Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients

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- 1 The single dose pharmacokinetics of orally administered nimodipine (60 mg) were investigated in normal subjects and in two groups of epileptic patients receiving chronic treatment with hepatic microsomal enzyme-inducing anticonvulsants (carbamazepine, phenobarbitone or phenytoin) and sodium valproate, respectively.
- 2 Compared with the values found in the control group, mean areas under the plasma nimodipine concentration curve were lowered by about seven-fold ($P < 0.01$) in patients taking enzyme-inducing anticonvulsants and increased by about 50% ($P < 0.05$) in patients taking sodium valproate.
- 3 Nimodipine half-lives were shorter in enzyme-induced patients than in controls (3.9 ± 2.0 h vs 9.1 ± 3.4 h, means $\pm$ s.d., $P < 0.01$), but this difference could be artifactual since in the patients drug concentrations declined rapidly below the limit of assay, thus preventing identification of a possible slower terminal phase. In valproate-treated patients, half-lives (8.2 ± 1.8 h) were similar to those found in controls.

Keywords nimodipine dihydropyridine calcium channel blockers pharmacokinetics anticonvulsants epilepsy drug interaction

Introduction

Nimodipine is a dihydropyridine calcium channel blocker which relaxes the cerebrovascular musculature preferentially to the systemic vasculature and is effective in the management of subarachnoid haemorrhage and ischaemic stroke (Langley & Sorkin, 1989). Apart from its vascular action, nimodipine is known to be a potent antagonist of transmembrane calcium influx in cerebral neurons. Since disturbances in neuronal calcium conductance have been implicated in the generation and propagation of seizure activity (Schmidt & Ried, 1989), many investigators have assessed the potential anticonvulsant action of nimodipine in animal models, demonstrating that the drug is effective in preventing and/or suppressing seizures induced by a wide variety of chemical (Dolin *et al.*, 1986; Meyer *et al.*, 1987; Morocutti *et al.*, 1986; Paczynsky *et al.*, 1990) and physical (De Sarro *et al.*, 1988; Meyer *et al.*, 1990) stimuli. Preliminary clinical observations support the hypothesis that nimodipine may exert valuable therapeutic effects in patients with seizure disorders (Brandt *et al.*, 1988; De Falce *et al.*, 1989).

Prior to the initiation of formal clinical trials on the

potential antiepileptic efficacy of nimodipine, it was considered important to assess whether its pharmacokinetics are affected by concomitant treatment with conventional anticonvulsants. Among the latter, carbamazepine, phenytoin, phenobarbitone and primidone are potent inducers of the hepatic microsomal drug metabolizing enzymes (Perucca *et al.*, 1984) and cause by this mechanism a large number of clinically significant interactions (Perucca, 1982; Pisani *et al.*, 1990), including a reduction in the oral availability of drugs which, like dihydropyridines, undergo substantial first-pass metabolism (Capewell *et al.*, 1988; Perucca & Richens, 1979). Of the main drugs used in the long-term treatment of the major epilepsies, only valproic acid is devoid of enzyme-inducing properties (Perucca *et al.*, 1984), but a risk of interaction still exists because of the capacity of this compound to act as an inhibitor of oxidative (Kapetanovic *et al.*, 1981) and non-oxidative (Jawad *et al.*, 1987) drug metabolism.

The purpose of the present study was to compare the pharmacokinetics of nimodipine in normal subjects and

in two groups of epileptic patients receiving chronic treatment with enzyme-inducing anticonvulsants and valproic acid, respectively.

Methods

Study population

The study, which was approved by the Hospital Ethics Committee, was conducted in three groups of subjects:

Group I included eight normal drug-free control subjects (four male/four female) aged 21 to 27 years.

Group II included eight epileptic patients (four male/four female), aged 19 to 31 years and receiving long-term treatment for at least 4 months with enzyme-inducing anticonvulsants (carbamazepine, phenobarbital or phenytoin), either alone or in combination.

Group III included eight epileptic patients (four male/four female), aged 19 to 39 years and receiving long-term treatment for at least 4 months with sodium valproate monotherapy.

Details of the subjects and their drug treatment are given in Tables 1, 2 and 3. While sex and age distributions were similar in the three groups, body weights tended to be higher for patients on valproate. Exclusion criteria were a history of drug or alcohol abuse, smoking (> 10 cigarettes/day), and the presence of any pathological condition other than epilepsy. All subjects gave their written informed consent to take part in the study.

Study design

Each subject received in the morning, after a light continental breakfast, a single oral 60 mg dose of nimodipine (2×30 mg tablets) together with 30 ml water. No food or drinks were allowed until 4 h after dosing, when a light meal was given. Heparinized blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 h after drug administration. Since nimodipine is light-sensitive, all samples were drawn into glass tubes wrapped in aluminium foil and the plasma was separated immediately and stored at -20°C protected from light until assayed. All subjects were kept under close medical supervision throughout the study.

Drug assay

The concentration of nimodipine in plasma was measured by capillary gas chromatography with electron-capture detection according to Raemisch *et al.* (1986). The lower limit of the assay was 0.1 ng ml^{-1} allowing plasma nimodipine concentrations to be measured for at least 24 h in control subjects.

Pharmacokinetic and statistical analysis

The elimination of nimodipine from plasma could be described by bi- or multi-exponential functions but the distribution phase(s) could not be characterized accurately owing to the limited number of samples. Values of the terminal elimination rate constant (λ_z) were calculated by linear regression of the log-linear portion of the elimination phase. Half-lives were calculated from $0.693/\lambda_z$. Areas under the curves (AUC) and areas under the first-moment curve (AUMC) were calculated by the linear trapezoidal rule with extrapolation to infinity. Extrapolated areas (means $\pm$ s.d.) accounted for $5.8 \pm 7.7\%$ of the total AUC (corresponding values for individual groups were $2.9 \pm 2.0\%$ in controls, $11.5 \pm 11.6\%$ in patients receiving enzyme-inducers and $3.2 \pm 1.5\%$ in patients on valproate). Mean residence times (MRT) were calculated as AUMC/AUC .

Statistical evaluation of the differences between drug treated groups and controls was done using Dunnett's *t*-test for multiple comparisons.

Results

Following administration of the single oral dose, the absorption of nimodipine was relatively rapid, peak plasma concentrations being achieved within 1.5 h in control and enzyme-induced subjects and within 0.75 h in valproate-treated patients (Tables 1, 2 and 3). Thereafter, the concentration of the drug declined rapidly in all groups. As illustrated in Figure 1, in patients taking enzyme-inducing anticonvulsants the concentrations of nimodipine were markedly lower compared with those observed in normal subjects. In patients taking sodium valproate the opposite was observed.

Pharmacokinetic parameters for the subjects included

Table 1 Pharmacokinetic parameters derived from plasma nimodipine concentration curves following administration of a single oral dose of the drug (60 mg) in eight normal subjects

Subject	Sex	Age (years)	Weight (kg)	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	AUC ($\text{ng ml}^{-1}\text{ h}$)
1	F	21	49	22	1.50	8.5	6.4	70.7
2	F	27	53	8	1.50	4.2	5.0	31.4
3	F	24	60	26	0.75	12.8	8.6	48.4
4	F	27	55	18	1.50	4.5	5.8	47.7
5	M	26	89	68	0.75	9.6	6.8	149.4
6	M	26	76	73	0.50	11.0	4.4	71.0
7	M	26	78	27	0.50	13.4	7.9	51.8
8	M	25	83	68	0.50	8.6	4.8	73.2
Mean		25	68	39	0.94	9.1	6.2	67.9
$\pm$ s.d.		2	15	26	0.48	3.4	1.5	36.0

Table 2 Pharmacokinetic parameters derived from plasma nimodipine concentration curves following administration of a single oral dose of nimodipine (60 mg) in eight epileptic patients receiving enzyme-inducing antiepileptic drugs (AEDs)

Subject	Sex	Age (years)	Weight (kg)	Daily dose (mg) and serum concentration (μM) of AEDs	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	AUC ($\text{ng ml}^{-1} \text{h}$)
1	M	19	78	PB 100 (66)	2.4	1.00	2.9	3.7	7.2
2	F	21	55	PB 25 (28) CBZ 600 (31)	5.3	0.50	4.4	3.2	10.4
3	F	26	59	PB 100 (80)	13.5	0.50	6.5	4.8	23.8
4	F	22	65	PB 100 (74)	2.4	1.50	6.8	9.9	10.0
5	M	31	64	PB 100 (85)	2.9	1.00	2.7	3.6	7.8
6	M	24	70	PB 200 (150) CBZ 1200 (27)	1.9	0.75	3.9	5.6	4.6
7	F	31	45	CBZ 1200 (40) CLZ 30	2.7	1.50	2.5	3.6	7.8
8	M	28	70	CBZ 1400 (32) PHT 450 (36)	2.9	0.75	1.2	1.8	3.5
Mean		25	63		4.2**	0.94	3.9**	4.5	9.4**
$\pm$ s.d.		5	10		3.9	0.40	2.0	2.4	6.3

** $P < 0.01$ (vs controls).

Abbreviations: CBZ: carbamazepine, CLZ = clobazam, PB = phenobarbitone, PHT = phenytoin.

Table 3 Pharmacokinetic parameters derived from plasma nimodipine concentration curves following administration of a single oral dose of the drug (60 mg) in eight epileptic patients receiving sodium valproate (VPA)

Subject	Sex	Age (years)	Weight (kg)	Daily dose (mg) and serum concentration (μM) of VPA	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	AUC ($\text{ng ml}^{-1} \text{h}$)
1	M	19	71	1900 (606)	40	0.75	7.1	5.8	102.8
2	F	21	76	1000 (469)	34	0.75	5.8	4.3	67.6
3	F	18	67	1000 (522)	63	0.50	9.3	13.5	177.2
4	M	39	118	2000 (413)	38	0.50	10.3	8.8	91.9
5	F	18	80	1000 (461)	49	0.25	11.2	7.0	72.4
6	F	19	63	1000 (531)	49	0.50	6.8	6.0	73.8
7	M	29	68	2000 (654)	64	0.75	7.4	5.4	147.8
8	M	30	75	1000 (735)	43	0.75	7.7	5.7	105.9
Mean		24	77	1362 (549)	48	0.59	8.2	7.0	104.9*
$\pm$ s.d.		8	17	501 (107)	11	0.19	1.8	2.9	39.0

* $P < 0.05$ (vs controls).

Figure 1 a) Plasma nimodipine concentrations (means $\pm$ s.d.) following a single oral dose of the drug (60 mg) in normal subjects (●) and in epileptic patients receiving chronic therapy with enzyme-inducing anticonvulsants (Δ) or sodium valproate (○). b) Same data plotted on a semi-log scale. $n = 8$ for each group.

in the three groups are reported in Tables 1, 2 and 3. In patients receiving enzyme-inducing anticonvulsants the AUC of nimodipine was on average more than seven-fold lower than that found in normal subjects ($P < 0.01$). Conversely, in patients on valproate nimodipine AUC was about 50% higher than in the control group ($P < 0.05$), the difference being even greater (86% increase in AUC) when a control subject (subject 5) with an AUC value more than 2 s.d. above the group mean was excluded from the comparison. Terminal elimination half-lives and MRT values were shorter in enzyme-induced patients than in controls, the difference being statistically significant for the former parameter only. Half-lives and MRT values in patients on valproate were similar to those found in controls.

Discussion

The results show that in drug-treated epileptic patients plasma nimodipine concentrations differ considerably from those observed in normal volunteers given the same nimodipine dose. Although proof that these differences were caused by antiepileptic drug therapy would require a within-subject (longitudinal) study design, the similarity of age and sex distribution characteristics between patients and controls and the differential findings in relation to type of associated treatment (enzyme inducers vs valproate) strongly suggest that the changes in nimodipine pharmacokinetics observed in patients with epilepsy are due to the interaction with anticonvulsant drugs.

Nimodipine is a highly lipophilic compound which is rapidly and probably completely absorbed from the gastrointestinal tract (Meyer *et al.*, 1983; Raemisch *et al.*, 1984, 1985) followed by extensive hepatic first-pass metabolism through dehydrogenation to the pyridine analogue, oxidative *O*-demethylation, oxidative ester cleavage and hydroxylation. This results in a bioavailability of 5 to 28% (Langley & Sorkin, 1989). The

marked reduction in plasma nimodipine concentrations observed in patients taking enzyme-inducing agents (carbamazepine, phenobarbitone or phenytoin) may be explained by induction of pre-systemic metabolism. A marked reduction in oral bioavailability owing to induction of first pass-metabolism in anticonvulsant-treated epileptic patients has been described previously for many high-clearance drugs, including metyrapone (Meikle *et al.*, 1972), lignocaine (Perucca & Richens, 1979) and other dihydropyridine calcium channel blockers such as felodipine (Capewell *et al.*, 1988). An alternative explanation for the reduction in nimodipine bioavailability in our patients could be a decreased gastrointestinal absorption, possibly mediated by a change in bile acid concentration (Klaassen, 1971). Although this explanation is unlikely for a lipophilic drug like nimodipine, it is of interest that phenytoin has been reported to decrease the absorption of frusemide (Fine *et al.*, 1977) and cyclosporine (Rowland & Gupta, 1987), whereas phenobarbitone has been reported to impair the absorption of griseofulvin (Riegelman *et al.*, 1970).

The observation that the half-life of nimodipine was shorter in epileptic patients taking carbamazepine, phenobarbitone or phenytoin appears to support the hypothesis that enzyme induction was responsible for the reduced bioavailability. However, it should be noted that for high hepatic clearance drugs such as nimodipine the half-life is more dependent on liver blood flow than on microsomal enzyme activity (Perucca & Richens, 1979). An increase in liver blood flow in epileptic patients receiving enzyme inducing anticonvulsants has been reported (Pirttiho *et al.*, 1982), and could play a role in shortening the half-life of nimodipine. An alternative possibility is that the reduction of nimodipine half-life in enzyme-induced patients was artifactual and related to the fact that in many of these patients, as clearly shown in Figure 1b, the concentration of the drug fell rapidly below the limit of assay, resulting in inability to detect any late terminal phase.

An additional finding of our study was the observation that in patients receiving valproate monotherapy the

plasma concentrations of nimodipine were considerably higher than those observed in normal subjects. Since the gastrointestinal absorption of nimodipine is considered to be almost complete (Meyer *et al.*, 1983; Raemsch *et al.*, 1985), this finding cannot be ascribed to improved absorption and is most likely explained by inhibition of first-pass metabolism. This explanation would be consistent with previous reports indicating that valproic acid may inhibit the oxidative metabolism of phenytoin (Perucca *et al.*, 1980), diazepam (Dhillon & Richens, 1982) and phenobarbitone (Kapetanovic *et al.*, 1981), as well as the glucuronide conjugation of lamotrigine (Jawad *et al.*, 1987). The fact that nimodipine half-life was not prolonged in valproate-treated patients does not argue against the occurrence of metabolic inhibition because, as discussed above, the elimination rate of this compound is more dependent on hepatic blood flow than on enzyme activity.

These results may have important clinical implications. Since the many metabolites of nimodipine which have been tested so far appear to be devoid of significant pharmacological activity (Raemsch *et al.*, 1984), the

profile of plasma nimodipine concentration may be considered to reflect that of pharmacologically active drug which is available to equilibrate with the receptor sites. The dramatic decrease of plasma nimodipine concentrations in patients receiving enzyme-inducing anticonvulsants suggests that increased doses of nimodipine may be needed to achieve adequate therapeutic effects in these patients. Conversely, valproate-treated patients may require smaller dosages. Further investigations are indicated to determine the effect (if any) of enzyme-inducing agents and valproate given in combination. In the light of the prospective role of nimodipine as a new antiepileptic agent, these interactions need to be considered carefully in the design and interpretation of clinical trials involving addition of this drug to pre-existing anticonvulsant therapy. Moreover, the findings of this study may already be relevant to current therapy since nimodipine is often used in patients with cerebrovascular disorders receiving anticonvulsants for the treatment or prevention of seizures related to ischaemic or haemorrhagic brain damage.

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