The effect of nisoldipine on apparent liver blood flow and effective renal plasma flow

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The effects of the acute and continued administration of the calcium antagonist nisoldipine on hepatic and renal blood flow and on renal function were studied in nine normotensive volunteers. There were no significant changes in supine blood pressure or heart rate but acute administration significantly increased both apparent liver blood flow and effective renal plasma flow. With continued administration these increases were attenuated and were not significantly different from placebo after 4 days treatment. Acute nisoldipine administration was also associated with significant increases in glomerular filtration rate and urinary sodium excretion.

Keywords nisoldipine liver and renal blood flow calcium antagonist

Introduction

As a group, calcium antagonist drugs cause dilatation of vascular smooth muscle. The individual calcium channel blockers are of diverse chemical structure and exhibit considerable variation in their affinities for non-vascular tissues, for different vascular beds and for arteries and veins. The dihydropyridine derivative, nifedipine, has been shown to increase significantly apparent liver blood flow when administered acutely (Feely, 1984). Similarly, both nifedipine and nifedipine intravenously (Yokoyama & Kaburagi, 1981, 1983) have been shown in clinical studies to increase renal blood flow. Recently we have reported that the acute administration of the calcium channel blocker, verapamil, caused a profound, significant increase in apparent liver blood flow but that with continued administration this increase was attenuated and was no longer significant. (Meredith *et al.*, 1985). The present study investigates the effect on hepatic and renal blood flow of acute and chronic administration of nisoldipine, a new dihydropyridine derivative calcium antagonist which, like nifedipine, is a relatively selective peripheral arteriolar vasodilator.

Methods

Nine male normotensive volunteers (aged 22–40 years; weight 52–76 kg) participated in the study which was approved by the Research and Ethics Committee of the Northern District of the Greater Glasgow Health Board. The subjects were studied on three separate days: with placebo, acute nisoldipine (20 mg) and a further dose of nisoldipine (20 mg) following 3 days of nisoldipine treatment (20 mg daily). Active drug and placebo were administered orally following an overnight fast. The placebo study day also formed part of a study of verapamil and has previously been described in full (Meredith *et al.*, 1985). Apparent liver blood flow was assessed from the clearance of indocyanine green (ICG) administered intravenously (0.5 mg kg⁻¹ body weight) by bolus injection, 1 h after drug dosing. Plasma ICG concentrations were determined by a spectrophotometric method (Svensson *et al.*, 1983) and apparent liver blood flow was calculated as previously described (Meredith *et al.*, 1985).

Effective renal plasma flow and glomerular filtration rate were estimated by determining the clearance of [¹²⁵I]-hippuran and [⁵¹Cr]-EDTA

respectively. The radiolabelled compounds were administered simultaneously by bolus i.v. injection 1 h after drug or placebo administration. The calculations were as detailed previously (Meredith *et al.*, 1985).

Student's paired *t*-test with Bonferroni correction where appropriate, was used for all comparisons. Results are expressed throughout as mean $\pm$ s.d.

Results

Acute administration of nisoldipine was associated with a significant ($P < 0.01$) increase in apparent liver blood flow, to 1310 ± 244 ml min⁻¹, when compared to placebo, 945 ± 219 ml min⁻¹ (Figure 1). However, with continued administration apparent liver blood flow returned towards placebo values at 1154 ± 214 ml min⁻¹ (Figure 1). There were no significant changes in the volume of distribution of ICG with acute and continued nisoldipine administration. Effective renal plasma flow exhibited a similar pattern to that observed in apparent liver blood flow, with a significant ($P < 0.01$) increase after acute

administration but a reduction towards placebo values with continued dosing (Figure 2). Glomerular filtration rate (GFR) was significantly ($P < 0.01$) increased to 123 ± 14 ml min⁻¹ with acute nisoldipine when compared to placebo values of 111 ± 15 ml min⁻¹. With continued administration the glomerular filtration rate (115 ± 17 ml min⁻¹) was not significantly different from placebo. The increase in GFR with acute administration of nisoldipine was paralleled by a significant ($P < 0.05$) increase in 24 h urinary sodium excretion (208 ± 39 mmol 24 h⁻¹ compared to 168 ± 68 mmol 24 h⁻¹ for placebo) which returned to placebo levels with continued administration (152 ± 41 mmol 24 h⁻¹).

Discussion

This study provides further evidence that the calcium antagonists cause increases in regional blood flow (Feely, 1984; Yokoyama & Kaburagi,

Figure 1 Effects on apparent liver blood flow of placebo, acute nisoldipine (20 mg) and after 4 days of nisoldipine.

Figure 2 Effects on effective renal plasma flow of placebo, acute nisoldipine (20 mg) and after 4 days of nisoldipine.

1981, 1983). Furthermore the present findings support our previous observations with verapamil (Meredith *et al.*, 1985) that the significant increases in hepatic and renal blood flow are associated with acute administration and are attenuated with continued drug administration. In contrast the effects of nisoldipine on systemic vascular responsiveness to the intravenous administration of angiotensin II and pressor catecholamines have been shown to be greater after 3 days dosing than after acute administration (Pasanisi *et al.*, 1985).

It is recognised that alterations in liver blood flow may significantly affect drug bioavailability and clearance (George, 1979). It is thus important to consider potential pharmacokinetic interactions if calcium antagonists are administered acutely with other drugs. We have recently

described such an interaction between prazosin and verapamil (Pasanisi *et al.*, 1984) in which, in comparison to the administration of prazosin alone, the co-administration of verapamil with prazosin resulted in increased peak blood levels and bioavailability of prazosin. This observation is consistent with increased hepatic and splanchnic blood flow. Whilst increased liver blood flow is an important determinant of the clearance of lipophilic drugs, it remains to be seen whether the observed increases in renal plasma flow and glomerular filtration rate with acute nisoldipine administration will significantly affect the renal elimination of co-administered polar drugs. The potential interaction involving drugs co-administered with calcium antagonists warrants further investigation.

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