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Human Pharmacokinetics of Orally Administered (24 *R*)-Hydroxycalcidiol

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Summary: To gain an insight in the regulation of (24*R*)-hydroxycalcidiol, we studied the pharmacokinetics of orally administered (24*R*)-hydroxycalcidiol in 6 healthy subjects without calcium supplementation, in 4 healthy subjects with calcium supplementation and in 6 patients with primary hyperparathyroidism. Various quantities related to calcium and vitamin D metabolism were also monitored.

In the healthy subjects without calcium supplementation, the basal (24*R*)-hydroxycalcidiol concentration (C_b) in serum was 2.4 ± 0.8 nmol/l (mean ± SD, n = 5), the terminal serum half-time ($t_{1/2}$) 7.2 ± 1.4 days, the production rate 0.05 ± 0.01 nmol/kg · day, and the production rate/[calcidiol] ratio (1.5 ± 0.4 × 10^{-3} l/kg · day). In the healthy subjects studied, the serum concentration vs time curves exhibited a second maximum after administration, possibly due to binding by intestinal cells or (partial) uptake by the lymph system. In the calcium-supplemented healthy subjects, the pharmacokinetic quantities were not significantly different while the area under the serum concentration-time curve and the estimated bioavailability were significantly decreased.

Basal concentration (C_b), production rate and the production rate/[calcidiol] ratio were significantly lower in patients with primary hyperparathyroidism but $t_{1/2}$ was unchanged.

Exogenous (24*R*)-hydroxycalcidiol had no clear effect on calcium and vitamin D metabolism.

In conclusion,

a) exogenous (24*R*)-hydroxycalcidiol has no clear effect on calcium and vitamin D metabolism,

b) clearance and production rate of (24*R*)-hydroxycalcidiol are not affected by calcium supplementation,

c) bioavailability is lower in the calcium-supplemented state,

d) basal concentration (C_b) and production rate are significantly decreased in patients with hyperparathyroidism.

Introduction

It is generally accepted that calcitriol (1α,25-dihydroxycholecalciferol) represents the biologically active metabolite of vitamin D_3 (1), while the function of (24*R*)-hydroxycalcidiol is still controversial. Human pharmacokinetics of (24*R*)-hydroxycalcidiol have been studied (2–5), but only one of these studies yielded reliable estimates for its clearance and production rate (5). In vitro and in vivo studies have demonstrated that the activity of rat 24-hydroxylase is modulated by parathyroid hormone (parathyrin) (6–8), calcitriol (7–11), dietary calcium (7, 10–13), and phosphorus (7, 10). Hence, production rate or clearance of (24*R*)-hydroxycalcidiol may be determined by these factors and may reflect abnormalities of calcium and vitamin D_3 metabolism.