

## AMINOPHYLLINE ALTERS PHARMACOKINETICS OF CARBAMAZEPINE BUT NOT THAT OF SODIUM VALPROATE - A SINGLE DOSE PHARMACOKINETIC STUDY IN HUMAN VOLUNTEERS

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**Abstract:** Pharmacokinetic interaction of aminophylline with single dose sodium valproate (400 mg) and carbamazepine (200 mg) was evaluated in normal healthy volunteers using a cross over design. Neither the serum concentrations nor the pharmacokinetic parameters of sodium valproate (SV) were altered by the co-administration of aminophylline (AMP). In contrast AMP significantly decreased the plasma concentrations of carbamazepine (CBZ). The Cmax of CBZ was significantly lowered from  $1.73 \pm 0.18$  to  $0.94 \pm 0.08$  µg/ml and the  $AUC_{0-1}$  was significantly decreased from  $76.19 \pm 6.20$  to  $52.66 \pm 1.84$  µg/h/ml ( $P < 0.05$ ). The pharmacokinetic parameters of CBZ that were altered in the presence of AMP were: the Tmax and  $t_{1/2}$  which was prolonged about threefold from  $5.60 \pm 1.60$  to  $16.80 \pm 7.94$  h and  $44.88 \pm 4.50$  to  $125.07 \pm 29.09$  h, respectively. The Vd was marginally increased from  $2.19 \pm 0.13$  to  $3.85 \pm 0.57$  L/kg and the Cl was decreased from  $34.07 \pm 3.78$  to  $25.26 \pm 5.15$  mL/min. None of these alterations are statistically significant. Bioavailability of CBZ was reduced by 29% in the presence of AMP, while that of SV was increased by about 8%. Results are of clinical significance because simultaneous administration of CBZ and AMP may reduce the efficacy of CBZ in epileptic patients.

<b>Key words:</b>	sodium valproate	aminophylline
	pharmacokinetics	carbamazepine

### INTRODUCTION

Asthma and Epilepsy are generally independent disorders, but may sometimes coexist in the same patient. In the USA, an estimated 40,000 persons suffer from both disorders (1). In India, there is no demographic or clinical information regarding seizure frequency in epileptic patients with co-existing asthma.

Asthma is commonly treated with theophylline, a methylxanthine drug which is potentially proconvulsant. Studies reviewing the effect of theophylline administration on seizure frequency or its effect on the efficacy of antiepileptic drugs in epileptic patients with co-existing asthma have not been published (1) though there has been one report of theophylline reducing the seizure protective effect of carbamazepine

(CBZ) in a New Zealand born Indian girl (2).

Animal studies in the field of experimental epilepsy have shown that aminophylline (AMP), the ethylene diamine derivative of theophylline, produced a dose dependent reduction in the anticonvulsant efficacy of CBZ but not that of sodium valproate (SV) (3, 4, 5).

The present study was, therefore, designed to investigate single dose kinetic interactions between human volunteers, since the pharmacological management of asthma with aminophylline and SV or CBZ in normal and epilepsy occurring in the same individual may lead to a potential pharmacokinetic drug interaction.

### METHODS

Six healthy male volunteers between the ages 20

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and 25 years participated in the study. All were non-smokers and non-obese, weight between 50-75 kg (mean  $60 \pm 1.93$ ). Complete physical examination including a detailed neurological examination, electrocardiogram, laboratory tests comprising complete blood count and haemoglobin, blood biochemistry consisting of plasma proteins, total and conjugated bilirubin, serum creatinine, alkaline phosphatase, aspartate transaminase (ASAT), alanine transaminase (ALAT), urine albumin and sugar were performed to confirm that the subjects included in study were normal. Study was formally approved by the institutional Ethical Committee and informed consent was obtained from all participants.

The pharmacokinetic parameters of SV *per se* and SV with AMP were assessed on two occasions separated by a two week wash out period. After a month's interval an identical pharmacokinetic study was done with CBZ *per se* and CBZ with AMP in the same group of volunteers except that one volunteer dropped out of the study for non-medical reasons.

Subjects abstained from food since 10 pm of the previous evening. Venepuncture was done using a 21 g scalp vein set with heparin lock and left *in situ*. For the SV study, blood samples (2 ml) were collected (without anticoagulant) predrug and at 0.33, 0.66, 1, 2.5, 4, 6, 8, 12, 24, 48 and 72 h post drug. For the CBZ study, samples (5 ml) were collected into heparinised tubes predrug and at 1/2, 1, 2, 4, 8, 12, 24, 36, 48, 72 and 96 h post drug. In all studies the cannulae were disconnected after the 12 h sample collection and the subjects sent home. Subsequent collections were taken by separate venepuncture. For SV analyses, the samples allowed to clot at room temperature centrifuged at 3000 rpm and serum separated. For CBZ analyses, the samples were centrifuged at 3000 rpm and the plasma separated. Serum and plasma thus separated were stored at  $-20^{\circ}\text{C}$  until analysed.

After collecting basal samples, 400 mg Sodium valproate (Epilex - Reckitt & Colman, India Ltd.) or 200 mg Carbamazepine (Tegretol - Hindustan CIBA GEIGY) was given with 150 ml of water. For the interaction studies, 600 mg Aminophylline (Vikas Pharmaceutical) was administered in three divided doses of 200 mg each, the first dose given with SV or CBZ and thereafter at 6 h intervals.

The following precautions were taken during the study: Subjects refrained from taking alcohol or xanthine containing beverages from previous day of test and for the duration of study. Drugs of the same batch number was used for all the volunteers on all occasions. Standard meals were given to all the volunteers on the day of test. Breakfast was always given  $2\frac{1}{2}$  h after drug administration.

*Analytical methods:* Total sodium valproate concentration was determined by Fluorescence Polarisation Immunoassay (FPIA), using TDX assay kits supplied by Abbott Laboratories, USA. This method is now most widely used due to its simplicity, small volume of sample required for analysis and availability of automated kits (6). In addition the method is rapid and sensitive upto 1 ng/mL.

CBZ concentrations in plasma were analysed by reverse phase High pressure liquid chromatography (HPLC) as described by Gerson et al (7). This method has the advantage of being easily transferable and flexible for meeting individual laboratory needs. The mobile phase could be adjusted to delay or accelerate the elution of individual drugs. Further, other drugs do not interfere with the expected therapeutic range of carbamazepine.

*Treatment of bioavailability data:* For calculation of pharmacokinetic parameters (PK) complete bioavailability was assumed both for SV and CBZ (8, 9, 10). Curve fitting was carried out by a model independent method with non-linear least-square regression analysis using computer designed programme, 'PHARMKIT'. This programme uses an algorithm called "SIMPLEX" for calculating non-linear least squares. The various PK parameters calculated were: elimination half life ( $t_{1/2}$ ); volume of distribution (Vd); and clearance (Cl). Area under the curve (AUC) was calculated using the trapezoidal method. Cmax and Tmx are the observed values. Relative bioavailability (F) was calculated using the formula:

$$F = \frac{\text{AUC SV} + \text{AMP} \times 100}{\text{AUC SV}} \frac{\text{AUC CBZ} + \text{AMP} \times 100}{\text{AUC CBZ}}$$

*Statistical analysis:* Plasma concentration time curves and the PK parameters were analysed by paired 't' test. The difference between the treatments was validated at the probability level of  $P < 0.05$ .

## RESULTS

Both SV and CBZ *per se* and when combined with AMP were well tolerated by all the subjects and there were no adverse or untoward reactions.

Fig.1 shows the serum concentration time curves for SV given alone and with AMP. After SV 400 mg, peak serum concentrations of  $43.48 \pm 2.08 \mu\text{g/ml}$  were achieved rapidly within 1 h, the levels declining exponentially over 12-72 h. AMP did not significantly alter the serum concentration achieved by SV at any point of time. Table I shows the mean  $\pm$  SE values of the pharmacokinetic parameters of SV, 400 mg when given alone and with AMP, 600 mg in three divided doses, revealing no significant difference in any of the parameters.

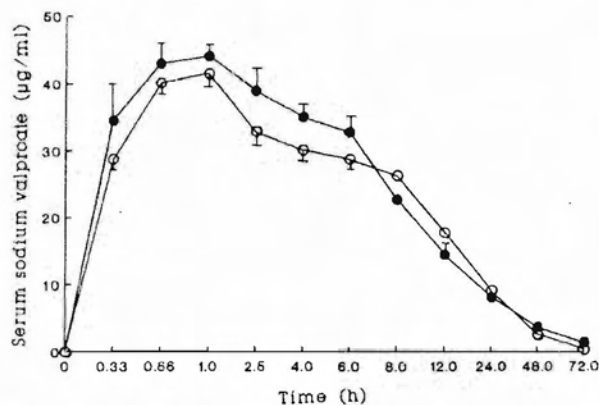


Fig. 1: Effect of aminophylline on serum concentrations (Mean  $\pm$  SEM) of sodium valproate o-----o before and after aminophylline ●-----●.

TABLE I: Kinetic parameters of sodium valproate (SV) (n=6) carbamazepine (CBZ) (n=5) before and after aminophylline (AMP).

Parameters	SV alone	SV + AMP	CBZ alone	CBZ + AMP
Cmax ( $\mu\text{g/mL}$ )	$43.48 \pm 2.08$	$50.22 \pm 3.75$	$1.73 \pm 0.18$	$0.94 \pm 0.08^*$
Tmax (h)	$00.88 \pm 0.06$	$00.97 \pm 0.33$	$5.60 \pm 1.60$	$16.80 \pm 7.94$
$t_{1/2}$ (h)	$12.81 \pm 0.96$	$13.15 \pm 1.56$	$44.88 \pm 4.50$	$125.07 \pm 29.09$
AUC ( $\mu\text{g/h/mL}$ ) (0-tn)	$666.38 \pm 50.22$	$708.66 \pm 544.58$	$76.19 \pm 6.20$	$52.66 \pm 1.84^*$
Vd (L/kg)	$0.17 \pm 0.01$	$0.17 \pm 0.01$	$2.19 \pm 0.13$	$3.85 \pm 0.57$
Cl (mL/min)	$9.63 \pm 0.54$	$9.30 \pm 0.70$	$34.07 \pm 3.78$	$25.26 \pm 5.18$
(F)	-	$108.79 \pm 11.76$	-	$71.00 \pm 13.99$

Cmax : Maximum plasma concentration  
 Tmax : Time to reach maximal plasma concentration  
 $t_{1/2}$  : Elimination half-life  
 AUC : Area under the concentration time curve  
 Vd : Volume of distribution  
 Cl : Total clearance  
 (F) : Estimated bioavailability after aminophylline  
 Mean  $\pm$  S.E. \* P < 0.02 (paired t-test)

The plots of mean plasma concentrations versus time of CBZ (200 mg) given with and without AMP over a period of 96 h is shown in Fig.2. When CBZ was given alone, mean plasma concentration showed two peaks, the first occurring at 1h and second at 4 h. When AMP was co-administered with CBZ, there was a delay in the appearance of the two peaks, the first occurring at 4 h and the second at 12 h. This finding was not consistent in all subjects. The occurrence of the second peak was validated by subjecting the concentration of CBZ just before the appearance of the second peak and at the time of the second peak to the paired 't' test and was found to be not significant.

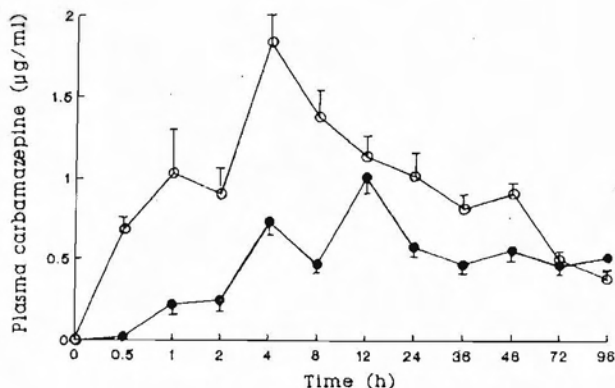


Fig. 2: Effect of aminophylline on plasma concentrations (Mean  $\pm$  SEM) of carbamazepine o-----o before and after aminophylline ●-----●.

When AMP was co-administered with CBZ, the plasma concentrations of CBZ achieved upto 48 h

were much lower than those achieved when CBZ was given alone. Thereafter, they were comparable. The decreases in plasma concentrations up to 48 h were significantly lower ( $P < 0.05$ ) at all points of time except at 12 and 24 h.

The Mean  $\pm$  SEM values of the different pharmacokinetic parameters obtained from five volunteers for CBZ per se and CBZ with AMP is shown in Table I. Significant reduction was seen for  $C_{max}$  and  $AUC_{(0-4)}$  the decreases being from  $1.73 \pm 0.18$  to  $0.94 \pm 0.08$   $\mu\text{g/mL}$  and  $76.19 \pm 6.20$  to  $52.66 \pm 1.84$   $\mu\text{g/mL/h}$  respectively ( $P < 0.05$ ). The  $T_{max}$  and  $t_{1/2}$  were prolonged approximately three fold from  $5.60 \pm 1.60$  to  $16.80 \pm 7.94$  h and  $44.88 \pm 4.50$  to  $125.07 \pm 29.09$  h respectively. The  $V_d$  values marginally increased from  $2.19 \pm 0.13$  to  $3.85 \pm 0.57$  L/kg while the  $Cl$  values were lowered from  $34.07 \pm 3.78$  to  $25.26 \pm 5.18$  mL/min. None of these alterations attained statistical significance probably because of interindividual variability and small sample size. Bioavailability of CBZ was reduced by 28.99% when co-administered with AMP whereas the bioavailability of SV was marginally increased by 8.79%.

#### DISCUSSION

Sodium valproate (SV) and Carbamazepine (CBZ) are among the most widely prescribed antiepileptic drugs (AEDs) and drug interactions with AEDs are important because of alterations in their efficacy, provoking seizure episodes necessitating increments in dosage with increased risk of toxicity. The results obtained in this study clearly indicate a qualitative difference in the pharmacokinetic profiles of SV and CBZ when given concurrently with aminophylline (AMP).

SV, rapidly absorbed after oral administration and its profile of serum time-concentration curve and pharmacokinetic parameters are in accordance with previous reports (11). AMP did not influence the overall pharmacokinetics of SV absorption or bioavailability. Although SV and AMP are known to have local gastric irritant effects, none of the subjects experienced any gastric discomfort and no site specificity for absorption has been demonstrated for SV (12). The lack of pharmacokinetic interaction between SV and AMP could be due to their different metabolic pathways. AMP is mainly oxidised and SV

is glucoronidated (13). It can be inferred from the  $C_{max}$  and  $AUC$  values with SV alone and SV with AMP that the seizure protection afforded by single dose of SV remains unimpaired.

The  $V_d$  of SV is 0.17 L/kg, indicating that SV is distributed chiefly in the rapidly exchangeable extracellular fluid. However, this value has been calculated on the basis of the total concentration of SV which is extensively protein bound and hence, appears very low.  $V_d$  values would be much larger if calculated on the basis of the concentration of free SV, but this was not estimated in this study. SV is more tightly bound to serum albumin than CBZ (14).

In contrast, the results obtained with CBZ and AMP showed a definite pharmacokinetic interaction. The most important pharmacokinetic interaction between AMP and CBZ was significant decrease in  $C_{max}$  and  $AUC$  and lowering of plasma concentration of CBZ at all points of time upto 48 h, except at 12 and 24 h. This lack of significance between the values obtained at 12 and 24 h is obvious. When CBZ is given alone the  $C_{max}$  is obtained at 4 h and subsequently begins to decline, whereas when AMP is given along with CBZ the  $C_{max}$  is delayed up to 12 h. The  $T_{max}$  and  $t_{1/2}$  of CBZ was also prolonged about three fold when AMP was co-administered. Inclusion of additional subjects may have made these differences statistically significant.

Alterations in the PK parameters could be the result of delayed absorption of CBZ in the presence of AMP as substantiated in the observation that the  $AUC$  of CBZ was significantly lowered in the presence of AMP without significant alteration in  $V_d$  and  $Cl$ . CBZ is absorbed erratically after oral administration, a factor which may be aggravated by the propensity of AMP to adversely influence local gastrointestinal process. Further the bioavailability of CBZ was decreased by about 28.99%.

Reduction in the efficacy of theophylline by CBZ has been reported (15). However, it is interesting to note that variety of drugs viz. cimetidine, erythromycin, verapamil, viloxazine (16) and fluoxetine (17) increase the plasma concentrations of CBZ and antiepileptic drugs such as phenobarbitone, phenytoin and primidone markedly reduce the serum concentrations of CBZ

(16). The only other drug reported to produce a similar effect is theophylline (2) and the present study is perhaps the first report in Indian subjects to confirm this observation from a single case.

To the degree that single dose studies may assist clinical information, the findings of the present study are of clinical significance because pharmacokinetic interaction between CBZ with AMP may reduce the efficacy of CBZ and may provoke seizure episodes in epileptic patients treated with CBZ. Such interaction may not occur with SV.

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