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Notes

Impairment of carbamazepine tablet disintegration in patients

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Summary

In a selected patient group, occurrence of incompletely disintegrated parts of carbamazepine immediate release tablets in the stool was investigated. The results show that fecal excretion of tablet parts was a common phenomenon in some patients. The conversion of carbamazepine to insoluble polymorphic forms during storage or in vivo may be a possible explanation for this result.

Carbamazepine is an anti-epileptic drug used in the treatment of generalized and partial seizures, trigeminal neuralgia and bipolar depression.

Carbamazepine is only slightly soluble in water, and absorption after oral administration is slow: peak plasma levels are attained at 4–24 h after oral administration of tablets. Absolute bioavailability of tablets is 70–90%. The pharmacokinetics of this drug are further complicated by a complex metabolism, resulting in the formation of at least one active metabolite (carbamazepine-10,11-epoxide), enterohepatic cycling and auto-induction of metabolic conversion. Consequently, pharmacokinetic profiles of carbamazepine show a fairly large inter-patient variation (Bertilsson and Tomson, 1986). Because of incidental reports that patients excreted parts of tablets via the feces, we performed a pilot study to investigate this problem.

Before commencing the study we obtained approval of the local institutional review board consisting of medical and scientific staff, the board of directors, nursing staff and parents. Patients participating in this study all had reportedly excreted tablet fragments in their stool. All patients (five males and four females, divided over two pavilions) suffered from profound mental retardation. The median age was 24 years (range 14–50 years), and the median weight 39 kg (mean 38 kg, range 23–57 kg). All patients were on carbamazepine medication and used two to five tablets of 200 mg carbamazepine daily, divided over two to three doses. Most patients were administered laxatives on a daily basis, mainly Plantago ovata-preparation (Metamucil®, Searle) and/or lactulose syrup. All patients wear diapers and rely heavily on support by the nursing staff in their daily routine.

Two brands of carbamazepine tablets were

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used during the study period: Tegretol® immediate release tablets (Ciba-Geigy) and Carbamazepinum PCH® 200 (Pharmachemie B.V., The Netherlands).

The defecation patterns of these nine persons were monitored over 8 consecutive weeks.

All feces of participating patients were examined for the occurrence of tablet fragments. Large fragments were collected for qualitative analysis.

The results are summarized in Table 1.

In the entire group of nine patients, a total number of 270 feces samples was examined during the study period. In 69 cases the nursing staff reported the appearance of tablet-like fragments. However, in the majority of cases these fragments were very small and could not be definitely identified as tablets. Qualitative analysis by infrared spectroscopy of three of these fine granular samples detected the presence of carbamazepine in two samples. The third sample did not contain detectable amounts of carbamazepine. The majority of these 'small-fragment' cases (53/69 = 77%) was reported in one pavilion of our institute. Because the patients in this pavilion are more closely monitored by the nursing staff than the patients in the other, a certain degree of over- or underreporting, respectively, may well contribute to this difference.

On three occasions (two patients) large fragments, clearly recognizable as tablets, were found in the stools. One patient (patient no. 5) received carbamazepine 200 mg, one tablet in the morning and one and a half tablet in the evening, and sodium picosulfate as laxative, 2 mg twice daily. He excreted a fragment of about 60 mg, which was positively identified as carbamazepine by IR spectroscopy. The second patient (patient no. 4) received carbamazepine 200 mg three times daily, phenobarbital 3×30 mg, sodium valproate syrup 2×600 mg and lactulose syrup 40 ml before breakfast. He twice excreted a large tablet fragment (approx. 60 mg) on days 28 and 38 of the study period. Both fragments were positively identified as carbamazepine. Because this patient used Tegretol® for several weeks and switched to the other formulation a day later, the fragments could with reasonable certainty be ascribed to Tegretol® (day 28) and Carbamazepinum PCH® (day 38), respectively.

Routine plasma levels showed normal values during the study period in all but one patient (no. 4) who had values of 3.0 and 3.5 ng/ml on days 34 and 48, respectively (therapeutic range 4–8 ng/ml). During the study period 14 insults were seen (6 patients), but except in patient no. 4 who had one insult (day 36) during the same period in

TABLE 1

Demographics and summary of results

Patient no.	Age (years)	Weight (kg)	Dose schedule carbamazepine	Number of feces samples	Number of feces with fragments	Percent
1	17	45	1-1-1	29	10	34
2	23	31	$1\frac{1}{2}$-$1\frac{1}{2}$-2	50	22	44
3	28	28	1-1-1	32	5	16
4	26	44	1-1-1	45	17	38
5	14	23	1-0-$\frac{1}{2}$	30	8	27
6	50	57	2-1-2	32	1	3
7	25	39	1-$\frac{1}{2}$-1	14	0	0
8	16	35	1-$\frac{1}{2}$-1	16	1	6
9	24	40	1-0-1	22	5	23
Total				270	69	21

which two large fragments were excreted, these insults were not related to an increased excretion rate of tablet fragments in other patients.

Carbamazepine shows appreciable inter-patient variation of pharmacokinetic profiles. Several external as well as patient-related factors may contribute to this variability. The aqueous solubility of carbamazepine is low, and carbamazepine tablets have a rather slow in vitro rate of dissolution: about 70–90% of the carbamazepine from the formulations used in this study was found to be dissolved after 60 min, in a dissolution test according to the USP. This slow dissolution rate may well contribute to the variability in absorption. Also, the moment of ingestion in relation to meals may be of importance. Finally, the individual metabolic make-up of the patient and the hepatic clearance will have a major contribution to pharmacokinetic variability (Bertilsson and Tomson, 1986).

In this study we present evidence for an additional complicating factor. The results suggest that with some patients excretion of tablet fragments is a rather common phenomenon.

The fact that one out of three tablet fragment samples did not contain detectable amounts of carbamazepine suggests that some particles appearing in the stool may have been falsely identified by the nursing staff as tablet pieces, or may be fragments of other tablets. Thus, although no definite conclusions may be drawn from the large number of fragments reported, the positive identification of two fragment samples as carbamazepine suggests that their occurrence in stool is more than sporadic. This is strongly supported by the appearance in the stool of large fragments, on three occasions, of carbamazepine tablets.

Gilman et al. (1988) report a case of carbamazepine malabsorption in a 6-year-old boy treated with Tegretol® immediate release tablets. They recovered a complete tablet (with imprint still legible) and several small pieces from the stool. To the best of our knowledge, no other reports of similar cases have been published.

Our study group consisted of patients with profound mental retardation, in an almost immobile state and on chronic laxative therapy producing very soft to fluid feces. This is the same type of patients as in the case reported by Gilman et al. (1988). The editorial comment following that article suggests that passage of tablet fragments may be more common in children than in adults. However, in our study large fragments were excreted by two patients of 14 and 26 years, respectively. In fact, the passage of incompletely disintegrated tablets may be related to the aberrant intestinal physiology of these patients, together with regular laxative administration. The exact reasons for the incomplete disintegration remain unclear. Rapid intestinal transit may well contribute to this phenomenon.

An additional explanation may concern the existence of polymorphic forms of carbamazepine. This substance is known to exist in several polymorphic forms, including three anhydrous and one dihydrate form which may differ in essential physicochemical properties, e.g., dissolution rate and solubility (Lefebvre et al., 1987; Lowes et al., 1987). These parameters may well affect absorption rate and bioavailability. It has been suggested that the mixed first- and zero-order absorption of carbamazepine may be caused by the presence of polymorphic forms in the dosage forms, or the conversion of one polymorph into another during the absorption process (Lefebvre et al., 1987). Furthermore, it has been shown that humidity may have a dramatic influence on the dissolution rate characteristics of carbamazepine tablets (Riad et al., 1986; Wang et al., 1989). Therefore, storage conditions (the tablets used in this study were kept in polyethylene containers of 1000 tablets, under ambient conditions of temperature and humidity) may have affected the disintegration properties of the tablets. As carbamazepine tablets consist largely of the active substance (tablets weigh 250–300 mg) this may well result in larger insoluble fragments in the stool.

In conclusion, environmental factors as well as specific intestinal (patho)physiology may affect the fate of carbamazepine tablets in the gastrointestinal tract, with possible consequences for its therapeutic effect.

Our study was performed in a small subgroup of patients. Confirmatory studies in a larger patient population appear to be warranted in order

to confirm these observations and determine their clinical relevance.

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