Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension

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- 1 The antihypertensive effect of alprenolol has been studied before, during and after additional pentobarbitone treatment.
- 2 The combined alprenolol-pentobarbitone treatment significantly decreased alprenolol levels by 59% and 4-hydroxyalprenolol by 24%. The effect was significant after three doses and declined over 4–5 days after pentobarbitone withdrawal.
- 3 The decreased alprenolol plasma levels were associated with increased pulse rate (6%), and systolic (8%) and diastolic (9%) blood pressure.
- 4 The inhibition of exercise tachycardia by alprenolol was reduced by 18% at the end of pentobarbitone treatment compared to initial monotherapy with alprenolol.
- 5 The interaction is probably clinically important in those patients with hypertension and angina pectoris that are treated with barbiturates and alprenolol.

Keywords alprenolol pentobarbitone interaction hypertension

Introduction

The β -adrenoceptor antagonist, alprenolol, is extensively eliminated during its first passage through the liver (Johnsson, 1974), probably due to its high affinity for cytochrome P-450 in the liver (Grundin *et al.*, 1974). The hepatic metabolic clearance in rats can be increased by treatment with pentobarbitone (Grundin *et al.*, 1974). In man such treatment decreases the availability of alprenolol and its main metabolite 4-hydroxyalprenolol (Alván *et al.*, 1977a,b). Pharmacodynamic studies have shown that this metabolite contributes to the β -adrenoceptor blocking effect of alprenolol (Collste *et al.*, 1979a) and that pentobarbitone treatment reduces the effect of alprenolol on exercise heart rate by about 20% (Collste *et al.*, 1979b). The plasma concentrations of alprenolol were correlated to the effect both before and after pentobarbitone treatment.

The cited studies have concerned the relationship between effect and plasma concentrations of single doses in healthy volunteers. This study aimed at revealing the clinical significance of this interaction. Furthermore, the time course of changes in plasma concentrations, pulse rate and blood pressure during such combined alprenolol-pentobarbitone treatment in hypertensive patients was studied.

Methods

Patients

Six non smoking patients (one male and five females; aged 29–51 years) with essential hypertension (WHO I-II) participated in the study. They had no subjective symptoms or evidence of

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concurrent disease. They did not use alcohol, tea or coffee excessively and they were instructed to refrain from alcohol and keep to their ordinary diet throughout the study. No drugs other than alprenolol and pentobarbitone were prescribed during the study. The study was approved by the ethics committee of the hospital and the subjects were included after being informed about the aims of the study.

Design of the study

All subjects were treated continuously with alprenolol 0.4 g twice daily (Aptin Duretter®, Hässle AB, Sweden) and their blood pressure was below 150/100 mm Hg (prior to study). This had been well controlled for at least 6 months. Before the study the patients were acquainted with the automatic blood pressure recorder Arteriosonde® (George *et al.*, 1975), which was used during the study to prevent bias. Pentobarbitone (0.1 g at bed time) was given for 10 days and the study lasted 14 days thereafter. The same alprenolol dose (0.4 g twice daily) was given throughout the study. Exercise tests were performed before pentobarbitone and on day 11 and 24 after its initiation. The exercise tests were performed before the morning dose and 2 h after dose intake. The effects were recorded without knowledge of alprenolol plasma concentrations.

The drug concentrations, resting pulse rate and sitting blood pressure were determined 12 h after the alprenolol evening dose before the first pentobarbitone dose and on days 2, 3, 4, 5, 6, 9, 11, 12, 13, 17, 18, 20, 23 and 24. Pentobarbitone concentrations were measured on days 6, 9 and 11. No food was allowed after midnight until morning or the 2 h samples had been drawn. Repeated alprenolol plasma concentrations and effects during a dose interval were measured before pentobarbitone and on days 11 and 24 after its initiation.

Calculations

The blood pressure was calculated as a mean of five measurements on each occasion. Resting pulse rate was calculated after 30 s palpation of the radial artery. The heart rate during the exercise test was calculated from electrocardiographic recordings during 10 watts increments of load at 1 min intervals on an electrically braked bicycle ergometer (Elema-Schönander) (Åström & Johnsson, 1976). The test was performed until the heart rate was about 120 beats min⁻¹. The load corresponding to a heart rate of 110 beats min⁻¹ was calculated for each subject. The heart rates at this load were then estimated from

the regression lines at every exercise test after dose. The drug effect was expressed as percentage change in relation to the test performed before pentobarbitone treatment. The area under the plasma concentration versus time curve was calculated using the trapezoidal technique. Differences between mean values were tested by Student's *t*-test.

Analytical methods

Venous blood (10 ml) was drawn into heparinized vacuum tubes (Venoject®) and gas chromatography was used for analysis of alprenolol and 4-hydroxyalprenolol (Kylberg-Hansen & Ervik, 1976) and pentobarbitone (Villén & Petters, 1983).

Results

The mean concentrations of alprenolol and 4-hydroxyalprenolol, blood pressure and pulse rate during the study are shown in Figures 1, 2 and 3. The plasma concentrations of alprenolol and 4-hydroxyalprenolol decreased markedly within 36 h and the decrease was significant ($P < 0.05$) after three evening doses of pentobarbitone. After barbiturate withdrawal the alprenolol plasma concentrations increased to pretreatment levels. The decrease was no longer significant 3 (alprenolol) and 4 days (4-hydroxyalprenolol) after stopping pentobarbitone.

The mean resting pulse rate increased from 67 to 75 beats min⁻¹ ($P < 0.05$) after 6 days intake of pentobarbitone but was not significantly changed 6 days after the barbiturate treatment had been stopped. The mean blood pressure increased from 138/93 to 143/97 mm Hg ($P < 0.05$) after 4 to 5 days barbiturate intake. After cessation of the barbiturate blood pressure gradually decreased and 8 to 10 days thereafter it did not differ from pretreatment values.

Alprenolol and 4-hydroxyalprenolol concentrations, pulse rate and blood pressure were investigated in more detail during three alprenolol dosage intervals—before, during and after treatment with pentobarbitone. The mean plasma concentrations in the six patients decreased from 157 to 65 nmol l⁻¹ for alprenolol and from 71 to 54 nmol l⁻¹ for 4-hydroxyalprenolol during the barbiturate treatment. The resting pulse rate increased, from 70 to 74 beats min⁻¹, systolic blood pressure from 134 to 145 mm Hg and diastolic from 89 to 97 mm Hg. The inhibition of exercise tachycardia was reduced by 11% before and 18% 2 h after oral alprenolol at the end of the pentobarbitone treatment

Figure 1 Mean plasma concentrations of alprenolol (●—●) and 4-hydroxylalprenolol (○—○) before, during and after pentobarbitone treatment in six patients. The subjects were treated with alprenolol 0.4 g twice daily and 0.1 g pentobarbitone at night (indicated in box). Significant changes compared with the prebarbiturate treatment are indicated by a star.

Figure 2 Mean systolic (●—●) and diastolic (○—○) blood pressure in six patients treated with alprenolol (0.4 g twice daily) and pentobarbitone (0.1 g at night). Significant changes compared with the prebarbiturate treatment are indicated by a star.

period, compared to initial period of monotherapy with alprenolol. Pentobarbitone plasma concentrations were measurable in all patients (range 0.6–7 $\mu\text{g ml}^{-1}$) at the two samples during the study.

Discussion

Kinetic drug interactions are of clinical importance mainly if therapeutic effects are altered. We have reported that pentobarbitone treat-

Figure 3 Mean resting heart rate in six patients treated with alprenolol (0.4 g twice daily) and pentobarbitone (0.1 g at night). Significant changes compared with the prebarbiturate treatment are indicated by a star.

ment reduces plasma concentrations of metoprolol (Haglund *et al.*, 1979) and alprenolol given in single doses (Collste *et al.*, 1979b). In the latter study the effects on exercise tachycardia also decreased in healthy volunteers concomitantly given pentobarbitone.

This study shows that pentobarbitone treatment markedly decreases the steady-state plasma concentrations of alprenolol after a few days barbiturate treatment. This is in agreement with the findings that barbiturates enhance warfarin metabolism within a few days (Breckenridge *et al.*, 1973). The mechanism of the increased clearance of alprenolol during concomitant pentobarbitone treatment is probably an induction of the liver microsomal cytochrome P-450 system as shown in model studies in the rat (Grundin *et al.*, 1974).

In this study the decrease in effects (blood pressure and pulse rate) during pentobarbitone treatment occurred somewhat later than the decline in alprenolol plasma concentrations and

seemed to persist longer after cessation of the barbiturate treatment. This is in agreement with earlier studies on metoprolol showing a lag time between adequate plasma concentrations and its effects in hypertension (Haglund & Collste, 1980).

The clinical importance of the alprenolol-pentobarbitone interaction has now been clearly demonstrated. It has been shown that this interaction not only influences effects like exercise induced tachycardia during experimental situations, but also blood pressure during treatment of hypertension. The fact that resting pulse rate also increased during pentobarbitone treatment might be of importance during treatment of angina pectoris.

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