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The rabbit: an animal model for comparative bioavailability studies of drugs

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Summary

A simple method for the study of comparative bioavailability of drugs in the rabbit was developed and tested by examining the absorption of three different brands of carbamazepine tablets marketed in Finland. With a plastic catheter–rubber balloon device an intact 200 mg tablet of carbamazepine was applied to the rear pharynx of the rabbits after a 22-h fast, and the bioavailability was measured from the carbamazepine and carbamazepine-10,11-epoxide serum levels for up to 24 h. Carbamazepine was fairly constantly absorbed with no great variations from rabbit to rabbit. The results agree with previous observations for the bioavailability of these brands of carbamazepine in humans.

Introduction

Before marketing a drug product, the manufacturer must show its bioavailability, and in the case of synonym drugs (generic equivalents) the bioavailability must be compared to drugs already marketed. Usually the bioavailability studies are performed on healthy volunteers and the bioavailability is then only compared to one (usually the original) product on the market in that particular country. Due to difficulties sometimes occurring in getting volunteers, due to relatively high cost and due to possible side-effects it would be desirable to have an animal model for these bioavailability studies. In addition, while the in vitro dissolution tests and other pharmaceutical and chemical analyses do not always give reliable information about the absorption properties of drugs as demonstrated in our laboratory (Venho et al., 1984), an animal model for comparative bioavailability studies in the quality control of drugs would be advantageous. Therefore we tested a rabbit method for this purpose by giving 3 different preparations of carbamazepine to rabbits as the marketed products and by measuring their absorption from blood levels attained, respectively.

Materials and Methods

Seven male rabbits weighing 3.1–4.7 kg were given a 200 mg tablet of carbamazepine (Tegretol/Ciba-Geigy, Switzerland; Temporol/Orion Pharmaceuticals, Finland; Neurotol/Farmos

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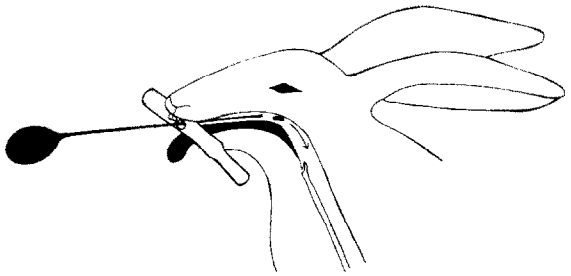

Fig. 1. The method of administering an intact tablet to rabbits. The mouth is held open and the tongue protruded with a wooden stick. The tablet is attached to the end of a plastic catheter connected to a rubber balloon. By pressing the balloon the tablet is deposited in the rear pharynx of the rabbit.

Group, Finland) at one week intervals, respectively. The rabbits were fasted overnight for about 22 h, but water was allowed ad libitum. On the following morning a 0-sample of blood was obtained from the marginal ear vein, and the carbamazepine tablet was applied to the rear pharynx of the rabbit with a plastic catheter–rubber balloon device through a hole in a wooden stick holding the mouth open and the tongue sufficiently protruded out of the mouth (Fig. 1). The tablet was pushed to the open end of the plastic catheter, and the air pressure generated by pressing the rubber balloon forced the tablet so far into the pharynx that the rabbit could not spit it out of the mouth. No water was given afterwards, but the rabbit was observed for some 20 min in order to ascertain that it really swallowed the tablet. Food was allowed at 3 h.

Blood samples were drawn from the marginal ear vein at 1, 3, 5, 7 and 24 h after the drug administration, the sera were separated and the samples stored at −18°C for some weeks until the drug concentration assay.

Carbamazepine and carbamazepine-10,11-epoxide in the serum samples were analyzed by HPLC (MacKichan, 1980) using lorazepam as the internal standard.

The bioavailability of carbamazepine and

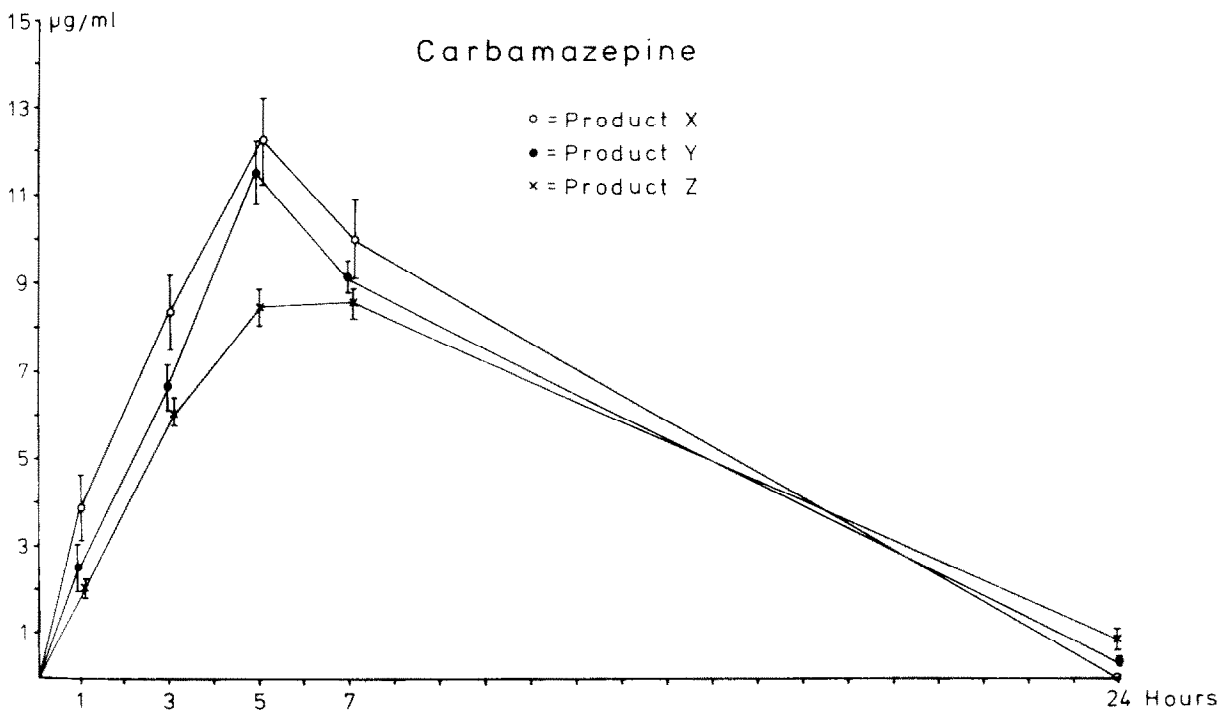

Fig. 2. Serum levels of carbamazepine in 7 rabbits (Means ± S.E.) after the administration of 3 different intact 200 mg tablets of carbamazepine. The AUC-values are shown in Table 1.

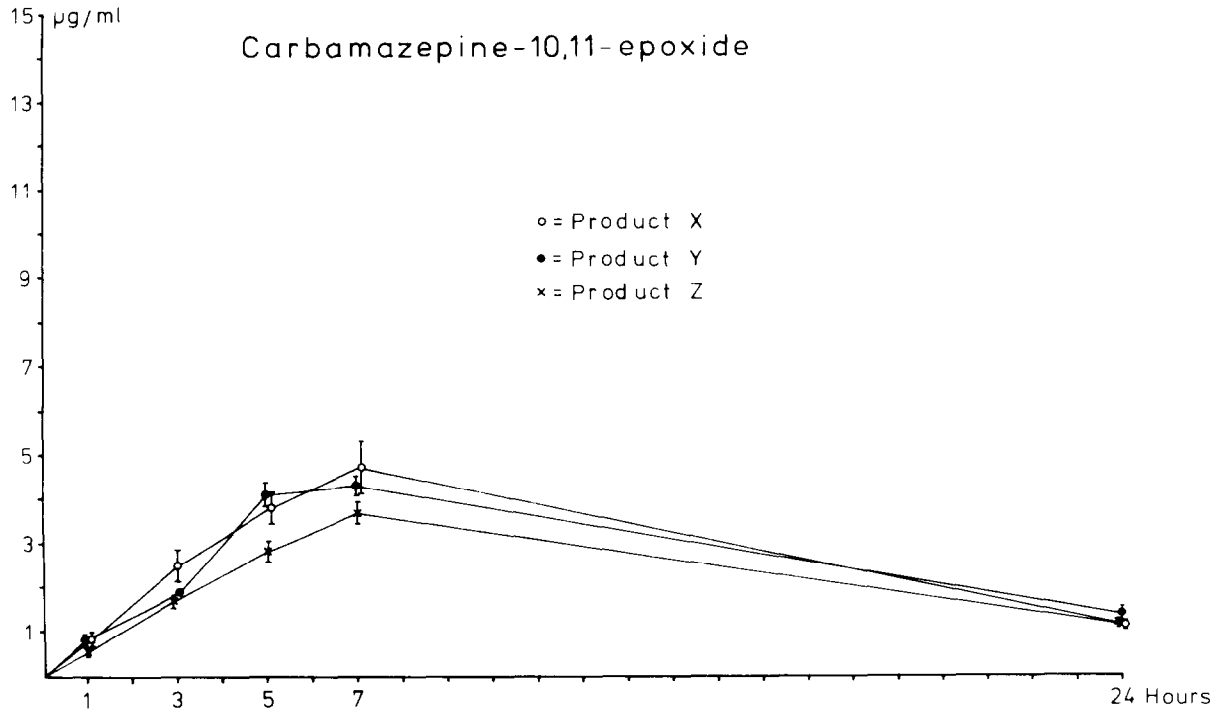

Fig. 3. The serum levels of carbamazepine-10,11-epoxide (the metabolite of carbamazepine) in the same rabbits as in Fig. 2.

carbamazepine-10,11-epoxide was calculated from the respective AUC-values measured by the trapezoidal rule. Student's paired *t*-test was employed as the statistical method.

Results

The average serum levels (mean ± S.E.) produced by the three preparations are shown in Figs. 2 and 3 and the numerical AUC-values in Table 1.

TABLE 1

THE AUC-VALUES OF CARBAMAZEPINE AND CARBAMAZEPINE-10,11-EPOXIDE (MEANS ± S.E.) IN 7 RABBITS

Product	AUC (µg/ml·h)	
	Carbamazepine	Carbamazepine-10,11-epoxide
Product X	141.3 ± 21.4	68.5 ± 14.8
Product Y	129.6 ± 9.3	65.5 ± 7.7
Product Z	106.1 ± 12.6	54.9 ± 1.7

Although Product Z seemed to be somewhat more slowly absorbed than the others, at no time of observation were there any statistically significant differences in serum levels of carbamazepine or its epoxide metabolite. The AUC-values did not differ significantly from each other either.

Discussion

In comparative bioavailability studies it is important to give the preparations in the final marketed dosage form and not as a solution in water, etc. After some preliminary experiments and a little training it was not difficult to administer carbamazepine tablets to the rabbits, and in the case of these tablets it was not necessary to give water, e.g. by stomach tube, to the rabbits. In the case of rapidly disintegrating and friable tablets one may have difficulties in giving them with the described technique to rabbits, however. The same probably holds true for gelatin capsules, which

may be liable to stick to the pharynx or oesophagus. Because the rabbits were not of equal weight the dosage/kg of body weight was different of course, just as in the case of human volunteer studies, but the role played by this fact can be minimized by giving every preparation to every rabbit.

The results obtained show no great variation from rabbit to rabbit demonstrating a fairly constant absorption from the gastrointestinal tract. Furthermore, the results are in good agreement with results obtained in humans using similar tablets (Pynnönen et al., 1978; Neuvonen, 1985). The carbamazepine levels obtained with the present dosage levels (about 40–60 mg/kg) are of the same order of magnitude as the levels in rats after 50 mg/kg (Brechbühler and Theobald, 1976), but the metabolite levels in rabbits remained lower.

In pharmacokinetic studies in animals with intact drug preparations dogs have often been used. Rabbits are easier to breed and are relatively cheap, which makes them more convenient as laboratory animals. The gastrointestinal tract of the rabbits differs from that of humans, however, and there are often difficulties in getting their stomachs empty because of the long stomach emptying time (Chiou et al., 1969). During the nighttime rabbits are liable to eat their feces directly from anus, and this tendency to coprophagy to a certain degree explains the slow emptying of the stomach even during a conventional overnight fast (Maeda et al., 1977). When using so-called "stomach emptying-controlled rabbits", Maeda et al. (1977) have found that the absorption of griseofulvin, indomethacin or nalidixic acid was much faster and more complete than after a conventional 24-h fast. Also there was a good correlation between the bioavailabilities of 3 different formulations of griseofulvin between the "stomach emptying-controlled rabbits" and humans (Maeda et al., 1979).

So, at least with the carbamazepine tablets studied the present method seems to be useful, and the results are in good correlation with the bioavailability studies made in humans. It is possible, however, that particularly in the case of acid-labile drugs more emphasis must be paid to stomach emptying when administering drug formulations with the described technique.

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