Bioavailability of rectally administered carbamazepine mixture

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The relative bioavailability of carbamazepine mixture was studied after oral and rectal administration to healthy subjects. The absorption was significantly slower after the rectal than after the oral route but the total bioavailability was similar provided the mixture was not defaecated within 2 h of administration. We conclude that carbamazepine can be administered rectally, e.g. to postoperative patients in doses corresponding with oral doses.

Keywords carbamazepine rectal administration bioavailability

Introduction

Carbamazepine is increasingly used as an anti-epileptic. The lack of parenteral and rectal formulations, however, sometimes complicates its administration, e.g. to unconscious patients. After facing this problem on several occasions, we have studied the possibility of administering carbamazepine mixture rectally.

Methods

Eight female, healthy volunteers participated in the randomized cross-over study. Care was taken to exclude early pregnancy.

The carbamazepine mixture used (Macrepan, Huhtamäki Ltd Pharmaceuticals, Finland) contained carbamazepine 20 mg ml⁻¹ and sorbitol 300 mg ml⁻¹ in water.

After an overnight fast 10 ml of the mixture (= 200 mg of carbamazepine) was administered at random to each subject either orally or rectally on separate occasions, at an interval of 1 week. Fasting was continued for the first 3 h after dosing. Physical activity was not limited and the subjects performed their normal laboratory and office work routines.

Venous blood samples for h.p.l.c. determination of serum carbamazepine and carbamazepine 10, 11-epoxide concentrations (MacKichan, 1980) were taken 1, 2, 3, 5, 8, 24, 48, 72 and 96 h

after the administration. The individual peak concentrations in serum, the peak times and the areas under the serum drug concentration-time curves during the first 96 h (AUC_{0-96h}, trapezoidal rule) were calculated. Side effects were recorded on a questionnaire.

Means $\pm$ s.e. mean are given. Student's *t*-test for paired values was used.

Results

Figure 1 shows serum concentrations of carbamazepine and carbamazepine 10, 11-epoxide in those six subjects (age 36 ± 3 years, weight 65 ± 3 kg) who did not defaecate within the first 2 h of the administration.

The absorption of carbamazepine was somewhat slower after the rectal than after the oral administration. The time of the peak concentration was 2.8 ± 1.2 h after the oral, and 5.2 ± 0.7 h after the rectal administration ($P < 0.05$). The peak concentration of carbamazepine in serum was 13.8 ± 0.6 $\mu\text{mol l}^{-1}$ after the oral, and 10.0 ± 1.7 $\mu\text{mol l}^{-1}$ after the rectal administration (a non-significant difference). The total bioavailability of carbamazepine, measured as the area under the serum carbamazepine concentration-time curve (AUC_{0-96 h}) was nearly the same during both phases of the study.

Figure 1 Serum concentrations and the areas under concentration-time curves (means $\pm$ s.e. mean) of carbamazepine and carbamazepine 10, 11-epoxide following the administration of carbamazepine mixture (= 200 mg of carbamazepine) either orally ($\bullet$) or rectally ($\circ$) in a cross-over manner to six subjects. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ in Student's paired t -test compared with corresponding parameters after oral administration.

The serum concentration of carbamazepine 10, 11-epoxide was lower ($P < 0.05$) during the first 5 h after rectal than after oral administration of carbamazepine.

Two subjects defaecated within 1 h of rectal administration. Here, the bioavailability of carbamazepine was only 10–20% of that during the oral phase.

Central side effects (dizziness) were more common after the oral (in six subjects) than after the rectal (in three subjects) administration.

Discussion

Rectally given carbamazepine was well tolerated, even in ambulatory subjects. The defaecation in two cases may have been caused by the laxative effect of sorbitol. In addition to carbamazepine 20 mg ml⁻¹, the mixture contained sorbitol 300 mg ml⁻¹, i.e. the dose of sorbitol given was 3 g. Because different carbamazepine mixtures contain different amounts of sorbitol they are not necessarily equal in tolerability and bioavailability, when given rectally. Larger doses of carbamazepine mixture may increase the laxative

effect but this seldom is a significant problem in those patients who need rectal carbamazepine, e.g. postoperative and unconscious patients. In any case, the possibility of sorbitol-defaecation should be kept in mind after high doses.

Central side effects were, if anything, more common after the oral than after the rectal administration. This may be due to the rapid absorption and high serum peak concentrations of carbamazepine after the oral intake when a formulation with a rapid absorption is used (Neuvonen, 1985).

The relative amount of carbamazepine 10, 11-epoxide in serum was about the same during both phases of the study. This is in accordance with the concept that carbamazepine is a poorly extracted drug with little or no first-pass metabolism.

It is concluded that carbamazepine mixture can be administered rectally. Although the absorption is somewhat slower the rectal bioavailability is nearly as good as the oral, provided that the mixture is not defaecated within 2 h of administration. A high concentration of sorbitol may render the oral mixture less suitable for rectal application.

References

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