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Pharmacokinetics of Mebudipine, a New Calcium Antagonist, Following Single Intravenous and Oral Administrations in Rats

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ABSTRACT: The pharmacokinetics of a new calcium antagonist, mebudipine, was studied after a single intravenous (0.5 mg/kg) and oral (10 mg/kg) administration to rats. After intravenous dosing, the plasma concentration of mebudipine declined biexponentially with a terminal half-life of 2.84 h. The blood clearance was 1.67 l/h/kg and the volume of distribution at steady state was found to be 6.26 l/kg. After oral dosing (10 mg/kg), the C_{max} of mebudipine was 25.9 ± 9.79 ng/ml. The oral bioavailability was low ($< 2\%$) suggesting a marked first-pass effect. The distribution of mebudipine into some tissues such as brain, heart, liver and kidney following intravenous administration (0.5 mg/kg) was studied and a rapid distribution of mebudipine into these tissues was found. It was concluded that brain, heart, liver and kidney are in the same compartment as plasma (central). Copyright © 2004 John Wiley & Sons, Ltd.

Key words: mebudipine; pharmacokinetics; HPLC; rat

Introduction

Mebudipine [(±)-t-butyl, methyl-1, 4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate] is a new 1, 4-dihydropyridine derivative, a calcium channel antagonist developed in our laboratories [1]. Previous studies have shown that mebudipine had some advantages over nifedipine, such as a longer biological half-life, longer time to reach maximum effect and more vasoselectivity [1, 2], and shows a higher potency in inhibiting the calcium evoked spikes in *Helix aspersa* [3]. In a previous study, a simple HPLC method was developed for the assay of mebudipine in plasma and its usefulness in a pharmacokinetics study was shown in rabbits after a single intravenous injection [4]. The plasma concentration versus time curve of mebudipine showed a typical two-compartmental decay after intravenous administration in rabbits [4].

In this paper, the pharmacokinetics of mebudipine was examined in rats after a single intravenous dose or oral administration using a previously established chromatographic method.

Materials and Methods

Chemicals

Mebudipine was synthesized in our laboratories [1]. All other chemicals were of HPLC or analytical grade.

Animal study

Male Sprague-Dawley rats (200 ± 25 g) were used. They were allowed free access to food and water during housing, but were fasted overnight before the study. The drug was

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