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PLASMA LEVELS OF PHENOBARBITAL RESULTING FROM SUSTAINED RELEASE TABLETS CONTAINING THEOPHYLLINE, PHENOBARBITAL AND EPHEDRINE

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SUMMARY

Plasma levels of phenobarbital were measured in 10 individuals with stable mild to moderate bronchial asthma who were receiving repeated oral doses of a commercial sustained release formulation containing phenobarbital (25 mg), theophylline (180 mg) and ephedrine (48 mg). Following the initial dose, the mean plasma level of phenobarbital was 0.72 μg/ml at 5 h and 0.62 μg/ml at 10 h. After 14 days, during which time the formulation was administered twice daily, the mean phenobarbital plasma level had increased to approximately 4 μg/ml. This value was maintained during 10 h following the last dose.

The degree of phenobarbital accumulation in plasma was predictable from previously calculated pharmacokinetic constants, and there was no evidence of autoinduction of phenobarbital metabolism. Phenobarbital is efficiently absorbed from this dosage form and plasma levels of phenobarbital accumulate 3–5 times more than those of theophylline during repeated dosing.

INTRODUCTION

Plasma levels of phenobarbital resulting from single and repeated oral doses of conventional tablets have recently been described (Viswanathan et al., 1978, 1979). Phenobarbital appears to be efficiently absorbed orally compared to intramuscular doses, and is cleared slowly from plasma with a half-life of 90 h. The elimination half-life is prolonged to 150 h following repeated doses of 30 mg/day (Viswanathan et al., 1979).

Phenobarbital is a component of a slow-release tablet [1] containing phenobarbital, theophylline and ephedrine, used commonly for the relief of chronic asthma. While the

[1] Tedral SA, Warner Chilcott.

theophylline and ephedrine are divided into both fast- and slow-release components, phenobarbital is present only in the fast-release portion of the tablet.

In a previous study, principally concerned with the comparative therapeutic efficacy of this drug combination and terbutaline, plasma levels of theophylline from the slow-release tablet were described (Bush et al., 1978). In view of the uncertain bioavailability of phenobarbital from this type of formulation, potential interference in phenobarbital absorption due to interactions with theophylline (Bettis et al., 1973), and also the possibility of accumulation in the body of the more slowly cleared phenobarbital with repeated doses, circulating levels of phenobarbital were examined in 10 individuals following single and repeated doses of the slow-release combination tablet.

MATERIALS AND METHODS

Subject details and study design have been described previously (Bush et al., 1978). Ten adults (6 male, 4 female) aged between 19 and 32 years (mean 25) with stable mild to moderate bronchial asthma participated in the study.

The original study was designed as a two-day cross-over comparing the theophylline combination with terbutaline. The two drug forms were administered alternately as single and repeated doses.

Following a 72 h period during which no bronchodilators were administered, subjects received one tablet containing 180 mg theophylline, 48 mg ephedrine and 25 mg phenobarbital twice daily, or 5 mg terbutaline thrice daily, for 14 days. Following a 72 h wash-out period subjects received the alternate therapy for a further 14 days. On sampling days, drug was administered with 100 ml water following overnight fast. No diet or water volume restrictions were applied on other dosing days. No drugs other than those concerned with the study were permitted throughout.

Ten ml of blood were collected in heparinized tubes from a forearm vein for drug assay at 0, 0.5, 1, 5 and 10 h following the first and last doses. Plasma was separated by centrifugation and stored at $-20^{\circ}C$ until assayed.

Phenobarbital was extracted from plasma and the concentrations were determined by a specific radioimmunoassay procedure (Viswanathan et al., 1977).

RESULTS

While the clinical aspects of the original study required the use of a cross-over design, the determination of circulating theophylline and phenobarbital levels related to only one of the two formulations tested. As no significant differences were observed in circulating levels of these compounds in the two days of the study, the data from all 10 individuals are combined in this analysis.

Individual plasma levels of phenobarbital

Results obtained on days 1 and 14 are shown in Fig. 1. On day 1, zero or very low phenobarbital levels were obtained in the predose sample. Levels then increased to a mean value of 0.72 μg/ml (range 0.24–1.73 μg/ml) at 5 h and 0.64 μg/ml (range 0.23–1.27 μg/ml) at 10 h. On day 14 mean plasma levels of phenobarbital had increased to 4.1

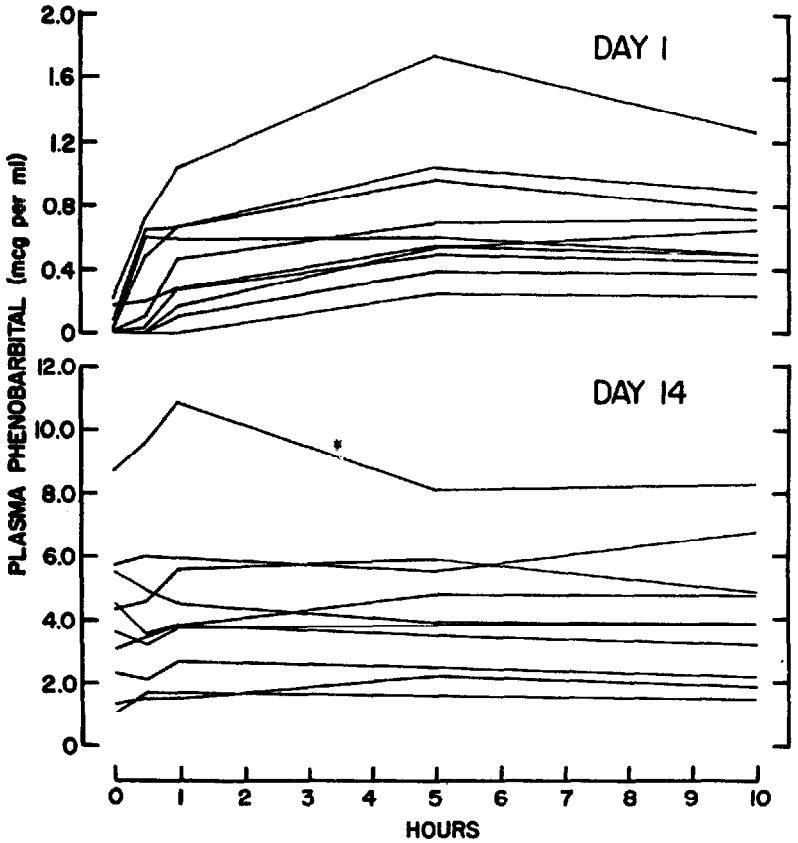

Fig. 1. Individual plasma levels of phenobarbital on the 1st and 14th day of a twice daily dosage regimen.

μg/ml (range 1.6–8.1 μg/ml) at 5 h postdosing, and 4.1 μg/ml (range 1.5–8.3 μg/ml) at 10 h. Although there was considerable inter-individual variation in plasma phenobarbital levels on both sampling days, the degree of variation was reduced on day 14 compared to day 1.

Individual subjects did not demonstrate consistently high or low phenobarbital levels on the two sampling days. The correlation coefficients between day 1 and day 14 phenobarbital levels were +0.50 at the 5 h sampling time, and +0.52 at 10 h.

DISCUSSION

Phenobarbital is included in the anti-asthmatic drug combination to counteract possible stimulation by ephedrine and also to act as a mild long-acting sedative for the apprehensive asthmatic patient.

Suggestions that complexation between theophylline and phenobarbital when formulated together may lead to reduced theophylline availability (Bettis et al., 1973) were not supported experimentally (Welling et al., 1976). Indeed, such an effect is unlikely due to the preponderance of theophylline present. However, the possibility remained that

absorption of phenobarbital may be impaired as a result of complexation in the presence of excess theophylline.

In a previous study, administration of a single 30 mg conventional phenobarbital tablet to healthy volunteers resulted in mean serum phenobarbital levels of 0.7–0.8 μg/ml during 2–8 h postdosing (Viswanathan et al., 1978), with peak levels occurring at approximately 3–5 h. Mean phenobarbital levels of 0.4–0.7 μg/ml during a similar postdosing time period in the present study suggests that, considering the relative dose sizes, the efficiency of phenobarbital absorption is similar from the two dosage forms. Insufficient blood samples were obtained following the combination tablet to permit comparison of drug absorption rates. However, from the peak height values alone, the rate of drug absorption appears also to be similar from the two dosage forms.

Following repeated doses of the combination tablet for 14 doses, peak plasma levels of phenobarbital ranged from 1.7 to 10.8 μg/ml with a mean value of 4 μg/ml. The only comparable data for conventional phenobarbital tablets was obtained in three healthy individuals who each received one 30 mg tablet daily for 21 days (Viswanathan et al., 1979). The mean peak phenobarbital level in serum after 15 days of dosing in that study was 7.5 μg/ml. As the daily dosage was 30 mg, compared to 50 mg used here, the extent of drug accumulation appears to be somewhat lower following the combination tablet compared to the conventional tablet. However, actual peak drug levels may have been missed in some instances following the combination tablet, due to infrequent sampling. The small subject population used in the previous study also precludes meaningful statistical comparison of the values.

Based on a 12 h dosing interval, steady-state plasma levels of phenobarbital should be from 8- to 13-fold higher than equivalent single dose values, depending on whether single or repeated dose half-lives are used for the calculation (2). The mean ratio of plasma phenobarbital levels on day 14 to those on day 1, excluding zero concentrations on day 1, was 9.2.

The relatively constant mean plasma levels of phenobarbital during 10 h on day 14 are also consistent with the drug's pharmacokinetic characteristics. Due to the long biological half-life of phenobarbital, the expected ratio of maximum to minimum plasma levels of steady-state is approximately 1.1. This is very similar to the observed mean ratio of 1.3.

It is noteworthy that, due to differences in their biological half-lives, plasma levels and also the total body load of phenobarbital accumulate to a far greater extent following repeated doses than those of theophylline. While phenobarbital levels increased by a factor of 10, theophylline levels increased by a factor of only 2 or 3 during the same period (Bush et al., 1978). Thus the clinical effect of phenobarbital resulting from this dosage form, however slight, will increase relative to that of theophylline during a dosing schedule and may not be detectable until several days of continuous therapy.

The plasma levels of phenobarbital obtained in this study indicate that the drug is efficiently absorbed into the circulation, and there is no evidence of theophylline–phenobarbital interactions. The degree of drug accumulation during repeated doses, and the pattern of drug levels obtained, are predictable, and are similar to those obtained from conventional phenobarbital tablets. There is no evidence of autoinduction of phenobarbital metabolism at the dosage level studied.

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