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Metabolism of the dihydropyridine calcium channel blockers mebudipine and dibudipine by isolated rat hepatocytes

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Abstract

The prototype 1,4-dihydropyridine (1,4-DHP) nifedipine, indicated for the management of hypertension and angina pectoris, has drawbacks of rapid onset of vasodilating action and a short half-life. Several newer analogues have been designed to offset these problems and these include mebudipine and dibudipine. These analogues contain *t*-butyl substituents that have been selected to alter the fast metabolism without altering pharmacological activity. In this study, the metabolism of mebudipine and dibudipine by isolated rat hepatocytes has been investigated. These compounds were extensively metabolized in 2 h by oxidative pathways, analogous to those known for nifedipine, and by *O*-glucuronidation after hydroxylation of the *t*-butyl substituents. The in-vitro half-lives of mebudipine (22 ± 7.1 min) and dibudipine (40 ± 9.8 min) were significantly longer than that of nifedipine (5.5 ± 1.1 min), which was investigated in parallel in this study. These newer 1,4-DHPs address the problem of the short half-life of nifedipine and have potential for further development in view of their comparable potency to nifedipine.

Introduction

The 1,4-dihydropyridines (1,4-DHPs) inhibit the trans-membrane influx of calcium ions into cardiac and vascular muscle cells and are indicated in the management of hypertension and angina pectoris (Roden 2001). The prototype, nifedipine (see Figure 1), is clinically effective but has a number of undesirable pharmacokinetic and pharmcodynamic properties, which include a rapid onset of vasodilating action, a short half-life and side effects such as reflex tachycardia, flushing, headache and dizziness (van Zwieten et al 1993; Borchard 1994). Nifedipine undergoes significant first-pass metabolism to highly soluble inactive metabolites. Several newer 1,4-DHP analogues, which seek to overcome these undesirable properties, have been developed and include amlodipine, felodipine, lacidipine, nicardipine, nitrendipine and barnidipine (Roden 2001).

Recently, we reported the synthesis of two new 1,4-DHP calcium channel blockers, mebudipine (see Figure 3) and dibudipine (see Figure 2) (Mahmoudian et al 1997). These compounds contain *t*-butyl substituents selected to decrease the fast metabolism of the 1,4-DHPs without altering their pharmacological activity. The incorporation of *t*-butyl substituents, as in terfenadine, has been used previously in drug development to manipulate the pharmacological half-life with some success. The half-life of the di (*t*-butyl) substituted dibudipine (2.5 h) determined in-vivo in the rat was longer than those of other DHPs such as nicardipine (0.1 h), benidipine (0.5 h), nisoldipine (0.4 h), nitrendipine (1.3 h), felodipine (1.5 h) and nilvadipine (1.3 h) (Teramura et al 1997) and comparable with that of the long-acting amlodipine (Stopher et al 1988). Also in a previous study, the pharmacological potencies of mebudipine and dibudipine were evaluated by studying their effects on guinea-pig isolated ileum and the pIC50 values for the inhibition of the contractile response to electrical stimulation were found to be similar to that of nifedipine (Mahmoudian et al 1997). The compounds also antagonize the contractile responses of K^+ depolarized guinea-pig ileum to cumulative concentrations of calcium with the inhibitory effects in the order mebudipine > nifedipine = dibudipine. The vasorelaxant actions of mebudipine and dibudipine have been reproduced in a human vascular preparation (Mahmoudian et al 1999).

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