$P > 0{\cdot}1$) pressure though both of these preparations were associated with greater rises of diastolic pressure than the other two combinations. From these results there is no evidence to suggest that an increase in progestogenic potency is associated with a larger change in blood pressure.

Discussion

The results of this further analysis have confirmed our previous report (Weir *et al.*, 1971 a) of a rise in systolic blood pressure in women taking oestrogen-progestogen oral contraceptives. Rises in diastolic pressure became statistically significant two years after starting treatment. Both rises of pressure are generally readily reversible (fig. 4). These findings are in accord with other series (Carmichael *et al.*, 1970; Spellacy and Birk, 1972; Clezy *et al.*, 1972) but the rises in blood pressure are not as great as those reported under less standardized conditions (Saruta *et al.*, 1970; Crane *et al.*, 1971).

Two studies have suggested that oral contraceptives are more likely to induce changes in blood pressure in women with a history of pre-eclampsia (Spellacy and Birk, 1972; Clezy *et al.*, 1972), though Smith (1972) did not confirm these findings. The data in the present prospective survey are still insufficient for us to comment about this, but elsewhere we have reported on 23 isolated cases of marked rises in blood pressure associated with taking oral contraceptives where there was no evidence that previous pre-eclampsia was a contributing factor (Weir *et al.*, 1974). Though a role for sodium and water retention in producing the initial rise in blood pressure has not so far been excluded, we have found no relation between the changes in blood pressure and changes in weight ($r = 0{\cdot}18$; $P > 0{\cdot}1$) or in sodium, potassium, or water balance (Weir *et al.*, 1971 b).

No increase in blood pressure has been found in women taking progestogen only (MacKay *et al.*, 1971; Spellacy and Birk, 1972), and the present study has shown that the changes in blood pressure are not related to the progestogenic potency of the combined preparations used. A rise in blood pressure during oestrogen administration, however, has been reported (Lim *et al.*, 1970; Crane *et al.*, 1971; Spellacy and Birk, 1972), and possibly the increase in blood volume, cardiac output, and blood pressure in women taking combined oral contraceptives (Walters and Lim, 1970) may be induced by the oestrogen component. To date, the effect of preparations with different oestrogenic potencies has not been adequately studied.

The increases in blood pressure in this prospective survey have not so far been accompanied by clinical complications and would not generally be regarded as clinically important. Nevertheless, mortality and morbidity statistics, mostly obtained for men (Pickering, 1968; Kannel *et al.*, 1971), suggest that a relatively small increase of blood pressure within the range found in this study carries a distinct risk. Possibly, therefore, prolonged administration of oestrogen-progestogen oral contraceptives may lead to levels of blood pressure which may increase morbidity and affect life expectancy.

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Interaction between Doxycycline and Barbiturates

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Summary

In a cross-over study of five hospitalized patients the half life of doxycycline was significantly shortened after 10 days' treatment with phenobarbitone. In five patients on continuous barbiturate therapy the half life of doxycycline was even shorter. Barbiturates or other agents inducing drug metabolism should be used cautiously in combination with doxycycline, since this might result in therapeutically inadequate serum concentrations of the antibiotic.

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Introduction

For treatment with bacteriostatic agents to be successful the serum antibiotic level must not fall below the minimum inhibitory concentration. Certain drugs interfere with the gastrointestinal absorption of tetracyclines (Waisbren and Hueckel, 1950; Neuvonen *et al.*, 1970). Hepatic metabolism seems to be important in the elimination of doxycycline and the drug does not accumulate significantly in renal insufficiency (Klinger *et al.*, 1970). Barbiturates and many other commonly used preparations stimulate metabolism of drugs through inducing hepatic microsomal enzyme activity (Breckenridge and Orme, 1971; Remmer, 1972; Prescott, 1973). The present study aimed to discover whether barbiturates modify the half life of doxycycline in man.

Patients and Methods

Ten chronically ill patients volunteered as subjects for the study. Their usual daily medication of digitalis and diuretics and, in

TABLE I—*Details of Patients in Group B*

Case No.	Sex	Age	Weight (kg)	Inducing Agent(s)	Daily Dose (mg)	Duration of Therapy	Half Life of Doxycycline (hr)
1	M.	60	65	Phenobarbitone Diphenylhydantoin Carbamazepine	100 400 300	5-7 years	5·6
2	M.	35	85	Pentobarbitone	150	6 weeks	5·7
3	F.	73	60	Amylobarbitone	200	30 years	7·9
4	M.	65	60	Phenobarbitone	100	12 weeks	8·1
5	F.	78	60	Pentobarbitone	100	5 weeks	11·0
						Mean ± S.E.	7·7 ± 1·0*

*Significantly shorter than during the control period in table II ($P < 0.005$).

five cases, of barbiturates was continued during the experimental period but no other drugs were being taken. The patients were divided into two groups of five. Group A consisted of three women and two men whose ages ranged from 48 to 82 years and their weight from 50 to 60 kg. They were each given a single dose of doxycycline hydrochloride 100 mg intravenously, and its half life was determined from blood samples taken 1, 3, 5, 8, 12, 24, and 36 hours later. Thereafter phenobarbitone sodium 50 mg was given thrice daily for 10 days, when the half life of a single dose of doxycycline was again determined as described above. The five patients in group B, of similar ages and weights to those in group A, had been taking barbiturate drugs as a hypnotic or antiepileptic for periods varying from several weeks to several years (table I). The half life of a single dose of doxycycline in these patients was determined as described above without discontinuing their barbiturates.

The serum concentration of doxycycline in each blood sample was measured both microbiologically by the agar-plate method of Bennett *et al.* (1966), on Bacto Penassay Seed Agar (Difco) with *Bacillus Cereus* A.T.C.C. 9,634 as test organism, and fluorometrically according to Kohn (1961). The fluorometric values were definitely higher than the microbiological, but the half lives of doxycycline did not differ. Means with standard errors (S.E.) were calculated and Student's *t* test both for paired and unpaired values was used for statistical evaluation.

TABLE II—*Effect of 10 Days' Treatment with Phenobarbitone on Half Life of Doxycycline*

Case No.	Half Life Before Phenobarbitone (hr)	Half Life After Phenobarbitone (hr)
1	10·4	7·2
2	14·9	12·0
3	16·1	10·6
4	17·5	11·7
5	17·8	13·8
Mean ± S.E.	15·3 ± 1·3	11·1 ± 1·1*

*Significantly shorter than during control period ($P < 0.005$).

Results

The half life of doxycycline was 15·3 ± 1·3 hours in the patients in group A during the control period. After 10 days' treatment with phenobarbitone the half life of doxycycline was 11·1 ± 1·1 hours, significantly shorter ($P < 0.005$) (table II). In patients in group B on long-term barbiturate therapy the half life of doxycycline was 7·7 ± 1·0 hours (table I), significantly shorter than in patients in group A during the control period ($P < 0.005$).

Discussion

The introduction of phenobarbitone to the drug regimen of patients in group A shortened the half life of doxycycline in each case, and in all the patients on long-term barbiturate therapy the half life was even shorter. Therefore it is reasonable to assume that the degree of induction of doxycycline metabolism correlates with the duration of barbiturate therapy and also depends on the type and dose of barbiturate (Breckenridge *et al.*, 1973). The half life of doxycycline did not return to normal for two weeks after the cessation of barbiturate therapy.

The clinical significance of enzyme induction is not limited to barbiturates, and the range of inducing agents is much wider (Remmer, 1972). In a preliminary study we found the half life of doxycycline to be shortened in patients taking diphenylhydantoin and certain other drugs known to be potent enzyme inducers. Perhaps other tetracycline derivatives are also affected, but obviously the clinical significance of enzyme induction is more important in relation to the long-acting lipophilic tetracycline derivatives in which the maintenance of adequate serum concentrations is dependent on the rate of metabolism and not on renal excretion. If possible, therefore, doxycycline should not be given in combination with barbiturates, and serum doxycycline levels should always be measured when this antibiotic is given with drugs known to be enzyme inducers.

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