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EFFECT OF INCREASED BIOAVAILABILITY OF PHENYTOIN TABLETS ON SERUM PHENYTOIN CONCENTRATION IN EPILEPTIC OUT-PATIENTS

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1 The bioavailability of a brand of phenytoin tablets used in Finland was improved in 1976. In the present retrospective study serum concentrations of phenytoin, measured before and after the change of bioavailability, are compared in 50 epileptic out-patients, who for various reasons used exactly the same dose of phenytoin tablets and of other drugs despite the increased bioavailability of phenytoin.

2 The mean increase of serum phenytoin steady-state concentration was about 70% after the change of bioavailability but there were considerable interindividual differences in the response. The mean increase in serum phenytoin was only 28% in patients with serum phenytoin concentrations 5 μg/ml or less but the mean increase was 100% in patients with serum phenytoin between 5 and 10 μg/ml. In patients with serum phenytoin concentrations more than 10 μg/ml the mean increase in concentration was 60–80% after the improvement of bioavailability. However, in these groups of patients some clinically manifested phenytoin intoxications enforced the patients to the control and to dose reduction obviously before the steady-state concentration of phenytoin was reached.

3 On the basis of our experiences and those reported in the literature some proposals are presented to be considered when the bioavailability of phenytoin or of another drug with a narrow therapeutic range and a dose-dependent kinetics has to be changed.

Introduction

The increase of the bioavailability of phenytoin products has been reported to cause phenytoin intoxications in some countries (Tyrer, Eadie, Sutherland & Hooper, 1970; Rambeck, Boenigk & Stenzel, 1977). The different bioavailability of various phenytoin tablets used in Finland was observed some years ago (Pentikäinen, Neuvonen & Elfving, 1975; Tammisto, Kauko & Viukari, 1976). After this, one product (Difhydan®) has been withdrawn from the market and the bioavailability of another product (Hydantin®) has been improved with the aim of some biopharmaceutical alterations. These new Hydantin tablets were released on 1st April 1976 and all the doctors were informed by the respective company about the possibility of increased serum phenytoin concentrations and about the signs of phenytoin intoxication.

For various reasons many patients continued to use the same number of Hydantin tablets as before despite the increased bioavailability. We report here the changes of serum phenytoin concentration in patients who regularly used the same dose of phenytoin (and in certain cases other antiepileptic drugs) before and after the change of bioavailability of these phenytoin tablets.

Methods

The subjects of this retrospective study were adult epileptic out-patients who had regularly visited the Pitäjänmäki Epilepsy Research Centre in Helsinki. All the patients, who were on long term phenytoin and who had visited the Centre between 1.1.1977 and 31.3.1977, were included in the study provided that they fulfilled the following criteria:

1. The dose of phenytoin and of all other possible antiepileptic and other regular drugs had been unchanged from the year 1975 to 1977.
2. There was no reason to be suspicious of the compliance of the patient.
3. Serum concentration of phenytoin had been measured at least once during the year 1975 or

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in 1976 before the 1st April, and during the visit between 1st January–31st March 1977. If there was more than one serum concentration value during the respective study period, the mean value was used.

According to the previous criteria a total number of 70 epileptic patients was approved for the study. Of these, 50 patients had been using Hydantin® tablets and 20 patients had been taking either of the two other phenytoin tablets (Enkefal® or Dihydantoin®) with unaltered bioavailability. The last mentioned 20 patients were included as control material to exclude the effect of other possible external factors in patients and to check the reliability of the serum phenytoin analyses. Three additional cases with the development of intoxication after the change of bioavailability are described to demonstrate the time course and new dose requirement.

Serum concentrations of phenytoin of all these patients were determined in the same laboratory using the same GLC-method of Kupferberg (1970).

Means ± s.e. mean are givens. Differences between the means were analysed statistically using Student's *t*-test for paired values.

Results

Mean serum concentration of phenytoin in patients using Hydantin tablets was 11.1 ± 0.7 μg/ml before the change of bioavailability and 18.6 ± 1.7 μg/ml ($P < 0.001$) after this. Thus there was a mean increase of 68% in serum phenytoin concentration.

When these 50 patients mentioned before are classified in four subgroups according to their serum phenytoin concentrations before the change in bioavailability, considerable differences in response to new tablets can be seen (Figure 1). In eight patients with serum phenytoin concentration 5 μg/ml or less there was a statistically non-significant increase of 1.0 μg/ml (28%) in the mean serum phenytoin concentration and only in two patients serum phenytoin concentration was at least doubled (Table 1).

In 15 patients with the initial serum phenytoin concentration between 5.1 and 10 μg/ml, a mean increase of 8.3 μg/ml (100%) ($P < 0.001$) was seen after the change of bioavailability. In this group of patients the concentration was at least doubled in six patients but no clinically clear intoxication was seen despite one rather high concentration.

In 18 patients with the initial serum phenytoin concentration between 10.1 and 15 μg/ml, a mean increase was 7.5 μg/ml (57%) ($P < 0.001$) and in five patients the concentration was more than doubled. Two clear phenytoin intoxications were seen in this group. In these patients the steady-state level of

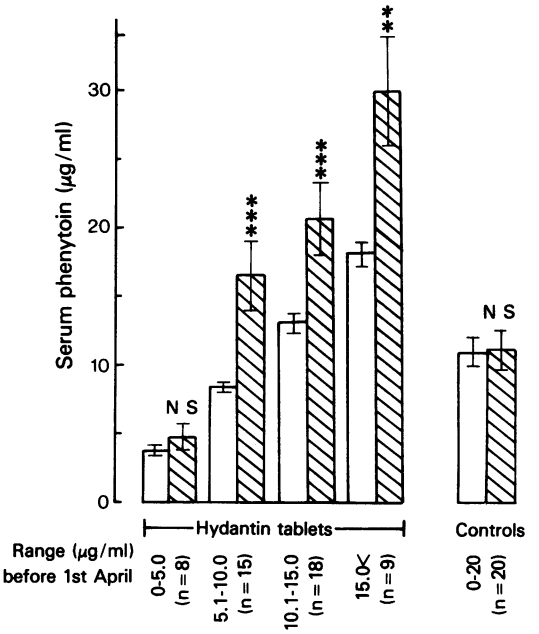

Figure 1 Mean ± s.e. mean serum phenytoin concentration in patients on long term phenytoin therapy, before (□, before April 1st 1976) and after (▨, after January 1st 1977) the increase of bioavailability of Hydantin® tablets. The subgroups refer to the concentration range before the change of bioavailability. The data concerning controls are from the respective time periods in patients using two other brands of phenytoin tablets with unaltered bioavailability. The daily dose of drugs have been unaltered in all patients. Difference between the values before and after the increase of bioavailability: $^{**}P < 0.01$, $^{***}P < 0.001$, NS non-significant.

phenytoin was perhaps not yet reached as the daily dose of phenytoin was reduced.

In 9 patients with the initial serum phenytoin concentration more than 15 μg/ml the mean increase was 12.2 μg/ml (67%) ($P < 0.01$). In this group five patients doubled their phenytoin concentration. Four patients rapidly developed clear signs of phenytoin intoxication and their daily doses of phenytoin were reduced obviously before the steady-state level was reached.

Figure 2 demonstrates the serum concentration of phenytoin in 10 typical epileptic patients with the increase of serum phenytoin level. Phenytoin concentrations were measured as routine control measurements some months before the change of bioavailability and in the first quarter of 1977. These data do not allow the evaluation of the exact time course of the phenomenon because the change to new tablets occurred in individual patients within a period of some months in 1976 and the determinations of serum phenytoin were carried out first in 1977.

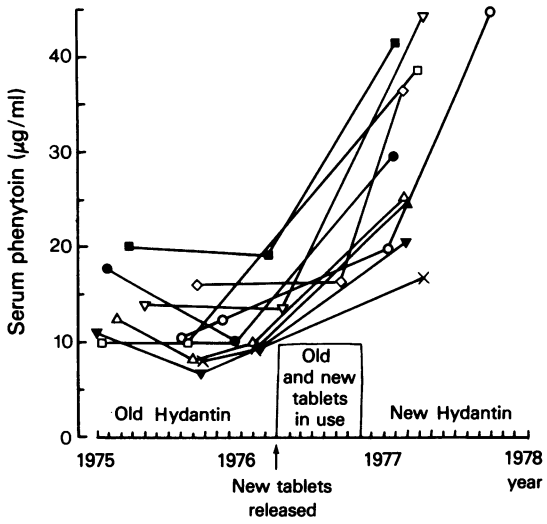

Figure 2 Serum concentrations of phenytoin in ten typical patients with increased serum phenytoin after the change of bioavailability. The daily dose of drugs have been unaltered in all patients. Due to the relative infrequent concentration determinations the exact evaluation of the time-course of the phenomenon is not possible.

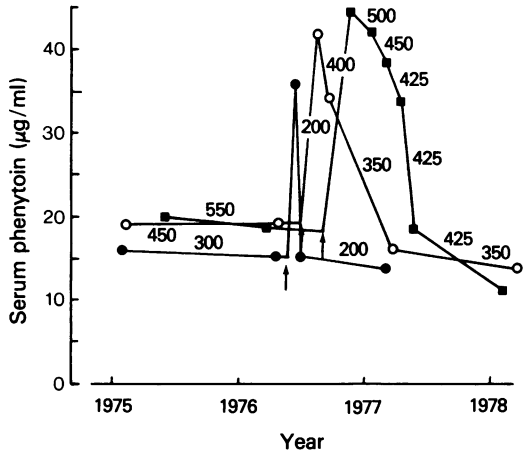

Figure 3 Serum phenytoin concentrations in three patients (●, female, 34 years; ○, female, 34 years; ■, male, 50 years) before and after the increase of bioavailability of phenytoin tablets. In all these patients clinical intoxication developed within 2–5 weeks after the change of bioavailability and the daily dose was reduced as indicated in the figure. The change to the new tablets occurred at the arrow.

Figure 3 shows more precisely the time course of the increase in serum phenytoin in three patients and the dose requirements to reach the previous serum phenytoin concentrations.

As can be seen in Figure 1 serum phenytoin concentration remained essentially unchanged in those patients who used either of the two other brands of phenytoin tablets during the respective time.

Discussion

The metabolism of phenytoin is dose-dependent in many patients already in therapeutic concentrations. Therefore even small changes in bioavailability could be expected to considerably alter serum phenytoin concentrations in patients on continuous phenytoin therapy (Houghton & Richens, 1974). This was observed also in the present study, and that in clinical practice it is difficult to prejudge those patients with most marked increase in serum phenytoin after improved bioavailability.

In a previous bioavailability study in healthy volunteers using single doses of 600 mg phenytoin the mean area under the serum phenytoin concentration curve was 57% higher with the new Hydantin tablets than with the old tablets (Neuvonen, Pentikäinen & Elfving, 1977). In the present study in epileptic outpatients there was a mean increase of about 70% in serum phenytoin concentration after the increase of

Table 1 The occurrence of phenytoin intoxication after the increase of the bioavailability of phenytoin tablets

	Serum phenytoin concentrations before the increase of bioavailability (μg/ml)			
	0–5.0	*5.1–10.0*	*10.1–15.0*	*over 15*
Total number of the patients	8	15	18	9
Mean ± s.e. mean daily dose of phenytoin (mg)	250 ± 27	350 ± 19	342 ± 16	363 ± 15
The number of patients at least doubling serum phenytoin concentration after the increase of bioavailability	2	6	5	5
The number of patients with clear clinical signs of phenytoin intoxication (evaluated by the neurologist)	0	0	2	4

bioavailability of phenytoin tablets. However, in certain individual patients serum phenytoin concentration was even decreased after the change in bioavailability. This might reflect altered compliance or some other factors which we, however, could not identify and in the absence of adequate rejection criteria the patients were included in the study.

In the group of patients with low initial serum phenytoin concentration (5 μg/ml or less) the mean increase in serum phenytoin was less than 30%. In these rather low concentrations the dose-dependency of phenytoin metabolism is less likely to occur and no harmful effects were observed in this group. The highest steady-state concentration after the increase of bioavailability was only 9.3 μg/ml.

In the patients with initial serum phenytoin concentration of 5.1–10 μg/ml, the mean serum phenytoin level was doubled after the increase of bioavailability. In this group the effect of dose-dependent metabolism of phenytoin was most typically seen because the lack of symptoms of clinical intoxication did not enforce the patients to visit their doctors before their normal visiting schedule.

In the group of patients with initial serum phenytoin concentration higher than 10 μg/ml, the mean increase in serum phenytoin levels was about 60–80%. One could anticipate even more pronounced increases in these groups. However, the development of symptoms of phenytoin intoxication in some patients enforced them to visit their doctor obviously before the steady-state concentration was reached. This caused the bias which should be kept in mind in evaluating the results of these groups. Furthermore there was some unexplained decrease in serum phenytoin concentrations which could reflect the impaired compliance. However, as the exclusion criteria were not fulfilled, these cases were also included in the study.

Mean serum phenytoin concentration remained rather constant during this observation period in those 20 patients who used either of the two other brands of phenytoin tablets with unaltered bioavailability. Therefore the laboratory analytical factors or the possibility of improved compliance of the patients are unlikely to explain the increases in serum phenytoin observed after the altered bioavailability of Hydantin tablets.

The present results demonstrate that the change of bioavailability of drugs with dose-dependent kinetics is a rather complicated problem. Although all the doctors and pharmacies were informed about the increased bioavailability of tablets as well as about the signs and time course of the possible phenytoin intoxication it was not possible to inform all the individual patients using phenytoin. Thus some patients with serum phenytoin concentrations between 10–20 μg/ml developed phenytoin concentrations about 40 μg/ml, and some even did so without nystagmus or ataxia, i.e. without clearcut clinical signs of phenytoin intoxication. In some patients the signs of intoxication developed within 2–3 weeks after the change of bioavailability but in certain patients serum phenytoin concentrations seemed to be still increasing 1–2 months after the increase of bioavailability. The same phenomenon was demonstrated also by Rambeck *et al.* (1977). The late development of intoxication seems to be related to the prolongation of the half-life of phenytoin as the metabolism is saturated. In accordance with the dose-dependent kinetics of phenytoin quite modest reduction of the daily dose resulted in the serum phenytoin level returning to the previous therapeutic level.

We propose the following procedures to be considered when the bioavailability of phenytoin, a drug with a narrow therapeutic range and dose-dependent kinetics, will be increased.

1. Comparative single dose studies in healthy volunteers, and especially steady-state studies in patients on long term antiepileptic therapy, should be done using old and new tablets before the release of the new tablets to general use.
2. During the transition period all the new tablet containers should have a clear extra label informing about the increased bioavailability and about the symptoms of phenytoin intoxication.
3. All the doctors and pharmacies should be informed about the change of bioavailability and about the time course and clinical signs of phenytoin intoxication. It should be stressed that the bioavailability studies can give only limited information about the dose requirements for an individual patient.
4. Those patients with serum phenytoin concentrations over 10 μg/ml (or over 5 μg/ml if the bioavailability is increased considerably) should be in a weekly follow up for 4 weeks. Serum phenytoin concentration should be checked if there are any subjective or objective signs of phenytoin intoxication, as well as in all these 'high risk patients' at the end of follow up period.

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