 5 to 20 mg/d for 2 months did not significantly affect serum electrolyte levels (Figure 5) or carbohydrate or lipid metabolism.

Discussion

In the present study, in patients with NYHA Class II to Class III CHF whose condition had been stabilized with digitalis or ACE inhibitors, torsemide5 to 20 mg/d had a beneficial effect on the clinical symptoms of CHF without affecting potassium serum levels. Eight weeks of torsemide treatment improved NYHA functional class in 44% of patients, especially those with more severe CHF. Our results are partially consistent with previous reports [14,15] that demonstrated the efficacy of 4 weeks of treatment with

torsemide 5 or 10 mg/d in improving mean NYHA functional class. However, these studies also describe slight decreases in serum potassium concentration of 0.11 mmol/L and 0.27 mmol/L after administration of 5 or 10 mg of torsemide, respectively; in contrast, we found no such decrease in serum potassium concentration after 8 weeks of torsemide therapy. This latter observation is noteworthy, because it is well known that excessive potassium loss can trigger life-threatening arrhythmias, especially in patients with CHF who are receiving concomitant digitalis therapy.

We detected a decrease in pulmonary congestion accompanied by a reduction in pulmonary rales. Body weight and peripheral edema showed statistically significant decreases during the study period, confirming the positive action of torsemide on fluid mobilization. These effects on the signs of CHF also occurred in the 84 patients who did not experience improvement in NYHA class.

Most patients were responsive to 10 mg/d; 20 mg/d was required to achieve an adequate response in ll%, and the initial dose of 10 mg/d was reduced to 5 mg/d in the remaining. Our data support the use of torsemide 5 mg ld as a starting dose in patients with CHF, with the dose increased to 10 mg/d or even 20 mg/d if symptoms do not improve.

Overall, as reported in other studies, [14-17] the incidence of adverse events with torsemide treatment was low. Only nine patients (5.3%) reported adverse events; the relationship of these events with the study drug could not be determined definitively in the presence of concomitant therapies. [18]

Two patients withdrew from treatment; one required hospitalization for suspected hepatoma, and the otherhad persistent left ventricular failure and multiple episodes of dizziness.

Conclusion

The present study demonstrates that torsemide is well tolerated, effective in treating moderate CHF, and useful when administered with digoxin or ACE inhibitors to reduce the signs and symptoms of CHF.

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