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Effects of polysorbate 80 on the pharmacokinetics of a carbamazepine suppository in the rabbit

J.E. Fontan, P. Arnaud and J.C. Chaumeil

Laboratoire de Pharmacie Galénique, Département de Pharmacotechnie, Faculté des Sciences Pharmaceutiques et Biologiques, Université René-Descartes Paris V, 4 avenue de l'Observatoire, 75270 Paris Cedex 06 (France)

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Summary

The effect of polysorbate 80 on the rectal absorption of carbamazepine from a fatty suppository was investigated in the rabbit. Each animal received successively (with a wash-out of 1 week between every administration) two oral capsules of 100 mg, a suppository of carbamazepine 200 mg without surfactant, and a suppository of carbamazepine 200 mg including 2% polysorbate 80. After oral administration, the following values were obtained: C_{max} 43 ± 17 μmol/l; T_{max}, 5.1 ± 2.3 h; AUC, 391 ± 204 μmol h l^{-1}. Subsequent to rectal administration of a suppository without polysorbate 80, the corresponding values were: C_{max}, 28 ± 2.9 μmol/l; T_{max}, 2.8 ± 1.3 h; AUC, 203 ± 29 μmol h l^{-1}. The inclusion of polysorbate 80 resulted in a C_{max} of 26 ± 6.2 μmol/l at 1.7 ± 0.5 h. The AUC value amounted to 242 ± 66 μmol h l^{-1}. In the rabbit, rectal administration of carbamazepine from a suppository is more regular than oral absorption from capsules. Polysorbate 80 could enhance the rate and reproducibility of rectal absorption of carbamazepine from a fatty suppository: the serum concentration at 45 min amounted to 20.9 ± 3.8 μmol/l for the suppository containing polysorbate 80 vs 14.6 ± 5.9 μmol/l for that without.

Introduction

Carbamazepine is indicated for the control of epilepsy, trigeminal neuralgia, bipolar affective disorder and acute mania. A rectal dosage form of carbamazepine is not commercially available, but is of particular interest when oral administration is impossible. Rectal administration of carbamazepine has been investigated in humans, using suspensions (Djimbo and Moes, 1986; Neuvonen and Tokola, 1987; Brouard et al., 1990) or suppositories (Johannessen et al., 1984). Carbamazepine is quite insoluble in water, its rectal absorption thus being limited by its rate of dissolution (Moolenar and Schoonen, 1980). The rate of dissolution of carbamazepine from a fatty suppository is enhanced in vitro by non-ionic surface-active agents, especially polysorbate 80 (Fontan et al., 1991). Therefore, in the rabbit, we investigated the pharmacokinetics of carbamazepine (with and without polysorbate 80) after rectal administration in comparison with an oral dose of carbamazepine.

Correspondence: J.E. Fontan, Laboratoire de Pharmacie Galénique, Département de Pharmacotechnie, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France.

Materials and Methods

Materials

Carbamazepine was supplied by Ciba-Geigy, Rueil-Malmaison, France (granulometry: 50–200 μm). Semisynthetic glyceride (Witepsol H 15®, Atlas-Chimie, Paris, France) was used as the suppository base. The melting point of this excipient was 34.5°C and its hydroxyl index was less than 15. Polysorbate 80 (Montanox 80®, Seppic, Paris, France) was used at a concentration of 2% of the total mass of the suppository.

Preparation of suppositories

1-g suppositories including carbamazepine 200 mg were prepared by the melting method, using a metal mould. Polysorbate 80, followed by carbamazepine, was incorporated into the Witepsol H 15® liquid mass at 40 ± 1°C to avoid polymorphic forms and caking. Hard gelatin capsules, containing carbamazepine 100 mg, were prepared (with lactose as adjuvant) using a volumetric method.

Control of suppositories and capsules

20 suppositories and capsules were used to measure the weight variations, according to the European Pharmacopeia. Homogeneity of mass was verified optically on the entire suppository and with a half-suppository cut either longitudinally or transversely. The carbamazepine content was determined spectrophotometrically (Fontan et al., 1991). The suppository base and surfactants did not absorb at this wavelength.

TABLE 1

Latin Square design for the experiments (OC, oral capsules; S, suppository without polysorbate 80; SP, suppository including 2% polysorbate 80)

Rabbit	Treatment		
A	OC	SP	S
B	OC	S	SP
C	SP	OC	S
D	SP	S	OC
E	S	SP	OC
F	S	OC	SP

Pharmacokinetics

Six 'Fauve de Bourgogne' rabbits, weighing 3.0 ± 0.3 kg, were fasted 16 h prior to the experiments to avoid defaecation, but water was given freely. After insertion of the suppository into the rectum, the anal end was pinched with a clip. Each animal received successively two capsules of carbamazepine 100 mg per os, a suppository of carbamazepine 200 mg without polysorbate, and a suppository of carbamazepine 200 mg including 2% polysorbate 80. Since carbamazepine is an enzyme inducer, an interval of 8 days was allowed as wash-out time before every subsequent experiment on the same animal. Furthermore, the study was performed using a Latin Square design with a three-way crossover (Table 1) to compare the results and avoid periodic effects.

Samples of heparinized blood were taken just before and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after rectal administration, and just before and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after

TABLE 2

Pharmacokinetic parameters (mean ± SD) of carbamazepine 200 mg administered to rabbits (n = 6) (OC, oral capsules; S, suppository without polysorbate 80; SP, suppository including 2% polysorbate 80; p, significance evaluated by Student's t-test for paired samples)

	$C_{45\,min}$ (μmol/l)		C_{max} (μmol/l)		T_{max} (h)		AUC (μmol h l^{-1})		$T_{1/2}$ (h)
OC	–		43 ± 17		5.1 ± 2.3		391 ± 204		4.7 ± 2.1
			NS		NS		t = 0.07		NS
		t = 0.05		t < 0.05		NS		NS	
S	14.6 ± 5.9		28 ± 2.9		2.8 ± 1.3		203 ± 29		3.5 ± 1.1
	t = 0.05		NS		NS		NS		NS
SP	20.9 ± 3.8		26 ± 6.2		1.7 ± 0.5		242 ± 66		5.2 ± 1.7

oral administration. Samples were immediately centrifuged for 10 min at 4000 rpm. Blood plasma was collected and stored at −15°C. All samples were analysed by an enzyme-multiplied-immuno assay (EMIT, Syva-Biomerieux, Lyon, France), which allowed determination of concentrations to 8.4 μmol/l (2 mg/l), with a coefficient of variation less than 5%. The area under the serum concentration-time curve (AUC) was calculated according to the trapezoidal method with extrapolation to infinity.

Student's *t*-test for paired samples was used for statistical analysis.

Results

In vitro results

Variations in weight were 0.142 ± 0.0035 g for the capsule, 1.232 ± 0.008 g for the suppository without surfactant, and 1.237 ± 0.013 g for the suppository containing polysorbate 80. The drug content of the commercial galenic forms was in the range of 99–105% of the theoretical amount.

In vivo results

The pharmacokinetic data are listed in Table 2.

The mean serum concentrations of each dosage form are depicted in Figs 1 and 2. Following oral administration, the maximal serum concentration of carbamazepine (C_{max}) was found to be 43 ± 17 μmol/l, being reached after 5.1 ± 2.4 h (T_{max}).

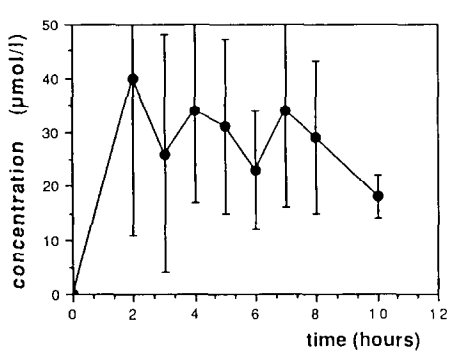

Fig. 1. Mean and SD serum concentrations vs time after oral administration of carbamazepine 200 mg to rabbits ($n = 6$).

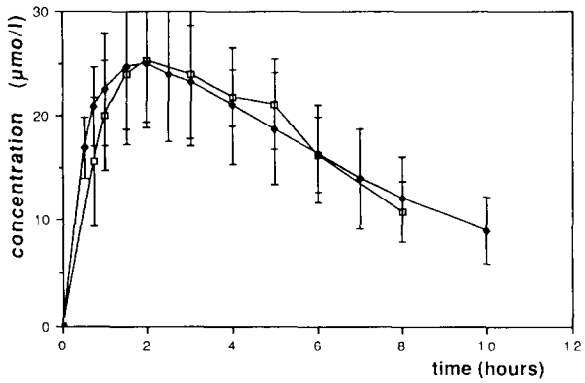

Fig. 2. Mean and SD serum concentrations vs time after rectal administration of carbamazepine to rabbits ($n = 6$). 200 mg suppository (◆ ——— ◆) including 2% polysorbate 80; 200 mg suppository (□ ——— □) containing carbamazepine alone.

The half-life ($T_{1/2}$) was determined to be approx. 4.7 ± 2.1 h, the AUC value being 391 ± 204 μmol h l^{-1}. Rectal administration of a suppository without polysorbate 80 resulted in a mean serum concentration at 45 min ($C_{45\,min}$) of 14.6 ± 5.9 μmol/l, and a maximal serum concentration of 28 ± 2.9 μmol/l at 2.8 ± 1.3 h. The half-life was 3.5 ± 1.1 h, and the AUC value amounted to 203 ± 29 μmol h l^{-1}. Administration of carbamazepine in the case of a polysorbate 80-containing suppository resulted in the following values: $C_{45\,min}$, 20.9 ± 3.8 μmol/l; maximal concentration, 26 ± 6.2 μmol/l at 1.7 ± 0.5 h; half-life, 5.2 ± 1.7 h; and AUC, 242 ± 66 μmol h l^{-1}.

Discussion

Polysorbate 80 enhanced both the rate and reproducibility of rectal absorption of carbamazepine from fatty suppositories. The mean serum concentration arising from oral administration showed considerable variability in the extent of gastrointestinal absorption of carbamazepine (Fig. 1). The mean values were erratic, and the standard-deviations (SD) were large. Consequently, the pharmacokinetic parameters evaluated for oral administration were inaccurate.

The serum concentration-time profile for rectal administration of the carbamazepine suppository without polysorbate 80 showed greater regu-

larity in the pattern of resorption. The single-compartment model fitted the data more closely. However, during the resorption phase, the SD values remained large (Fig. 2).

The resorption phase could be more regular with the suppository including 2% polysorbate 80: the SD values of the resorption phase were lower. Furthermore, resorption was more rapid with polysorbate 80: the mean serum concentrations at 45 min were determined to be 20.9 and 12.9 μmol/l, respectively, for the suppository with and without polysorbate 80 ($p = 0.05$).

Statistical analysis demonstrated no significant difference in the values of C_{max}, $T_{1/2}$ and AUC between the two suppositories (Table 2).

The T_{max} of the suppository containing polysorbate 80 appeared shorter than that of the suppository without polysorbate, although no statistical evidence was obtained ($p = 0.07$). The C_{max} of the oral form was greater ($p = 0.05$) and the T_{max} was found to be longer ($p < 0.05$). The inaccuracy in the values of the oral parameters could be the reason for the lack of statistical differences between the values of oral vs rectal AUC. These data are inconsistent with the experimentally determined values on humans reported by Johannessen et al. (1984), who obtained a value of T_{max} of 12.3 h for rectal administration using a fatty suppository base vs 5.1 h for oral administration of tablets.

Polysorbate 80 can enhance drug absorption via two mechanisms: on the one hand, a drug-surfactant interaction (including micellar solubilization) and a direct action on rectal mucosa (solubilization of membrane components and release of proteins from the rectal mucosa) (Gibaldi and Feldman, 1970). On the other, enhancement of resorption could have been inhibited by intrarectal micellar solubilization (Djimbo and Moes 1986).

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