Relationship between systemic drug absorption and gastrointestinal transit after the simultaneous oral administration of carbamazepine as a controlled-release system and as a suspension of ^{15}N -labelled drug to healthy volunteers

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- 1 Plasma drug concentrations after a single oral administration of a suspension of carbamazepine (CBZ) and a 20/200 CBZ Oros osmotic pump system were measured in eight healthy male volunteers. The oral suspension contained 100 mg CBZ labelled with the stable isotope nitrogen-15, whilst the Oros contained 200 mg unlabelled CBZ. Plasma concentrations of [^{15}N]-CBZ and CBZ were measured simultaneously by gas chromatography-mass spectrometry.
- 2 The position of the CBZ Oros (labelled with indium-111) in the gastrointestinal tract was followed by gamma scintigraphy. Plasma drug concentrations after the two treatments were used to relate pharmacokinetic with transit data.
- 3 The Oros was taken after breakfast and gastric emptying occurred between 1.1–>11 h post-dosing (median, 5.3 h). Small intestinal transit times ranged from 1.5–>3.6 h, with a median of 2.2 h. There were wide individual variations in colonic transit, and the total transit time ranged from 10–60 h (median, 22 h).
- 4 Relative systemic bioavailability of CBZ from the Oros was reduced compared with that from the suspension (mean dose normalised AUC ratio = 0.69 ± 0.17 ; mean dose-normalised AUC ratio = 0.85 ± 0.13 , allowing for actual release from the Oros system).
- 5 The *in vivo* absorption of drug into the systemic circulation from the Oros was estimated using the Wagner-Nelson method. This showed that absorption of CBZ was rapid when the Oros was present in the stomach and small intestine, the rate being determined by the release of drug from the system. Deviations from the *in vitro* release rate were more apparent when the system entered the colon. In most subjects there appeared to be decreased absorption of CBZ from the Oros when the system was located in the colon.

Keywords carbamazepine Oros stable isotope gamma scintigraphy intrinsic crossover

Introduction

Carbamazepine (CBZ) is an anticonvulsant of proven efficacy in the management of epilepsy. It is also used as an analgesic in the treatment of the paroxysmal pain of trigeminal neuralgia. Currently the compound is given orally as either a conventional tablet, a slow-

release tablet or as a syrup. Recently a 20/200 CBZ Oros controlled release (CR) drug delivery system has been developed. This formulation is based on an osmotic pump system and is designed to release drug at a constant rate over a prolonged period of time (Theeuwes *et al.*,

1985). CBZ has a narrow therapeutic window and the CBZ Oros system has been developed to reduce the fluctuations in plasma drug concentration.

The gastrointestinal (g.i.) transit of Oros CR dosage forms can have an important bearing on the plasma drug concentration-time profile (Davis *et al.*, 1988b). The combined use of gamma scintigraphy and a pharmacokinetic evaluation can provide detailed information on the *in vivo* performance of pharmaceutical dosage forms. Such evaluations typically take the form of cross-over studies in which a novel system is compared against a standard reference product.

We describe a single dose cross-over study with CBZ performed on one study day, using stable isotope technology and a gas chromatography-mass spectrometry (GC-MS) analytical procedure. This 'intrinsic cross-over' design has the following advantages over the conventional cross-over design;

- The problem of intra-subject variability between different study days is avoided.
- The study can be performed over a shorter period of time, a particular advantage for a compound such as CBZ which has a long terminal plasma elimination half-life (approximately 35 h after a single dose; Chan *et al.*, 1985). Hence plasma drug concentrations have to be followed for at least 7 days post-dosing to characterise fully the profile. The stable isotope approach avoids the necessity to have a second sampling period.
- Fewer blood samples need be withdrawn from each volunteer.

A combination of gamma scintigraphy and pharmacokinetic evaluation was used to relate the position of the formulations in the g.i. tract to drug absorption.

Methods

Subjects

The study was conducted in eight healthy male volunteers, aged 19–25 years (mean 22 years) who weighed 66–88 kg (mean 75 kg) with a height range of 1.71–1.87 m (mean 1.78 m). They were all non-smokers who did not consume excessive quantities of alcohol. Clinical examination and standard biochemical and haematological tests prior to the study confirmed that values were in the normal range. The subjects were not receiving any other medication and none had any evidence or history of intolerance to CBZ or other anticonvulsant drugs.

The study was performed in accordance with the guidelines of the declaration of Helsinki on Biomedical Research Involving Human Subjects (Venice revision, 1983). Approval was obtained from the Ethics Committee of Nottingham University Medical School and the subjects gave their written informed consent.

Dosage form and dosing

The volunteers attended the study centre having fasted for at least 12 h overnight, and a basal blood sample (10 ml) was taken from a forearm vein. They were asked

to empty their bowels at the beginning of the study day, and the times of subsequent bowel movements during the 7 day study period were recorded.

A 2% w/v suspension containing 100 mg ^{15}N -labelled CBZ (5 ml) was administered to each volunteer, followed by 100 ml water. The water contained 4 MBq $^{99}\text{Tc}^{\text{m}}$ -labelled diethylenetriaminepentaacetic acid (DTPA) to permit a scintigraphic outline of the g.i. tract to be established. A 10 ml blood sample was withdrawn at 0.5 and 0.75 h after dosing.

Forty-five minutes after administration of the suspension, all subjects received a light breakfast consisting of two slices of toast, butter, marmalade and orange juice. One hour after administration of the suspension a blood sample was withdrawn, followed immediately by administration of a 20/200 CBZ Oros with 100 ml water. This single unit dosage form is an osmotic pump system containing 200 mg CBZ which, after a lag time, is designed to release the drug at an initial zero-order rate of 20 mg h^{-1} for 4–8 h. Thereafter the release rate declines. The Oros technology has been fully described elsewhere (Theeuwes *et al.*, 1985).

Sixteen blood samples were withdrawn from a forearm vein over 7 days.

The volunteers were permitted to consume non-alcoholic drinks when required, but no sooner than 2 h after the administration of the Oros. Standard light meals were given at 4 and 10 h after administration of the CBZ suspension. Thereafter volunteers resumed their normal eating habits. Subjects maintained a reasonable level of activity during the study period, following their usual routine as far as possible.

Drug assay

Plasma concentrations of CBZ (from the Oros) and ^{15}N -labelled CBZ (from the suspension) were determined simultaneously using GC-MS. The lower limit of the assay (50 ng ml^{-1}) was defined as the lowest concentration where acceptable accuracy ($100 \pm 15\%$) and precision (C.V. $< 15\%$) was obtained. The S:N ratio was > 20 at this concentration for both compounds. The calibration range was from 50–500 ng ml^{-1} . Quality control samples analysed over this range resulted in an overall accuracy and precision of 103.4 (5.2%) and 102.5 (5.3%) for CBZ and ^{15}N -CBZ, respectively.

There is only one mass unit difference between CBZ and ^{15}N -CBZ. Therefore, the resulting isotopic abundance measurements for ^{15}N -CBZ had to be corrected to account for the contribution due to the natural abundance ^{13}C from CBZ. These deconvolutions were applied to all data prior to final measurement.

Labelling of the Oros and scintigraphic procedures

Oros dosage forms do not disintegrate in the gut lumen. In order to follow the position of the Oros, as it moved through the different regions of the g.i. tract, it was labelled by the incorporation of 1 MBq ^{111}In -labelled ion-exchange resin powder (Amberlite CG 120, Poole, Dorset), into an adhesive (clear nail polish, Boots) which was coated onto a small area around the edge of the Oros. The *in vitro* release profiles of labelled Oros dosage forms were determined prior to the study using

a flow cell dissolution method [DISSOTEST dissolution apparatus (volume unlimited)]. The release characteristics of these labelled systems resembled closely those of the unlabelled form.

The transit of the Oros in the g.i. tract was recorded with the subjects standing in front of a gamma camera (Maxicamera-GEC 40 cm field of view, fitted with a medium energy collimator) and by acquiring images at frequent intervals over the period of the study. Static images of 60 s duration were recorded and the data were stored on computer for subsequent analysis. The position of the Oros was determined by reference to the $^{99}\text{Tc}^{\text{m}}$ -DTPA images and external anatomical markers. The markers were $^{99}\text{Tc}^{\text{m}}$ -labelled adhesive patches positioned over the right lobe of the liver (Davis *et al.*, 1988a).

The presence of the Oros in the faeces was established by gamma-scintigraphy. The spent system was recovered and the amount of drug remaining in it was measured. The time of recovery was recorded and total transit time was calculated. Scintigraphic imaging ceased upon recovery of the Oros in the faeces for each volunteer. In all cases the indium label was still attached to the recovered units.

Pharmacokinetic analysis

AUC(0, t) was calculated as the area under the plasma drug concentration-time curve from zero to the last datum point of time t , using the linear trapezoidal rule. Total AUC (AUC) was calculated from the sum of AUC(0, t) and C_t/λ_z where C_t was the concentration at the last time point and λ_z was the terminal elimination rate constant. The latter was calculated by linear regression of the terminal linear portion of the log plasma drug concentration-time curve. The last 5 data points were used for these calculations for both formulations (48–168 h and 47–167 h post-dosing following the suspension and the Oros, respectively). The plasma terminal elimination half-life ($t_{1/2,z}$) was calculated from $0.693/\lambda_z$.

The residual amount of drug remaining in each Oros was determined. The AUC value for the Oros was dose-normalised using both the nominal dose (200 mg) and after correcting for the actual amount of drug released from the system. Both of these values were compared with the dose-normalised AUC following administration of the suspension.

Since the time-course of plasma CBZ concentrations after i.v. administration can be adequately described by a mono-exponential function, drug release from the Oros was estimated by the Wagner-Nelson method (Wagner & Nelson, 1964). For each subject, the total AUC following the Oros and the terminal elimination rate constant (λ_z) following the suspension were used for this purpose. The Wagner-Nelson calculation expresses cumulative drug absorption as a percentage of the total amount absorbed. In order to generate an absorption function for each subject, these cumulative percentage absorption values were multiplied by the appropriate relative bioavailability (dose normalised AUC Oros [200 mg dose]/dose normalised AUC suspension [100 mg dose]).

Results

Gastrointestinal transit

The transit of the Oros through the g.i. tract in each subject is illustrated by diagrams prepared from the scintigraphic images (Figure 1). The gastric emptying time, small intestinal, colonic and total transit times are shown in Table 1. In subjects 3, 7 and 8, colon arrival and small intestinal and colonic transit times could not be determined from the scintigraphic images. Total transit times were, however, determined for these individuals.

Gastric emptying of the Oros occurred between 1.1–>11 h post-dosing (median, 5.3 h). Such a spread of gastric emptying is to be expected since the subjects ate a standard breakfast immediately before taking the Oros, in order to delay the emptying of the system from the stomach. Small intestinal transit times, however, were consistent, ranging between 1.5–>3.6 h (median, 2.2 h). Total transit times (mouth to anus) ranged from 10–60 h (median, 22 h). Subjects 1 and 6 had relatively rapid total transit times for the Oros (10.0 and 11 h, respectively). By contrast, subjects 2 and 7 had the longest transit times of 34 and 60 h, respectively.

Intact systems were recovered from all eight subjects. The amounts of drug remaining in these systems (Table 2) were consistent with the *in vitro* release rate (Figure 2) and with total transit times (Table 1). In the two subjects with fastest transits approximately 30% of

Table 1 Individual g.i. transit data after oral administration of a 20/200 Oros as determined by scintigraphy

Subject	Gastric emptying (h)	Small intestinal transit (h)	Colon arrival (h)	Colonic transit (h)	Total transit (h)
1	1.1	2.2	3.3	6.7	10
2	2.7	2.0	4.7	29.3	34
3	7.3	>3.6	—	—	22
4	2.3	3.2	5.5	16.5	22
5	9.1	1.5	10.6	12.4	23
6	3.2	1.5	4.7	5.9	11
7	8.2	>2.8	—	—	60
8	>11	—	—	—	22
Median	5.3	2.2	4.7	12.4	22

Figure 1 Schematic representation of the position of the Oros in the g.i. tracts of all eight subjects. (Numbers indicate time after dose in hours.)

Table 2 Dose-normalised pharmacokinetic parameters following administration of a 20/200 CBZ Oros (0.8465 mmol)

Subject	Total AUC* ($\mu\text{mol l}^{-1} \text{mmol}^{-1}$ of dose h)	C_{max} * ($\mu\text{mol l}^{-1} \text{mmol}^{-1}$ of dose)	t_{max} (h)	Oros/ suspension AUC ratio		% of dose recovered	Defaecation frequency (day ⁻¹)
				*	**		
1	275	5.1	11	0.36	0.54	32.5	2.3
2	559	7.8	31	0.85	0.90	5.9	0.6
3	572	7.2	11	0.69	0.79	12.9	0.7
4	443	7.2	11	0.65	0.76	14.8	0.7
5	509	7.7	23	0.75	0.85	11.3	1.0
6	370	6.4	11	0.56	0.82	31.8	0.6
7	793	9.8	11	0.87	0.93	6.5	1.3
8	677	10.1	23	0.78	0.95	18.5	1.0
Mean	525	7.7		0.69	0.82	16.8	1.0
s.d.	166	1.6		0.17	0.13	10.3	0.6
Median			11				

* Dose of CBZ from the 20/200 Oros taken to be 200 mg (0.8465 mmol).

** Dose from the Oros corrected for the actual amount released.

the dose was not released from the Oros, whilst approximately 6% of the dose was recovered in the spent systems in the two subjects with the slowest transits. The corresponding values in the other four subjects, who had total transit times of 22–23 h, ranged from 11–19% of the dose.

Pharmacokinetic data

Mean plasma CBZ concentrations following oral administration of the CBZ suspension and the Oros are

shown in Figure 3. The dose-normalised pharmacokinetic parameters are given in Tables 2 and 3.

Following administration of the 100 mg CBZ suspension, peak plasma drug concentrations were achieved after 0.75–6.0 h (median, 1.75 h). Peak concentrations (C_{max}) were 5.92–7.74 $\mu\text{mol l}^{-1}$ (mean $\pm$ s.d., $6.72 \pm 0.73 \mu\text{mol l}^{-1}$). The mean C_{max} after the Oros was $6.49 \pm 1.39 \mu\text{mol l}^{-1}$ (range, 4.36–8.57 $\mu\text{mol l}^{-1}$, achieved 11–31 h post-dosing (median t_{max} , 11 h). Dose normalised AUC and C_{max} values are shown in Tables 2 and 3. The mean dose-normalised AUC value was lower after the

Figure 2 Cumulative *in vivo* absorption of CBZ from the Oros system (●—●) in individual subjects compared with cumulative *in vitro* release (—). Annotations indicate arrival of the Oros in the small intestine (SI), colon and defaecation of the device (Out).

Figure 3 Plasma CBZ concentrations after the administration of a 2% suspension of [¹⁵N]-labelled CBZ (○) and a 20/200 Oros (●) (mean ± s.e. mean).

Oros than after the CBZ suspension. Relative bioavailability for the system (Table 2), calculated from the ratio of dose-normalised AUC values (Oros/suspension), ranged between 0.36–0.87 (mean, 0.69). When corrected for the actual amount of CBZ delivered, relative bioavailability for the Oros ranged from 0.54–0.95 (mean, 0.82). The terminal elimination half-life ($t_{1/2,z}$) was similar following the suspension (28.8–49.8 h; mean 38.8 h) and the Oros (30.9–51.2 h; mean 39.3 h).

Estimates of cumulative *in vivo* drug release in each subject following oral administration of the Oros are shown in Figure 2. The position of the Oros in the g.i. tract is appended to the plots. Furthermore, a standard mean *in vitro* release profile is plotted on the same graph, to illustrate where the *in vivo* absorption from the Oros differed from the *in vitro* release rate.

In subjects 3, 7 and 8, it was not possible from the scintigraphic analysis to determine the time when the Oros arrived in the colon. Consequently, for these subjects it was difficult to relate any changes in the *in*

Table 3 Dose-normalised pharmacokinetic parameters following administration of a 2% suspension containing 100 mg (0.4233 mmol) of ^{15}N -labelled CBZ

Subject	Total AUC* ($\mu\text{mol l}^{-1} \text{ mmol}^{-1}$ of dose h)	C_{max} ($\mu\text{mol l}^{-1} \text{ mmol}^{-1}$ of dose)	t_{max} (h)
1	761	17.4	0.75
2	659	17.4	0.75
3	829	14.9	3.00
4	683	14.0	5.00
5	678	14.6	0.75
6	661	18.2	2.00
7	907	16.5	6.00
8	872	14.0	1.50
Mean	756	15.9	
s.d.	101	1.7	
Median			1.75

vivo absorption profile to the position of the Oros in the intestine. Subjects 2 and 4 showed the clearest relationship between the rate of drug input and the location of the osmotic pump system. In subject 2, the *in vivo* absorption profile closely followed the *in vitro* release pattern, until the system entered the colon, 4.9 h after dosing. *In vivo* absorption then appeared to stop almost completely from 5–11 h post-dosing, indicating little or no absorption of CBZ from the colon. Close inspection of the scintigraphs (Figure 1) revealed that this latter period corresponded to a time when the Oros was stationary in the ascending colon. Between 11 and 23 h, absorption increased again, although the rate was slower than before the system entered the colon. This renewed *in vivo* absorption may have coincided with the movement of the Oros through the colon. A similar pattern was observed in subjects 1, 4 and 6. The *in vivo* absorption profiles were similar to the *in vitro* release profiles while the Oros were located in the stomach and small intestine. The rate of *in vivo* absorption then appeared to slow down once the Oros entered the colon. Finally, in subject 5 the *in vivo* and *in vitro* profiles followed fairly similar patterns, although the rate of absorption appeared to be reduced whilst the Oros was in the colon. The rate of *in vivo* absorption, however, had already begun to slow down before the Oros emptied from the stomach. In this subject the Oros was retained in the stomach for 9.5 h.

Discussion

The administration of a CBZ 20/200 Oros after a standard breakfast led to delayed and variable gastric emptying of the dosage form. Gastric emptying of an Oros (oxprenolol Oros 16/260) after administration to fasting subjects has previously been shown to be rapid and reasonably consistent (Davis *et al.*, 1988b).

Total transit time ranged from 10–60 h. These times are similar to those recorded previously in a small number of individuals given an Oros on an empty stomach (Davis *et al.*, 1988b; John *et al.*, 1985).

The dose-normalised pharmacokinetic parameters demonstrate that the CBZ 20/200 Oros behaves as a

slow-release formulation; producing a reduced C_{max} and increased t_{max} compared with the oral suspension. The mean AUC value was, however, also reduced following dosing with the Oros.

Deviations from the *in vitro* release rate were more apparent when the Oros entered the colon. The data suggest that there was decreased absorption of CBZ when the Oros was located in the colon. CBZ appeared to be rapidly absorbed when the Oros was in the stomach or small intestine; the rate of absorption being determined by the release of drug from the system. It is not possible from the present study to distinguish whether the decreased *in vivo* absorption of drug when the Oros was in the colon was due to low absorption of CBZ into the systemic circulation from the colon or to reduced release of drug from the Oros when it was located in the colon.

The semi-permeable membrane of the Oros dosage form permits only the passage of water into the system. Thus dissolution of the core and subsequent delivery of the drug should not be influenced by factors such as pH, ionic strength or luminal environment. This has been demonstrated by *in vitro* measurements under different conditions (Theeuwes *et al.*, 1985). Other than dosage form characteristics, drug delivery should be influenced only by intra-luminal osmolarity and temperature, both of which show little physiological variability throughout the gut (Theeuwes *et al.*, 1985).

Little is known about the colonic absorption of CBZ. Rectal absorption of the drug from suppository or suspension has been observed by previous workers (Johannessen *et al.*, 1984; Graves *et al.*, 1985; Neuvonen & Tokola, 1987). Although the absorption was significantly slower via the rectal route, the total bioavailability was similar as long as the formation was not defaecated (Neuvonen & Tokola, 1987).

The bioavailability of CBZ from the Oros was lower than that from the oral suspension. A variable proportion of the dose was not released from the system. However, whilst this explains part of the reduction in bioavailability, it does not completely account for the reduced AUC obtained from the Oros.

In conclusion, the present study has shown that a single dose cross-over study with CBZ can be performed with one treatment period, using stable isotope technology and GC-MS analysis.

Our findings also illustrate the value of combining a pharmacokinetic interpretation with a determination of the position of the dosage form in the g.i. tract, when evaluating an Oros controlled release system. CBZ was released from the Oros and absorbed efficiently when the system was in the stomach and small intestine. However, systemic absorption of CBZ was reduced when the Oros was situated in the colon. In two subjects

rapid expulsion of the dosage form occurred, leading to a reduction in bioavailability.

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