Clinical pharmacokinetics of the nifedipine/co-dergocrine combination in impaired liver and renal function

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SUMMARY

Following a single oral dose of 20 mg nifedipine combined with 2 mg co-dergocrine to 24 subjects, the pharmacokinetics of this drug were studied. 8 normotensive subjects had normal renal and hepatic function, 8 patients had chronic renal insufficiency (creatinine clearance < 30 ml.min⁻¹) and 8 patients had liver cirrhosis which was confirmed by liver biopsy. The area under the plasma level time curve (AUC∞) of co-dergocrine increased from 0.59 ± 0.41 ng.ml⁻¹.h (mean ± SD) in the normals to 1.24 ± 0.95 ng.ml⁻¹.h in liver cirrhosis (P < 0.05) and to 1.81 ± 0.9 ng.ml⁻¹.h in renal failure (P < 0.05 compared with the control group). Corresponding values for the nifedipine AUC∞ were 564.5 ± 268 ng.ml⁻¹.h, 1547.5 ± 1134 (P < 0.05) and 929 ± 533 ng.ml⁻¹.h (P < 0.05; gas chromatographic method). The incidence of adverse effects was lower in patients with renal failure than in subjects with normal renal and liver function as well as in those with liver cirrhosis.

INTRODUCTION

Co-dergocrine is a mixture of hydrogenated ergot alkaloids widely used as an antihypertensive agent in some European countries (1–7). From early investigations in the 40s it was presumed that its blood pressure lowering effect in experimental animals (8) was due to α-adrenergic blockade. Recent analysis of its pharmacology, however, proved the cardiovascular response to low doses of co-dergocrine being due to stimulation of pre-junctional dopamine-D₂-receptors and a reduction of noradrenaline release (9). This has been confirmed in normal subjects (2), as well as in hypertensive patients (3, 10).

Treatment with the dihydropyridine nifedipine often leads to stimulation of the sympathetic nervous system and to increased levels of plasma noradrenaline both after acute and chronic use (10, 11). Therefore, from the pharmacological point of view, the combination of co-dergocrine and nifedipine is reasonable and should lead to an additive antihypertensive activity of both components and a reduction of dihydropyridine-specific adverse effects, like headache and tachycardia. Patients with arterial hypertension frequently suffer from concomitant diseases with organ damage, specifically from renal failure. Thus, the aim of the present study was to investigate pharmacokinetics and tolerability of the nifedipine/co-dergocrine combination in patients with impaired renal and liver function, comparing them with the data of healthy subjects.
MATERIALS AND METHODS

Subjects

24 subjects were investigated (17 male, 7 female) after they had given their informed written consent to participate in the study. The study protocol was approved by a local hospital ethics committee. 8 normotensive subjects had normal liver and renal function (creatinine clearance $\geq 90$ ml.min$^{-1}$, mean $110.6 \pm 12.5$ ml.min$^{-1}$, antipyrine clearance $>35$ ml.min$^{-1}$, mean $46.4 \pm 5.7$ ml.min$^{-1}$, age $46 \pm 10$ years, body weight (b.w.) $71 \pm 9$ kg; x ± SD). 8 patients suffered from liver cirrhosis proven by biopsy (mean antipyrine clearance $25.5 \pm 12.2$ ml.min$^{-1}$, mean creatinine clearance $98.8 \pm 6.9$ ml.min$^{-1}$; age $49 \pm 12$ years; b.w. $71 \pm 7$ kg). 8 patients had chronic renal insufficiency (mean creatinine clearance $23.9 \pm 4.3$ ml.min$^{-1}$; age $61 \pm 8$ years; b.w. $62 \pm 9$ kg). The three groups of subjects studied did not differ significantly in the parameters of age and body weight. All subjects had no signs of gastrointestinal, endocrine or pulmonary disease. They were treated with a single oral dose of 2 mg co-dergocrine plus 20 mg nifedipine in a new sustained-release-form (Pontuc®, Sandoz AG, Niirnberg, Germany) (2 tablets ingested with 100 ml water). 30 min afterwards, a standardized breakfast was allowed. Blood samples for estimation of co-dergocrine and nifedipine plasma levels were taken before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 36 h afterwards. At the time of blood sampling, blood pressure and heart rate of the subjects investigated were measured.

Assays

Co-dergocrine plasma levels were determined by a new specific radioimmunoassay (12, 13) which recognizes the 5'-aliphatic side chain of the tricyclic peptide moiety of dihydroergocornine and dihydroergocriptine and the 5'-aromatic side chain of the peptide moiety of dihydroergocristine.

None of the identified metabolites of co-dergocrine showed any cross-reactivity to the sera, which is specific for the 5' aliphatic side chain of the tricyclic peptide moiety of dihydroergocristine. The limit of detection was 10 pg.ml$^{-1}$, the interassay variability was 8.4%, the intra-assay variability 5.4%. Nifedipine plasma levels were estimated by gas chromatography (GC) (14).

The limit of detection was 0.5 ng.ml$^{-1}$ the inter-assay variability 7.6% and the intra-assay variability was 7.8%. In GC the metabolites of nifedipine were separated from nifedipine. Nifedipine and co-dergocrine are both non-racemic formulations, meaning that there are no relevant enantiomers which have to be detected in a kinetic study.

Computational analysis

The plasma concentration-time profiles were analyzed by standard non-linear regression techniques. As software, ‘PCNONLIN’ (15) was used. Initially the curves were fitted with a weighting factor of 1/C to an open one-compartment pharmacokinetic model described by the following equation:

$$C = \frac{D/V \cdot K01}{(K01 - K10) \cdot (\exp(-K10 \cdot t) - \exp(-K01 \cdot t))}$$

Table I: Intra-individual comparison in healthy volunteers: pharmacokinetics (x ± SD) of nifedipine and co-dergocrine. (Interaction study of nifedipine and co-dergocrine prior to this study)

<table>
<thead>
<tr>
<th>Combination</th>
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<tbody>
<tr>
<td>Co-dergocrine* 4 mg</td>
<td>Nifedipine† 40 mg</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>1.61 ± 1.65</td>
</tr>
<tr>
<td>C_{max} (pgeq.ml$^{-1}$)</td>
<td>433 ± 150</td>
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<tr>
<td>AUC (pgeq.ml$^{-1}$ h)</td>
<td>2308 ± 546</td>
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Relative bioavailability

Analytical methods: nifedipine HPLC (8), co-dergocrine RIA (6b). For abbreviations, see Table II

*new slow release form

**standard slow release form (Adalat® retard)