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The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids

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Patients taking oral contraceptive steroids (OCS) are known to suffer contraceptive failure while taking anticonvulsants such as phenobarbitone, phenytoin and carbamazepine. We have studied the single dose kinetics of ethinyloestradiol (EE_2); 50 μg, and levonorgestrel (Ng); 250 μg in groups of women before and 8–12 weeks after starting therapy with phenytoin ($n = 6$) and carbamazepine ($n = 4$). The area under the plasma concentration-time curve (AUC) was measured over a 24 h period for each steroid and significant reductions were seen with both anticonvulsants. Phenytoin reduced the AUC for EE_2 from 806 ± 50 (mean ± s.d.) to 411 ± 132 pg ml^{-1} h ($P < 0.05$) and for Ng from 33.6 ± 7.8 to 19.5 ± 3.8 ng ml^{-1} h ($P < 0.05$). Carbamazepine reduced the AUC for EE_2 from 1163 ± 466 to 672 ± 211 pg ml^{-1} h ($P < 0.05$) and for Ng from 22.9 ± 9.4 to 13.8 ± 5.8 ng ml^{-1} h ($P < 0.05$). These changes are compatible with the known enzyme inducing effects of phenytoin and carbamazepine. Patients taking these anticonvulsants will need to be given increased doses of OCS (equivalent to 50–100 μg EE_2 daily) to achieve adequate contraceptive effects.

Keywords ethinyloestradiol levonorgestrel phenytoin carbamazepine enzyme induction

Introduction

Drug interactions with oral contraceptive steroids (OCS) have become more important in recent years with the gradual reduction in the dose of ethinyloestradiol from 80–100 μg/day to the present usual dose of 30–35 μg/day. Anticonvulsant drugs have been widely implicated as causing contraceptive failure in women taking OCS and this was first described by Kenyon (1972). In a review of the literature Coulam & Annegers (1979) implicated phenytoin, phenobarbitone, methylphenobarbitone, primidone, carbamazepine and ethosuximide as being likely to interact with OCS. Phenytoin appears to be the most commonly implicated anticonvulsant and this was confirmed by Back *et al.* (1988) who examined the reports to the Committee on Safety of Medicines in the United Kingdom. Over the period 1973–1984, 43 cases of contraceptive failure were reported due to an interaction of anticonvulsants with OCS therapy and 25 of these cases involved phenytoin. There is a plethora of data in animals (Conney, 1967) and in man (Park & Breckenridge, 1981) to demonstrate the enzyme inducing ability of phenobarbitone, primidone, phenytoin and carbamazepine and we have already demonstrated an interaction between phenobarbitone and OCS (Back *et al.*, 1980). There is however little direct data concerning the effect of phenytoin or carbamazepine, two

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commonly used anticonvulsants on the kinetics of OCS and we have therefore conducted a study to examine these interactions.

Methods

Ten female patients aged between 16 and 37 years were studied, and their weights were between 45 and 61 kg. All had presented following epileptic (tonic-clonic) seizures but were in good health otherwise as judged by full clinical examination and laboratory investigations. No patient had received OCS in the preceding 3 months. After investigations to ascertain the cause of their seizures (including electroencephalography and computerised tomographic scans of the head) the decision was taken on clinical grounds to start long term anticonvulsant therapy with either phenytoin or carbamazepine. Prior to starting anticonvulsant therapy and after receiving written informed consent from each patient, they were given a single oral dose of Eugynon 50 (containing 50 μg of ethinyloestradiol (EE_2) and 250 μg levonorgestrel (Ng)), at 09.00 after an overnight fast. A butterfly cannula was placed in a forearm vein and blood samples (10 ml) were taken prior to the dose of Eugynon 50 and at 1, 2, 3, 4 and 6 h afte dosing. Blood samples were also taken at 8, 11 and 24 h after dosing by individual venepunctures. The blood samples were centrifuged at 1000 *g* for 10 min and the supernatant plasma was removed and stored at −20 °C prior to analysis.

Six patients were treated with phenytoin (200–300 mg/day) and four patients were treated with carbamazepine (300–600 mg/day). The single dose study with Eugynon 50 was repeated in each patient 8–12 weeks after starting their anticonvulsant and blood samples taken over 24 h as before. The morning dose of anticonvulsant was given 2 h after the dose of Eugynon. All patients were taking no other drug therapy during the course of the study and ethics committee approval was obtained from the institutional ethics committee. Plasma concentrations of EE_2 (Back *et al.*, 1979) and levonorgestrel (Back *et al.*, 1981) were measured by specific and sensitive radioimmunoassays. Plasma concentrations of phenytoin and carbamazepine were measured in samples of blood taken prior to the regular dose of anticonvulsant by the technique of high performance liquid chromatography. The area under the plasma concentration versus time curve (AUC) was measured using the trapezoidal rule and statistical analysis was performed using Student's *t*-test for paired samples.

Results

All the ten women completed the studies without untoward effect. In all women their tonic-clonic seizures were controlled in spite of, in some cases, relatively low plasma concentrations of anticonvulsant.

Phenytoin studies

The values for the AUC measurements before and during phenytoin therapy are shown in Table 1 and the plasma concentration time curves are shown in Figure 1.

There was a significant reduction in the AUC value for EE_2 from 806 ± 50 pg ml^{-1} h in the control state to 411 ± 132 pg ml^{-1} h during treatment with phenytoin ($P < 0.05$). The reduction in AUC was in general between two and four fold although in one woman (number 4) the AUC for EE_2 actually increased during phenytoin therapy. There was also a significant reduction in the AUC for Ng from 33.6 ± 7.8 ng ml^{-1} h before treatment to 19.5 ± 3.8 ng ml^{-1} h during phenytoin therapy ($P < 0.05$). As with EE_2 most patients showed a two to three fold fall in the AUC for Ng during phenytoin therapy but in one individual (number 3) the AUC increased during phenytoin therapy. The plasma concentrations of phenytoin, for which the therapeutic range is estimated to be 10–20 μg ml^{-1}, were very variable with four patients below the range and one above it. All patients had good fit control and no patient manifested any side effects of phenytoin either on questioning or on clinical examination.

Carbamazepine studies

The values for the AUC measurements before and during carbamazepine therapy are shown in Table 1 and the plasma concentration-time curves are shown in Figure 1. There was a significant reduction in the AUC value for EE_2 from 1163 ± 466 pg ml^{-1} h to 672 ± 211 pg ml^{-1} h during treatment with carbamazepine ($P < 0.05$). All four women showed a fall in the AUC of EE_2 which fell by between 6 and 66% of the control value. There was also a significant reduction in the AUC for Ng from 22.9 ± 9.4 ng ml^{-1} h before treatment to 13.8 ± 5.8 ng ml^{-1} h during carbamazepine therapy ($P < 0.05$). Again all four women showed a reduction in the AUC for Ng during carbamazepine treatment which fell to between 29 and 57% of the initial value. The plasma concentrations of carbamazepine were mostly within the therapeutic

Table 1 Area under the plasma concentration *vs* time curve for ethinyloestradiol and levonorgestrel in patients taking phenytoin or carbamazepine

Patient	Daily phenytoin dose (mg day^{-1})	Plasma phenytoin concentration (μg ml^{-1})	Ethinyloestradiol AUC (pg ml^{-1} h) Control	Ethinyloestradiol AUC (pg ml^{-1} h) Treatment	Levonorgestrel AUC (ng ml^{-1} h) Control	Levonorgestrel AUC (ng ml^{-1} h) Treatment
1	250	1.0	641	303	41.8	22.6
2	200	3.5	956	326	23.1	17.2
3	200	7.0	944	234	10.5	13.7
4	200	3.0	785	1060	18.9	5.9
5	300	11.5	770	332	46.7	25.4
6	300	23.0	740	208	60.8	32.2
Mean ± s.d.			806 ± 50	411 ± 132*	33.6 ± 7.8	19.5 ± 3.8*

*$P < 0.05$

Patient	Daily carbamazepine dose (mg day^{-1})	Plasma carbamazepine concentration (μg ml^{-1})	Ethinyloestradiol AUC (pg ml^{-1} h) Control	Ethinyloestradiol AUC (pg ml^{-1} h) Treatment	Levonorgestrel AUC (ng ml^{-1} h) Control	Levonorgestrel AUC (ng ml^{-1} h) Treatment
1	400	8.0	1833	630	14.9	10.5
2	300	3.5	1024	960	20.2	8.7
3	600	8.0	750	451	20.1	14.3
4	600	4.5	1047	648	36.6	21.9
Mean ± s.d.			1163 ± 466	672 ± 211*	22.9 ± 9.4	13.8 ± 5.8*

*$P < 0.05$

range (4–8 μg ml^{-1}) although this is less well defined than for phenytoin since carbamazepine epoxide concentrations are not usually measured and this metabolite has anticonvulsant activity.

Discussion

These studies have shown a fairly consistent effect of the anticonvulsants phenytoin and carbamazepine on the kinetics of EE_2 and Ng, with both anticonvulsants causing a significant fall in the AUC values for each steroid. Rigorous pharmacokinetic calculations have not been performed since, without a parenteral dose, we do not know the exact bioavailability of EE_2 and Ng in these patients. While we know the bioavailability of both EE_2 and Ng under control conditions, to measure this during anticonvulsant therapy would have required an intravenous dose of both EE_2 and Ng which we felt was not justified in these patients. Nevertheless, the fall in the AUC of both steroids is most likely to be due to the known enzyme inducing effects of phenytoin and carbamazepine (Park & Breckenridge, 1981) even though we have no independent measure of enzyme induction in these patients. During therapy with enzyme inducing drugs the amount of metabolites produced will increase and this could be a cause for concern if they were pharmacologically active or accumulated in the plasma. Ethinyloestradiol sulphate is the only metabolite known to accumulate in plasma (Orme *et al.*, 1983) and this is not pharmacologically active. The oxidized metabolites of ethinyloestradiol (mainly the 2-hydroxy metabolite) are not known to have pharmacological activity. We do not believe therefore that the recommended dose increase in OCS will adversely affect the side effect profile of these drugs. We have not measured sex hormonal binding globulin (SHBG) in this study, unlike our earlier study with phenobarbitone. Ethinyloestradiol does not bind to SHBG and the increased binding of progestogens to SHBG that is seen during therapy with drugs such as phenytoin and phenobarbitone (Backström &

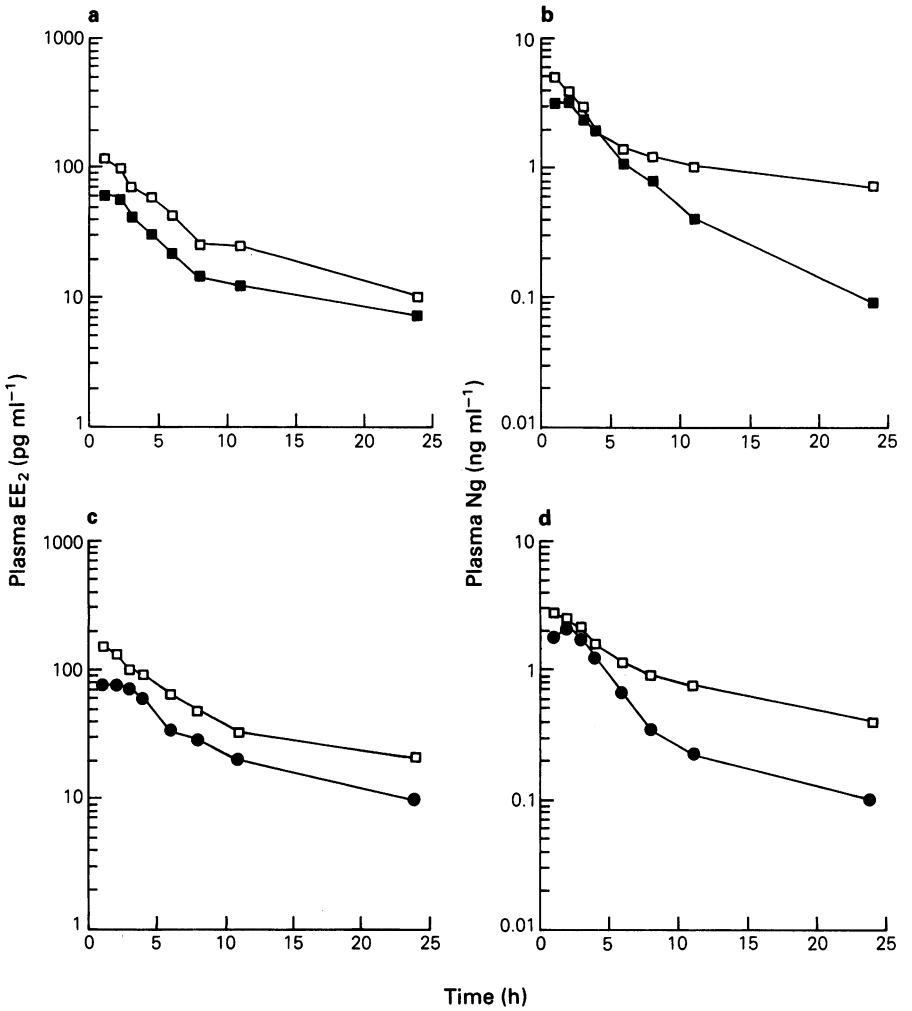

Figure 1 Plasma concentrations of ethinyloestradiol (EE_2) (pg ml^{-1} a and c) and levonorgestrel (Ng) (ng ml^{-1} b and d) in women after a single oral dose of Eugynon 50 before (□) and during treatment with phenytoin (■) (a and b) or carbamazepine (CBZ, •) (c and d). Mean values only are shown.

Sodergard, 1977) would tend to increase total concentrations of levonorgestrel in plasma. We feel that an absorption interaction is most unlikely and to try to minimise this possibility the doses of anticonvulsant and Eugynon 50 were separated by at least 2 h. We have not performed any pharmacodynamic studies in these patients since we gave only single doses of OCS. In our earlier studies with phenobarbitone (Back *et al.*, 1980) the design of the studies over 3 months allowed pharmacodynamic assessments to be made and breakthrough bleeding was noted in two patients. However, the design of these studies means delaying anticonvulsant therapy for 1 month while control measurements are performed and we felt that in the current climate this was quite unacceptable on ethical grounds. We believe that the changes seen in the kinetics of the OCS would be expected to cause a pharmacodynamic interaction in most women and this is in keeping with the current literature on anticonvulsants (Back *et al.*, 1988).

In the past, because of this interaction women were advised not to use OCS if they were taking anticonvulsants. This advice is now outmoded and the current advice is that the combined OCS can be used provided increased

doses are used. Phenytoin is not commonly given to young women because of its cosmetic effects (acne, greasy skin, hirsutism etc) and its potential for teratogenic effects but carbamazepine is widely used. We currently start such patients, who request oral contraception, on a preparation containing 50 μg EE_2 (such as Eugynon 50) and increase the dose if necessary as judged by breakthrough bleeding in cycles 2 (or 3) of OCS use. The degree of change seen here in the kinetics of EE_2 and Ng, and our clinical experience shows that most patients will be controlled from a contraceptive point of view by preparations of EE_2 that give a total daily dose of between 80 and 100 μg daily, provided the anticonvulsant therapy is continued. In women taking sodium valproate, no increase in OCS dose is needed since sodium valproate is not an enzyme inducer and studies have shown that this drug does not interfere with OCS therapy (Crawford *et al.*, 1986).

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