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Omapatrilat in patients with hepatic cirrhosis

Pharmacodynamics and pharmacokinetics

Received: 12 July 2000 / Accepted in revised form: 14 February 2001 / Published online: 25 April 2001
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Abstract Objective: The pharmacodynamics and pharmacokinetics of omapatrilat, a member of a new class of cardiovascular compounds, the vasopeptidase inhibitors, were evaluated in subjects with hepatic cirrhosis (n = 10) and in healthy subjects (n = 10) matched for age, weight, gender and smoking history.

Methods: All subjects received omapatrilat 25 mg orally once daily for 14 days. Plasma renin and urinary atrial natriuretic peptide (ANP) levels were measured to assess the effect of omapatrilat on cirrhotic subjects. The effect of omapatrilat on blood pressure as well as changes in ANP and plasma renin levels were not altered by hepatic impairment. Pharmacokinetic parameters were determined from plasma omapatrilat concentrations.

Results: There were no significant differences between the two subject groups with regard to log-transformed area under the curve or maximum observed plasma concentration. Systemic accumulation was similar in the two groups.

Conclusion: These results suggest, based on findings in otherwise healthy cirrhotic subjects, that no adjustment of standard dosing regimens is indicated for hypertensive patients with mild to moderate cirrhosis.

Keywords Omapatrilat · Vasopeptidase inhibitors · Pharmacokinetics

Introduction

The renin–angiotensin–aldosterone system (RAAS) plays an important role in the regulation of extracellular fluid volume and blood pressure. Activation of the RAAS leads to the release of renin, followed by the production of angiotensin I, which is then converted to the active hormone angiotensin II by angiotensin-converting enzyme (ACE). Patients with chronic liver disease often exhibit increased plasma renin activity [1, 2]. Schrier et al. showed that peripheral arterial vasodilation is one of the earliest clinical findings in patients with hepatic cirrhosis, as a result of enlargement of the intravascular compartment [3]. This is followed by a rise in cardiac output and transient renal sodium and water retention to fill the intravascular compartment. At this stage, total blood volume is expanded, cardiac output is increased and peripheral arterial vasodilation is present. They proposed two possible stimuli for increased renin secretion: plasma volume expansion followed by inadequate normalisation of renal haemodynamics, plasma renin, aldosterone, norepinephrine and vasopressin concentrations; or the activation of baroreceptors through contraction of an “effective” circulatory compartment [3].

Vasopeptidase inhibitors (VPIs) are a new class of cardiovascular compounds currently under investigation for the treatment of hypertension and heart failure. VPIs, in a single molecule, simultaneously inhibit neutral endopeptidase (NEP) and ACE, producing regulation of the cardiovascular system through restoration of the balance between vasodilation and vasoconstriction [4]. Several benefits can be obtained from simultaneous inhibition of these enzymes. Inhibitory control of NEP and ACE independently prevents activation of the RAAS, leading to suppression of plasma and tissue ACE, elevation of plasma renin and reduction of aldosterone formation. At the same time, increased natriuretic peptide levels result in vasodilation, sodium excretion, inhibition of sympathetic nervous activity and decreased vascular smooth muscle growth. Combined NEP and ACE inhibition has an additive effect on bradykinin elevation in plasma, tissues and urine since both enzymes are involved in bradykinin breakdown [4, 5, 6].
Omapatrilat (BMS-186716) is currently under clinical investigation. The inhibitory constants for NEP and ACE indicate high equipotent inhibitory activity against both enzymes [7]. Oral doses of omapatrilat produce a dose-dependent increase in the urinary excretion of atrial natriuretic peptide (ANP) [8, 9]. In normal volunteers, urinary and plasma cyclic guanosine monophosphate (cGMP) elevation further support NEP inhibition [8, 9]. Omapatrilat has produced significant decreases in plasma/serum ACE activity and plasma angiotensin II levels in healthy volunteers, confirming this drug’s ability to inhibit ACE [7, 8, 9]. Omapatrilat also produces a marked elevation in plasma renin levels [10].

The pharmacokinetic profile of omapatrilat in healthy male volunteers and patients with renal impairment has been determined [11, 12]. Omapatrilat is rapidly absorbed, with a time of maximal concentration (t_{max}) of 2 h and 30% bioavailability [data on file, Bristol-Myers Squibb Co. (BMS), Princeton, New Jersey, USA, 1996]. Single oral doses up to 500 mg and repeated doses up to 125 mg once daily for 10 days were generally well tolerated and demonstrated rapid oral absorption and a prolonged elimination profile [11]. Oral doses of omapatrilat were extensively metabolised, primarily by formation of disulfide linkages with endogenous thiols and through amide hydrolysis, S-methylation and S-oxidation [12] (Fig. 1). This metabolic pathway is similar to what has been seen with the ACE-inhibitor captopril [13]. The effective half-life (t_{1/2}) of omapatrilat is 14–19 h [11]. The volume of distribution of omapatrilat is high, indicative of extensive extravascular drug distribution [11] (B. Malhotra et al., unpublished observations).

Hepatic cirrhosis is known to activate the RAAS and increase plasma renin activity. Inhibition of ACE has been shown to increase plasma renin levels via an angiotensin II feedback mechanism. The purpose of this study was to determine whether the effectiveness of omapatrilat, as measured by response in blood pressure and changes in ANP and plasma renin levels, was altered by hepatic impairment and whether adjustment of the dosing regimen should be recommended for patients with cirrhosis.

**Materials and methods**

**Subjects**

This was a multiple-dose, open-label, parallel-group study of ten healthy subjects and ten subjects with hepatic cirrhosis. Medical history and liver biopsy (or laparoscopy) were used to confirm hepatic cirrhosis. The disease status of subjects with hepatic cirrhosis was either Childs-Pugh class A (five patients) or class B (five patients). Cirrhotic patients were matched for age, weight, gender and smoking history with a group of healthy subjects. All subjects were required to give written informed consent prior to participation in the study. An ethics committee (Ethik-Kommission bei der Landessärztekammer Hessen) approved the protocol and informed consent.

Inclusion criteria for healthy and cirrhotic subjects were the same except for hepatic disease-related parameters. All laboratory values were to be normal (with the exception of hepatic disease-related parameters for the cirrhotic subjects). Cirrhotic patients were to receive standard therapy for cirrhosis-related diseases. Use of pre-study concomitant drugs was recorded for the cirrhotic patients, and the dosages of these drugs were not changed in the 14 days before study start.

Exclusion criteria for healthy subjects were as follows: nursing or pregnant women; history or evidence of cardiovascular, hepatic, renal, pulmonary, neuromuscular, haematopoietic, metabolic, or allergic disease; evidence of organ dysfunction; history of serious allergy or asthma; use of any drugs (including over-the-counter preparations) in the 30 days before the first dose of omapatrilat;

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**Fig. 1** Chemical structures of major metabolites of omapatrilat

![Chemical structures of major metabolites of omapatrilat](image)