ANTIPYRINE ELIMINATION IN SALIVA AFTER LOW-DOSE COMBINED OR PROGESTOGEN-ONLY ORAL CONTRACEPTIVE STEROIDS

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- 1 A 'low-dose' combined oral contraceptive steroid (OCS) preparation containing 30 μg ethinyl-estradiol and 150 μg levonorgestrel was found to reduce significantly antipyrine clearance in a group of women acting as their own controls.
- 2 An OCS preparation containing only a progestogen (75 μg norgestrel) did not reduce antipyrine clearance in a second group of women.
- 3 The evidence suggesting that the oestrogen component of combined OCS preparations could be responsible for the reduction in antipyrine clearance is discussed.

Introduction

There have been several reports of a reduction in antipyrine elimination in women taking oral contraceptive steroids (OCS). Some of these investigations have utilised OCS preparations containing both oestrogens and progestogens (combined preparations) which have had a high oestrogen content (high-dose preparations) (O'Malley *et al.*, 1970, 1972; Carter *et al.*, 1974, 1975). Only two investigations (Homeida *et al.*, 1978; Abernethy & Greenblatt, 1981) have used currently preferred low-dose OCS preparations (50 μg oestrogen or less). It has not been determined whether the oestrogenic or progestogenic component of the combined preparations is responsible for the reduction in antipyrine elimination. It seemed appropriate to investigate the ability of a single preparation of either the low-dose combined or progestogen-only type to alter antipyrine elimination in two groups of women.

In all of the above investigations antipyrine levels have been determined from plasma samples whereas other workers have measured antipyrine in saliva. This latter technique is recommended because it is non-invasive and saliva antipyrine levels correlate with those of plasma (Vesell *et al.*, 1975; Fraser *et al.*, 1976).

Methods

Compounds

Antipyrine (phenazone B.P. 1980) was obtained

from a commercial source (Roussel Laboratories Ltd). The low-dose combined OCS was ethinyl-estradiol 30 μg with levonorgestrel 150 μg (Ovranette, Wyeth) and the progestogen-only OCS was norgestrel 75 μg (Neogest, Schering), both in manufacturer's standard packs.

Patients

The women studied were attending the Edinburgh Family Planning Centre and were requesting oral contraception. All were residents of the Edinburgh area, were white and were in good health. Patients had not been pregnant within the last year, were not lactating, had not taken any OCS for at least 1 year and were drug-free. Patients were between the ages of 22 and 28 years for the low-dose combined OCS and between the ages of 18 and 41 years for the progestogen-only OCS. The combined OCS was taken for 21 day periods alternating with 7 day periods free of OCS. The progestogen-only preparation was taken continuously. Written informed consent was obtained from each patient and approval for the study given by the Ethics of Research Subcommittee of the Lothian Health Board.

Antipyrine administration

Antipyrine elimination kinetics was determined during the menstrual cycle immediately prior to starting the OCS and again in the 11th week of the combined OCS regimen and between the 11th and 14th

weeks of the progestogen-only regimen. Patients were supplied with a dose of antipyrine (15 mg/kg) to be mixed with 150 ml of sterile orange juice to be taken in their homes 30 min before breakfast.

Sterile tubes (Sterilin) were supplied for mixed saliva samples collected at 3, 5, 8, 12, 24 and 32 h after the oral dose of antipyrine. Saliva samples were kept in the patients' refrigerators until the end of the sampling period when they were collected and frozen at -20°C prior to analysis. A chewing gum base (Wrigley Ltd) was used to stimulate salivation.

Antipyrine analysis

A modification of the g.l.c. method of Chambers & Jefferson (1981) required 1 ml saliva samples and used phenoxybenzamine hydrochloride as the internal reference standard. The column was 5% OV 17 on 100–120 mesh Gas Chrom Q at a temperature of 260°C while the temperature of both the injection port and flame ionisation detector was 275°C .

Results

Antipyrine elimination

Antipyrine half-life ($T_{1/2}$) was determined for each patient from the slope of the least squares regression line fitted to the plot of log saliva antipyrine concentration against time. The corresponding apparent volumes of distribution (V_d) and saliva clearances (Cl) were calculated (Riggs, 1963) from the equation:

$$\text{Cl} = \frac{\text{Dose antipyrine (mg/kg)}}{C_0} \cdot \frac{0.693}{T_{1/2}}$$

$$\text{where } \frac{\text{Dose antipyrine}}{C_0} = V_d$$

and C_0 is the theoretical saliva antipyrine concentration at zero time.

Table 1 shows that after a combined OCS containing $30\text{ }\mu\text{g}$ of ethinyloestradiol with $150\text{ }\mu\text{g}$ levonorgestrel there was a significant reduction of 29% in antipyrine clearance ($P < 0.05$) with a concomitant increase in $T_{1/2}$ of 62% ($P < 0.05$); V_d and patient weight showed no change.

After treatment with an OCS containing $75\text{ }\mu\text{g}$ of norgestrel there was no significant change in antipyrine elimination nor in the weight or V_d of the patients (Table 2).

Discussion

The initial reports that high-dose combined OCS caused a reduction in antipyrine elimination (O'Malley *et al.*, 1970, 1972) compared women receiv-

Table 1 Antipyrine kinetics (mean $\pm$ s.e. mean, range in brackets) before and after a low-dose combined OCS (Ovranette)

	Before OCS	After OCS	Mean % change
<i>Patient's characteristics</i>			
Number	6	6	
Age (years)	26 ± 1.1 (22–28)		
Weight (kg)	59.7 ± 2.8 (52.2–69.0)	60.1 ± 2.9 (51.7–70.8)	
<i>Antipyrine kinetics</i>			
$T_{1/2}$ (h)	9.1 ± 0.5 (6.9–10.4)	$14.7 \pm 1.8^*$ (11.7–21.5)	+ 61.7
V_d (ml kg^{-1})	483 ± 29 (368–586)	524 ± 20 (437–566)	+ 10.6
Cl (ml $\text{kg}^{-1} \text{h}^{-1}$)	37.7 ± 4.0 (27.3–52.2)	$26.6 \pm 3.1^*$ (16.2–33.4)	– 29.1

*Statistical difference from control significant, $P < 0.05$, as tested by paired *t*-test.

Table 2 Antipyrine kinetics (mean $\pm$ s.e. mean, range in brackets) before and after a progestogen-only OCS containing $75\text{ }\mu\text{g}$ norgestrel (Neogest)

	Before OCS	After OCS	Mean % change
<i>Patient's characteristics</i>			
Number	12	12	
Age (years)	25 ± 1.9 (18–41)		
Weight (kg)	55.2 ± 1.3 (48.5–62.1)	54.9 ± 1.3 (48.5–61.7)	
<i>Antipyrine kinetics</i>			
$T_{1/2}$ (h)	9.2 ± 0.7 (5.4–13.5)	9.1 ± 0.9 (5.8–15.2)	– 1.4
V_d (ml kg^{-1})	547 ± 27 (400–765)	569 ± 46 (239–833)	+ 3.9
Cl (ml $\text{kg}^{-1} \text{h}^{-1}$)	44.2 ± 4.9 (30.1–79.1)	47.6 ± 6.6 (20.4–92.6)	+ 6.2

Differences before and after OCS were not statistically significant $P > 0.05$ (paired *t*-test).

ing OCS with a control group and measured antipyrine from plasma. Subsequently, using each subject as her own control, the now preferred method, Carter *et al.* (1974, 1975) showed a reduced elimination of antipyrine in only 8 out of 14 women treated for 3 months on high-dose OCS. Homeida *et al.* (1978) using this method, although with a low-dose OCS, showed a 21% decrease in antipyrine clearance with an increase in liver volume. This indicates an even larger decrease in clearance if drug metabolizing activity is corrected for liver volume. Additionally, other women on discontinuing OCS therapy showed a mean 30% increase in antipyrine clearance in the

month following cessation of OCS. It is of interest that the demethylation of aminopyrine, as measured by a breath analysis technique, was also significantly inhibited by combined OCS preparations (Hertz *et al.*, 1978).

Some studies have shown that both OCS preparations and environmental factors, such as smoking and diet, may affect antipyrine elimination (Fraser *et al.*, 1977, 1979). These studies involved measurement of antipyrine in saliva but did not specify the OCS used. The reduction which we found in antipyrine clearance after the low-dose combined OCS is in accord with the previous results using this type of preparation.

Antipyrine metabolism *in vivo* is thought to be dependent on the activity of liver oxidative drug metabolising enzymes (Vesell *et al.*, 1973; Miller *et al.*, 1978). The mode of action of OCS on this enzyme activity is uncertain. Oestrogens bind to these enzymes and several oestrogens and progestogens competitively inhibit them *in vitro* (Goble, 1975; Juchau & Fouts, 1966). Oestrogens have also been shown to decrease the activity and turnover of the enzymes in rats, but only in concentrations considered to be far greater than those after usual doses in man (MacKinnon *et al.*, 1977).

The progestogen-only OCS used in our study produced no change in antipyrine elimination, V_d or body weight. Although the dose of progestogen in our combined OCS is equivalent to 4 times the dose of that in the progestogen-only therapy, it is tempting to suggest that even in the combined OCS this dose of progestogen is without effect on antipyrine elimina-

tion. This suggestion is in part confirmed by the results of Abernethy & Greenblatt (1981) in that seven out of eight women were given a combined OCS of very low progestogenic potency (Heinen, 1971) yet their reduction in antipyrine clearance is almost identical to the reduction we found using a combined OCS of much higher progestogenic potency.

Animal studies, where progestogens can inhibit or induce drug metabolism (Juchau & Fouts, 1966; DuBois & Kinoshita, 1965), are not necessarily at variance with our findings in women, but could merely indicate differences in dose, the particular OCS used and species. It is noted that the 17-hydroxyprogesterone derivative, medroxyprogesterone, can, when used in very high doses for the treatment of endometrical carcinoma, actually cause an increase in antipyrine elimination (Rautio *et al.*, 1979). Clarification of these points might be helped by future studies in women using progestogens or oestrogens of different potency.

If it is confirmed that progestogen-only OCS are without effect on antipyrine elimination, then it does imply that the concern that the elimination of any drug which is metabolized by liver microsomal enzymes will be impaired when the drug is administered with an OCS (Homeida *et al.*, 1978) is not applicable to progestogen-only preparations.

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