Lack of a pharmacokinetic interaction between phenobarbitone and gabapentin

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Twelve subjects received a single oral dose (300 mg) of gabapentin and serial blood and urine samples were collected for drug measurements. Oral phenobarbitone (30–90 mg/day) was then administered to steady-state, and the gabapentin single dose study was repeated on day 42. Gabapentin was administered from days 49 to 52 to achieve steady-state, and further blood and urine samples were collected for drug measurements. Trough plasma phenobarbitone concentrations were monitored at frequent intervals. No statistically significant differences were observed in gabapentin $C_{\max}$, $t_{\max}$, AUC, $t_{1/2}$ or urinary drug recovery following single doses of gabapentin alone or combined with phenobarbitone. Phenobarbitone did not alter the disposition of gabapentin at steady state. Mean trough steady-state phenobarbitone concentrations were not significantly affected by concomitant gabapentin administration.

Keywords gabapentin phenobarbitone antiepileptics pharmacokinetics

Introduction

Gabapentin [1-(aminomethyl)-cyclohexane-acetic acid] is one of a series of gamma-aminobutyric acid (GABA) analogues which have been studied as possible anti-convulsants. The drug is effective against seizures in animal models of epilepsy (Bartoszyk *et al.*, 1986) and in humans (Crawford *et al.*, 1987). However, its mechanism of anticonvulsant action may not involve GABA-mediated neurotransmission. While the drug is still undergoing clinical study in human epilepsy, and also after it is first introduced into therapeutics, it seems probable that it will be employed mainly as 'add-on' therapy in patients with resistant seizure disorders. It is therefore important to know whether gabapentin will interact pharmacokinetically with co-administered anti-convulsants, including phenobarbitone, which might be prescribed as such, or formed *in vivo* from primidone or methylphenobarbitone. Vollmer *et al.* (1986) have shown that gabapentin is not metabolised significantly in man, which makes such interactions less likely. However, a study was thought justified, designed to assess the effects of chronic phenobarbitone intake on the pharmacokinetics of gabapentin, and also to evaluate the effects of a short course of gabapentin on steady-state plasma phenobarbitone concentrations.

Methods

The study was carried out in 12 healthy adult (male (8) and female (4)) volunteers who gave informed consent to participate after the protocol was approved by The University of Queensland Institutional Ethics Committee. The subjects' ages ranged from 18 to 44 years (mean $21.6 \pm \text{s.d. } 9.3$ years) and their weights from 51 to 85 kg (mean $68.2 \pm \text{s.d. } 9.5$ kg). Two female subjects took oral contraceptives, and one received nitrofurantoin for treatment of a chronic urinary tract infection. The two tobacco smokers in the series did not smoke during the study period. An additional two subjects commenced but did not complete the study because of drowsiness while taking phenobarbitone. Their data have not been included.

Study protocol

After preliminary clinical examination and routine biochemical and haematological screening, all subjects took a single oral dose of 300 mg gabapentin on day 1 and a pharmacokinetic study (I) was then carried out, and all urine for 48 h from dosing was collected. Beginning 1 week later, all subjects received oral phenobarbitone 30 mg daily on days 8 to 14, 60 mg daily on days 15 to

21 and 90 mg daily on days 22 to 59. This regimen was designed to minimise the risk of unacceptable sedation, yet to allow a reasonable chance of obtaining clinically relevant steady-state plasma phenobarbitone concentrations (above 10 mg l^{-1}). On day 42, while continuing phenobarbitone intake, the subjects took a single dose of 300 mg gabapentin orally, and a further pharmacokinetic study (II), with urine collection as before, was carried out. Phenobarbitone intake (90 mg day^{-1}) was continued and on the morning of day 49 the subjects took the first of 10 oral doses of gabapentin (each of 300 mg) at 8 h intervals. At the end of this period (day 52) steady-state conditions should have applied for gabapentin. Following the final (10th) dose of gabapentin a third pharmacokinetic study (III) with urine collection was carried out. Oral phenobarbitone intake (90 mg day^{-1}) continued to day 59, when the study ended. Subjects then tapered off their phenobarbitone intake. Plasma phenobarbitone concentrations were measured twice a week from days 35 to 49, to check that steady-state conditions applied, daily from days 49 to 52 (during the period of regular gabapentin intake), and from days 57 to 59. All single steady-state plasma drug concentration measurements were predose (trough) ones.

Pharmacokinetic studies

All three pharmacokinetic studies in each subject followed the same design. After an overnight fast a forearm venous cannula was inserted, a pre-dose blood sample was collected and the subject emptied his or her bladder. At 0 h the subject swallowed a 300 mg gabapentin capsule with 100–200 ml water. Thereafter venous blood was collected as close as possible to 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 32.0 and 48.0 h. Blood samples after 12 h were obtained by individual venepuncture. All urine was collected over the intervals 0–8, 8–16, 16–24 and 24–48 h. During each study the subjects followed their usual diets and were ambulant.

Analytical procedures

Gabapentin concentrations in plasma and urine were measured by capillary column gas chromatography (Hooper *et al.*, 1990). In brief, gabapentin and the internal standard (a structural analogue) were isolated from plasma using an ion exchange resin, and the methyl ester/*N*-trifluoroacetyl derivatives were prepared. Chromatography was performed on a bonded phase methyl silicone megabore capillary column. For both plasma (0.2 – $20.0 \text{ } \mu\text{g ml}^{-1}$) and urine (5 – $500 \text{ } \mu\text{g ml}^{-1}$) the linearity was excellent over the clinically relevant concentration ranges, with coefficients of determination of about 0.999. For plasma, precision (R.S.D.) ranged from 6.2% at $0.5 \text{ } \mu\text{g ml}^{-1}$ to 2.3% at $10 \text{ } \mu\text{g ml}^{-1}$ ($n = 18$ obtained by pooling results from six replicates on three separate occasions). Accuracy for the same specimens was 4.8% at $0.5 \text{ } \mu\text{g ml}^{-1}$ and 2.8% at $10 \text{ } \mu\text{g ml}^{-1}$. Analogous data for urine assays showed precision of 4.0% at $20 \text{ } \mu\text{g ml}^{-1}$, 6.8% at $500 \text{ } \mu\text{g ml}^{-1}$, with accuracy of 12.2% and 5.6% at the same two concentrations.

Phenobarbitone concentrations in plasma were measured by a conventional reversed phase h.p.l.c. procedure with u.v. detection, monitoring at 215 nm. Briefly, the proteins were precipitated from plasma (to which an internal standard, alphenal, had been added) by addition of acetonitrile (2 volumes), and an aliquot of the clear supernatant was injected onto a C_{18} column, using a mobile phase of acetonitrile (23% v/v) in phosphate buffer, 0.1 M, pH = 6 at a flow rate of 1 ml min^{-1} . The method gave linear calibration curves over the phenobarbitone concentration range 1.0 – $50.0 \text{ } \mu\text{g ml}^{-1}$ in plasma. The lower assay limit was $0.5 \text{ } \mu\text{g ml}^{-1}$, and accuracy and precision were within 10%.

Pharmacokinetic analysis

Plasma concentration-time data from each study were described by a biexponential equation:

$$C = C(0) (e^{-k \cdot t} - e^{-k_a t})$$

where C = plasma drug concentration at a given time

$C(0)$ = theoretical concentration at zero time

k = elimination rate constant

k_a = absorption rate constant

t = actual time – lag time

Curve fitting was done using the program 'Stemfit' (Stem Software, Brisbane), which employs the Fehlberg modification of the Marquardt algorithm to achieve a least squares fit to the experimental data.

The elimination half-life ($t_{1/2}$) was calculated as $\ln 2/k$. Area under the concentration-time curve was calculated to the last measurable concentration-time point ($\text{AUC}(0, t)$) using trapezoidal rule integration, with a correction for the calculated absorption lag time. $\text{AUC}(t, \infty)$ was calculated as C_t/k where C_t was the last measured concentration (Gibaldi & Perrier, 1982). Total AUC was then determined as the sum of $\text{AUC}(0, t)$ and $\text{AUC}(t, \infty)$. For pharmacokinetic studies I and II oral clearance (CL_o) was calculated as oral dose/AUC, while for study III steady-state clearance was calculated as: oral dose each 8 h/AUC(0,8). Renal clearance was calculated as total amount excreted in urine/AUC. Peak plasma drug concentration ($C_{\max}$) and the time at which it occurred ($t_{\max}$) were read directly from the data.

Statistical analysis

Pharmacokinetic parameters for studies I, II and III were compared using 2 factor ANOVA, with application of Duncan's multiple range test, where indicated.

Results

Clinical results

In general, gabapentin was well tolerated, although five subjects experienced transient episodes of drowsiness, disinhibition and difficulty in concentrating during the 3 days of regular gabapentin intake. No significant

Table 1 Pharmacokinetic parameters for the 12 subjects studied

Subject		Lag time (h)	k _a (h ⁻¹)	k (h ⁻¹)	t _½ (h)	AUC (μg ml ⁻¹ h)	CL _o (l kg ⁻¹ h ⁻¹)	CL _R (l kg ⁻¹ h ⁻¹)	fe (48)	C _{max} (μg ml ⁻¹)	t _{max} (h)	r ²
A	I	0.82	1.171	0.134	5.2	33.74	0.15	0.10	0.65	3.77	3.00	0.982
	II	0.79	1.136	0.160	4.3	30.43	0.17	0.08	0.49	3.55	2.00	0.895
	III	–	0.259	0.178	3.9	32.57	0.16	0.08	0.53	3.36	4.08	0.934
B	I	0.39	1.121	0.100	7.0	33.93	0.10	0.07	0.71	2.57	3.00	0.997
	II	0.00	1.526	0.118	5.9	32.33	0.11	0.05	*>0.49	3.29	3.16	0.931
	III	–	0.528	0.100	6.9	41.18	0.09	0.06	0.73	4.15	2.00	0.987
C	I	0.57	2.144	0.105	6.6	34.38	0.13	0.08	0.61	3.02	1.78	0.991
	II	0.41	0.969	0.168	4.1	20.39	0.22	0.11	0.48	2.06	2.00	0.962
	III	–	3.826	0.072	9.6	20.40	0.22	0.06	0.29	5.19	0.95	0.935
D	I	1.23	0.706	0.118	5.9	27.74	0.14	0.07	0.52	2.28	4.00	0.995
	II	0.35	0.653	0.115	6.0	22.48	0.18	0.09	0.50	1.64	6.00	0.972
	III	–	0.481	0.220	3.2	41.22	0.10	0.04	0.42	5.78	3.00	0.938
E	I	0.75	0.698	0.172	4.0	25.74	0.19	0.09	0.50	2.48	3.50	0.989
	II	0.50	0.566	0.184	3.8	22.71	0.21	0.12	0.55	2.48	3.08	0.906
	III	–	0.799	0.104	6.7	31.96	0.15	0.12	0.76	4.72	2.00	0.956
F	I	0.50	0.606	0.181	3.8	15.73	0.25	0.08	*>0.31	1.75	3.00	0.992
	II	0.02	0.801	0.198	3.5	16.69	0.24	0.12	0.49	2.18	2.00	0.981
	III	–	2.176	0.160	4.3	24.23	0.17	0.08	0.51	4.22	1.50	0.984
G	I	0.03	0.331	0.162	4.3	22.78	0.18	0.06	*>0.32	2.07	4.10	0.902
	II	0.50	0.830	0.117	5.9	29.56	0.14	0.07	*>0.52	2.42	4.00	0.985
	III	–	0.310	0.126	5.5	27.89	0.14	0.09	0.64	3.76	1.52	0.965
H	I	0.58	0.619	0.244	2.8	22.79	0.21	0.12	0.60	3.33	3.05	0.966
	II	0.74	0.751	0.172	4.0	19.09	0.25	0.11	0.45	2.20	4.08	0.823
	III	–	0.933	0.115	6.0	17.19	0.27	0.27	1.00	4.39	2.00	0.958
I	I	0.31	0.816	0.123	5.6	18.83	0.25	0.03	*>0.12	1.70	4.00	0.963
	II	0.50	0.397	0.186	3.7	25.99	0.18	0.10	0.57	2.45	4.00	0.978
	III	–	0.959	0.094	7.4	23.21	0.20	–	–	3.02	1.50	0.924
J	I	0.17	0.871	0.115	6.0	33.82	0.12	0.07	0.62	3.09	3.00	0.981
	II	0.25	1.362	0.092	7.6	27.88	0.14	0.10	0.75	2.26	2.75	0.978
	III	–	1.333	0.100	6.9	31.85	0.13	0.02	0.20	4.53	1.50	0.970
K	I	0.53	0.401	0.206	3.4	34.10	0.14	0.11	0.80	3.90	3.92	0.970
	II	0.87	0.474	0.169	4.1	34.67	0.13	0.10	0.72	3.08	6.00	0.984
	III	–	0.422	0.247	2.8	34.14	0.14	0.04	0.31	4.51	2.50	0.968
L	I	0.39	1.104	0.208	3.3	46.46	0.13	0.01	*>0.11	5.88	2.00	0.989
	II	0.00	0.519	0.197	3.5	41.45	0.14	0.08	*>0.56	4.55	4.00	0.966
	III	–	0.514	0.230	3.0	50.55	0.12	0.04	0.33	7.05	2.03	0.971

Mean ± s.d.

Study I	0.52	0.808	4.8	0.17	0.07#	0.63#	2.99	3.20
	±	±	±	±	±	±	±	±
	0.32	0.511	1.4	0.05	0.03	0.10	1.16	0.76
Study II	0.41	0.805	4.7	0.18	0.10#	0.56#	2.68	3.59
	±	±	±	±	±	±	±	±
	0.30	0.393	1.3	0.05	0.04	0.11	0.80	1.38
Study III	–	1.021	5.5	0.16	0.09#	0.52#	4.56	2.05
		±	±	±	±	±	±	±
	–	1.043	2.1	0.05	0.08	0.24	1.08	0.83

ANOVA – for differences between Studies I, II and III

<i>F</i>	=	0.9958	0.5920	1.3316	1.2765	0.8193	0.8533	25.289	10.619
<i>df</i>	=	1,11	2,22	2,22	2,22	2,21	2,22	2,22	2,22
<i>P</i>	=	0.340	0.562	0.285	0.299	0.454	0.447	<0.00001	0.0006

AUC = AUC for studies I and II, and AUC(0,8) for study III.

* Known incomplete urine collection. # Known underestimates.

alterations in the results of clinical biochemical, haematological, or urine tests were observed, nor were there any changes on physical examination.

Pharmacokinetic results

Mean plasma gabapentin concentrations following single doses of gabapentin alone (study I) and concomitantly with phenobarbitone (study II) were almost identical (Figure 1). The calculated pharmacokinetic parameters for the individual subjects, and the mean values, are presented in Table 1. Analysis of variance showed that there were no statistically significant differences in any pharmacokinetic parameter between studies I and II. Comparison of the pharmacokinetic parameters following administration of single (studies I and II) and multiple (study III) doses of gabapentin revealed statistically significant ($P < 0.05$) differences between $C_{\max}$ and $t_{\max}$ values (as expected), but no significant differences for the other parameters.

Over the three studies, urinary excretion of unchanged gabapentin accounted for an average of $56 \pm \text{s.d. } 17\%$ of the oral drug dose. Except for study H III, renal clearances were consistently lower than oral clearances.

Mean steady-state predose plasma phenobarbitone concentrations in the subjects prior to the second gabapentin dose, during the period of continuous gabapentin intake, and 1 week after this period were $14.6 \pm \text{s.d. } 2.3$, $13.9 \pm \text{s.d. } 2.2$ and $13.8 \pm \text{s.d. } 3.0 \mu\text{g ml}^{-1}$ respectively, there being no significant differences between these values.

Discussion

The plasma gabapentin concentration-time data obtained in the study were generally well fitted by the chosen function, as shown by the coefficient of determination (r^2) in Table 1. The mean elimination half-life of gabapentin ($5.0 \pm \text{s.d. } 1.6 \text{ h}$) was in reasonable agreement with previously published values (Vollmer *et al.*, 1986). Gabapentin is said not to be metabolised in humans but the present study has found that a mean of only 56% of the oral dose was excreted unchanged in urine over a mean period of nearly 10 half-lives of the drug. However, this figure and the renal clearance values are underestimates, since some urine collections were incomplete.

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Figure 1 Mean (with standard error bars) plasma gabapentin concentrations in the 12 subjects following a single oral dose (300 mg) of gabapentin alone (Study I; open circles, broken lines) and following phenobarbitone intake (Study II; closed circles, full line).

Previous studies in humans (Bartoszyk *et al.*, 1986) have found up to a mean of 77% of the gabapentin dose in urine, collected for 96 h following single doses.

The absorption and disposition parameters of gabapentin before and after chronic phenobarbitone intake were similar, and regular gabapentin intake did not cause any statistically significant change in phenobarbitone clearance. Under steady-state conditions the $C_{\max}$ value for gabapentin was higher, as would be anticipated, due to drug accumulation, and the $t_{\max}$ occurred earlier, as would be expected theoretically (Gibaldi & Perrier, 1982). The study showed that a short course of gabapentin had no statistically significant effect on steady-state plasma phenobarbitone concentrations.

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