Clinical Pharmacokinetics of Mibefradil

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Abstract

Mibefradil, a tetralol derivative, is a new long-acting calcium antagonist used for the treatment of patients with hypertension and chronic stable angina pectoris. The drug is virtually completely metabolised, with less than 3% of an oral dose excreted unchanged in urine. Its metabolism occurs via parallel pathways, which fall into 2 broad categories: esterase-catalysed hydrolysis (producing the major plasma metabolite) and cytochrome P450 (CYP) 3A4–mediated oxidation.

Plasma protein binding is greater than 99.5%, predominantly to $\alpha_1$-acid glycoprotein. Oral multiple dose administration of mibefradil 50 or 100mg once daily is associated with inhibition of the CYP3A4 pathway of metabolism, increasing the half-life and bioavailability of the parent compound. The intensity of the
Mibefradil belongs to a new class of calcium antagonist, the tetralol derivatives. At the recommended dosage of 50 or 100mg once daily, this compound is effective in the treatment of patients with hypertension and chronic stable angina pectoris. Unlike traditional calcium antagonists, mibefradil selectively blocks T-type (transient, low-voltage–activated) calcium channels.\[1,2\] It dilates peripheral and coronary vessels, resulting in a reduction in arterial pressure and peripheral vascular resistance, and an increase in coronary artery blood flow.\[3\]

Treatment with mibefradil is associated with a moderate, dose-dependent decrease in heart rate, probably due to blockade of T-type calcium channels in pacemaker cells in the sinoatrial node.\[4\] Unlike some other calcium antagonists, mibefradil lacks a negative inotropic effect on the myocardium at therapeutic plasma concentrations.\[5,6\] Atrioventricular nodal conduction time appears to be affected minimally at therapeutic doses.\[7\] It does not produce reflex tachycardia, as commonly seen with dihydropyridine calcium antagonists, and is not associated with significant increases in plasma neurohormonal levels.\[7\]

The purpose of this review is to focus on the clinical pharmacokinetic properties of mibefradil. To achieve this, other relevant properties of the drug are also discussed: drug elimination pathways, plasma protein binding and drug interactions. The complexity of the drug interactions recently resulted in a voluntary withdrawal of mibefradil from the market.

1. Analytical Methods

A sensitive and specific assay has been developed to study the pharmacokinetics of mibefradil.\[8\] The assay involves liquid-liquid extraction of a biological sample, reversed-phase high performance liquid chromatography (HPLC) separation and fluorescence detection (excitation $\lambda = 270$nm and emission $\lambda = 300$nm) of sample components. Each sample was eluted with a mobile phase flow-rate of 2 ml/min (0.12 L/h). The mobile phase comprised 38:62 v/v acetonitrile and aqueous solution (KH$_2$P$_4$ 39.3 mmol/L and sodium-pentanesulphonic acid 8.2 mmol/L). Retention times were 10.7 minutes for mibefradil and 12.2 minutes for the internal standard Ro 40-6792. The calibration curves with concentrations of mibefradil ranging from 10 to 500 $\mu$g/L were linear ($r^2 > 0.99$). The detection limit for mibefradil was 0.5 $\mu$g/L when 0.5ml of plasma or urine was used.

2. Metabolism

In general, less than 3% of an oral dose of mibefradil is recoverable unchanged in urine, and elimination is almost exclusively by metabolism. Figure 1 illustrates the major metabolites of mibefradil circulating in plasma following administration to humans. These were identified using chromatographic methods and mass spectroscopy. The metabolism of mibefradil occurs via parallel pathways, which can be divided into 2 broad categories: esterase-catalysed hydrolysis and cytochrome P450 (CYP) 3A4–mediated oxidation. Oxidative metabolism by other isoforms of CYP is negligible. Hydrolysis of the side-chain produces Ro 40-5966