EFFECT OF NIMODIPINE, A DIHYDROPYRIDINE CALCIUM CHANNEL ANTAGONIST ON THE PHARMACOKINETICS OF CARBAMAZEPINE IN RHESUS MONKEYS

M. C. GUPTA*, S. K. GARG, B. P. DAS AND V. K. BHARGAVA

Departments of Pharmacology,

Post Graduate Institute of Medical Education & Research,
Chandigarh – 160 012

           and

Post Graduate Institute of Medical Sciences,
Rohtak – 124 001

Abstract : Calcium channel antagonists have been shown to have an anticonvulsant activity in a variety of seizure models and also to potentiate the anticonvulsant activity of other standard antiepileptic drugs like carbamazepine, phenytoin and valporoate. A pharmacokinetic interaction may be involved in such potentiation. This cross over single dose study was carried out to find out if there was a pharmacokinetic interaction between carbamazepine, a commonly used antiepileptic drug and nimodipine, a dihydropyridine calcium channel antagonist in rhesus moneys. Carbamazepine 46 mg/kg and nimodipine 9.6 mg/kg was administered through a nasogastric tube and blood samples were collected at 0.5, 1, 2, 3, 6, 9, 12, 24, 48, 72 and 96 hours after drug administration and were assayed for carbamazepine. Nimodipine caused a significant increase in peak plasma concentration (C_{max}) of carbamazepine and a decrease in plasma absorption half life ($t_{1/2}$ α). There was no significant change in other pharmacokinetic parameters between the two groups. The results of the study suggest that concurrent administration of carbamazepine and nimodipine may cause a significant rise in carbamazepine concentration as may contribute to a potentiation of anticonvulsant effect of carbamazepine and an increase in the incidence of adverse effects warranting that nimodipine should be prescribed cautiously in epileptic patients receiving carbamazepine and it might be very appropriate to do therapeutic drug monitoring of carbamazepine in such patients.

Key words: carbamazepine   dihydropyridine   nimodipine
                       pharmacokinetics   cytochrome p450.

INTRODUCTION

Calcium channel antagonists have an anticonvulsant activity, has been demonstrated in a number of seizure models both *in vitro* and *in vivo* (1–4). Nimodipine,

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*Corresponding Author and address : 25/8FM, Medical Enclave, PGIMS, Rohtak–124 001 Ph.: 01262 – 42151

a dihydropyridine calcium channel antagonist has been shown to be effective against pentylenetetrazole and maximal electroshock induced convulsions in rats (5, 6). Nimodipine has also been found to have an anticonvulsant activity in a number of other seizure models like, against the seizures induced by L-glutamate in the rats and by cefazolin, pentylenetetrazole and bicuculline in the rabbits (1, 7, 8).

Co-administration of nitrendipine with diphenylhydantion have been found to increase the protective potential of this drug against experimental seizures (9). Since antiepileptic drugs have a high potential for drug interactions with calcium channel blocking drugs because of the common metabolic pathways, the potentiation of anticonvulsant activity of carbamazepine by nimodipine needs to be explored in terms of a pharmacokinetic interaction between these two drugs. The present study was carried out in rhesus monkeys to investigate whether this potentiation of carbamazepine cation by nimodipine could be because of a pharmacokinetic interaction.

METHODS

The study was conducted in six adult male rhesus monkeys (Macaca mulatta) weighing between 5 to 9 kg in a cross over fashion after obtaining ethical clearance. The monkeys were housed under standard laboratory conditions at ambient temperature with 12 hours day night cycle Animals were handled by well trained staff and were provided food in the form of black grams and bananas and water ad libitum.

Carbamazepine (Tab. Tegretol, Hindustan Ciba Geigy Limited, Mumbai (India) which was finely powdered and nimodipine powder [Torrent Pharmaceuticals, Ahmedabad, (India)] were dissolved in polyethylene glyco–400 (PEG–400) and were administered at a dose of both the drugs calculated according to the surface area ratio of the monkeys in relation to man.

After an overnight fast monkeys were given CBZ (46 mg/kg) by means of a nasogastric tube at 8.00 AM. Food was withheld for at least next 3 hours. Two millilitre of blood was collected from small saphenous vein, in heparinised tubes at 0.5, 1, 2, 3, 6, 9, 12, 24, 48, 72 and 96 hours after the drug administration. After a wash out period of 10 days monkeys were given CBZ (46 mg/kg) along with nimodipine (9.6 mg/kg) at 8.00 AM and blood samples were again collected at similar time intervals.

The plasma was separated by centrifugation at 3,000 rpm for 10 minutes and stored at–20°C until assayed for CBZ by the HPLC technique (10). The intraassay and interassay coefficient of variation was 7.0% and 5.0% respectively and the assay sensitivity was 100 ng/ml. The plasma data was analysed for various pharmacokinetic parameters using open one compartment model. Peak plasma concentration (C_{max}) and time to reach peak concentration (T_{max}) was calculated from the actual plasma data of each monkey. Area under the plasma concentration–time curve AUC $_{0-t}$ was calculated by trapezoidal rule. AUC $_{t-\infty}$ was calculated by dividing the last observed concentration in plasma by the elimination

rate constant (Kel). $AUC_{0-\infty}$. Absorption rate constant (Ka) was calculated by residual method while absorption half life (t½ α = 0.693/Ka. Rate constant for elimination was calculated by regression analysis of the monoexponential decline of the concentration time plasma curve and elimination half life (t½ β) was calculated from formula t½ β = 0.693/Kel. Paired student's 't' test was used for statistical analysis and P value <0.05 was considered as statistically significant.

RESULTS

Figure 1 compares the plasma concentration (Mean ± SEM) of CBZ at different time points before and after single oral dose of nimodipine. The plasma concentration of CBZ was significantly higher in the test group from 0.5 to 3.0 hours as compared to the controls. Thereafter plasma levels of CBZ in the test group were not significantly different as compared to control group. The plasma CBZ levels in both the group could be detected only up to 12 hours.
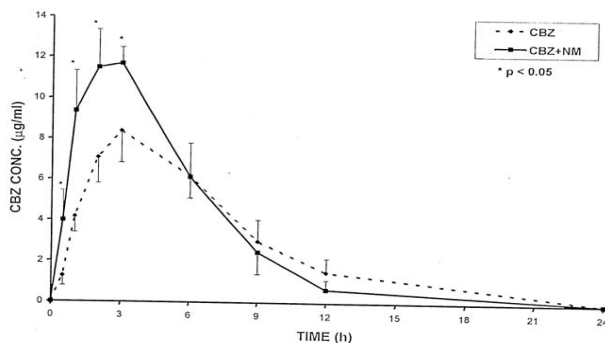

Fig. 1 : Plasma concentration of CBZ (Mean ± SEM) at different time points and after single oral dose of nimodipine (NM) in rhesus monkeys (n = 6).

Table I shows values of various pharmacokinetic parameters for carbamazepine before and after single dose administration of nimodipine. The peak plasma concentration (C_{max}) of CBZ was significantly increased after nimodipine administration. The average peak concentration of 8.39±1.07 µg/ml and 11.68±1.27 µg/ml respectively in the two groups was found to correlate will with therapeutic concentration in man i.e. 4-12 µg/ml (11). The absorption half-life ($t_{½} \alpha$) was

TABLE I : Pharmacokinetics of CBZ before and after single oral dose of nimodepine in rhesus monkeys.

Pharmacokinetic Parameters		CBZ	
		Before nimodipine	After nimodipine
T_{max}	(h)	2.67±0.21	2.5±0.34
C_{max}	(µg/ml)	8.39±1.07	11.687±1.27*
$T_{½}\alpha$	(h)	0.96±0.12	0.75±0.13*
$T_{½}\beta$	(h)	3.95±1.38	3.42±0.48
AUC_{0-}	(µg.h/ml)	72.39±18.34	75.58±7.65

Values represent Mean ± SEM; n=6; *P<0.05

decreased significantly in the nimodipine treated group while the elimination half life ($t_{\frac{1}{2}}$ β) though decreased in the nimodipine group, the decrease was statistically insignificant. Area under the time concentration curve (AUC) though increased after nimodipine administration was not significantly different compared to AUC when carbamazepine was given alone.

DISCUSSION

Nimodipine co-administration with conventional antiepileptic drugs may be required in some cases of drug resistant seizures after head injury and in cases of intractable epilepsy. In this study nimodipine co-administration increased the C_{max} by 39% and reduced the absorption half life ($t_{\frac{1}{2}}$ α) of CBZ significantly while the T_{max} was shortened, but not statistically significant, indicating that nimodipine enhances the rate of absorption of CBZ in rhesus monkeys. Both nimodipine and carbamazepine are metabolised mainly by CYP3A4 isoenzyme (12, 13) which is present in the liver and enterocytes of the gut wall. The possible mechanism of the increased rate of absorption of CBZ and an increase in the C_{max} could be attributed to inhibition of metabolism of CBZ by nimodipine due to competition between the two drugs for the same metabolic pathway i.e. CYP3A4 isoenzymes of the gut wall and the liver. Further CBZ induces its own metabolism also (14), an inhibitory interaction is likely to produce an increase in carbamazepine concentration of greater magnitude. The findings of the present study are in agreement with the earlier reports involving other calcium channel antagonists. A 40–50% rise in concentration of CBZ associated with

neurotoxicity has been shown with concurrent administration of diltiazem which returned to pretreatment levels following withdrawal of diltiazem and increased again by 50% on rechallenge (14). A similar rise in CBZ concentration has also been reported with verapamil (15).

Lack of significant effect on area under the plasma concentration time curve (AUC) and elimination half life could be because of the fact that the metabolism of CBZ follows first order kinetics (11) i.e. the rate of elimination of CBZ is directly proportional to its plasma concentration. This may explain the steep fall in plasma CBZ levels during the elimination phase in the nimodipine treated animals.

Another factor which may contribute, can be that nimodipine is extensively bound (up to an extent of 98%) to plasma proteins (16), it may cause displacement of carbamazepine from the plasma protein binding sites. However it may not be of any great consequence because there is an abundance of plasma protein binding sites for both nimodipine and carbamazepine and saturation of the binding sites is generally unlikely in the doses in which these drugs are used.

Results of the study clearly indicate that the reported potentiation of anticonvulant effect of carbamazepine is not only because of a pharmacodynamic interaction between carbamazepine and nimodipine but also involved is a pharmacokinetic interaction between these two drugs where administration of nimodipine causes a very significant rise in plasma concentration of carbamazepine which could account for its

enhanced anticonvulsant efficacy. It can be of great clinical importance, because this rise in concentration of carbamazepine is not only responsible for an enhanced effect, it may also lead on to a much increased incidence of toxicity of CBZ which is a drug with a relatively narrow therapeutic index. It would be prudent to conduct these studies in epileptic patients receiving these two drugs. Till that time, caution is warranted while administering nimodipine to a patient on CBZ therapy. Also, it may be very appropriate to carry out therapeutic monitoring of carbamazepine in such epileptic patients who are taking these drugs concurrently.

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