Summary

Oral contraceptive steroids are of 2 types: oestrogens, of which ethinyloestradiol is the most important, and progestagens, of which levonorgestrel and norethisterone are the most commonly used. All these steroids can be measured by a number of analytical techniques but there is little doubt that radioimmunoassay is the most convenient. All the steroids are well absorbed in humans but while levonorgestrel is completely bioavailable, norethisterone has an average bioavailability of 70%. Ethinyloestradiol, too, is subject to presystemic metabolism with a mean bioavailability of 40 to 45%. The main site of presystemic metabolism is the gut wall, with the production of ethinyloestradiol sulphate. The progestagens norethynodrel, ethynodiol diacetate and lynoestrenol are quantitatively metabolised to norethisterone.

The pharmacokinetics of the contraceptive steroids are best described by a 2-compartment open model. The terminal plasma half-life of levonorgestrel varies from 11 to 45 hours and of norethisterone from 5 to 14 hours. The β-phase half-life of ethinyloestradiol varies from 6 to 20 hours. The apparent volume of distribution of these contraceptive steroids (after intravenous administration) is between 1.5 and 4.3 L/kg. During long term treatment with oral contraceptive steroids, steady-state plasma concentrations of ethinyloestradiol (24 hours after administration) are between 10 and 200 pg/ml. Plasma concentrations of norethisterone and levonorgestrel at steady-state are higher than predicted from the single-dose kinetics because of enhanced binding of the progestagens following the induction of sex hormone binding globulin (SHBG) by ethinyloestradiol. Concentrations are in the range of 1.6 to 15.2 ng/ml for norethisterone and 0.8 to 4.5 ng/ml for levonorgestrel.

All the contraceptive steroids are bound to proteins in plasma. Ethinyloestradiol is 97 to 98% bound to plasma albumin. The progestagens are bound both to albumin (levonorgestrel 93 to 95%; norethisterone 79 to 80%) and more specifically to SHBG. The binding capacity of SHBG can be enhanced by treatment with ethinyloestradiol or with more conventional enzyme-inducing drugs such as phenobarbitone, carbamazepine or rifampicin.

Norethisterone and levonorgestrel are chiefly metabolised by reduction in the A ring and this is followed by conjugation with glucuronide or sulphate. The metabolism of levonorgestrel is stereoselective. Ethinyloestradiol is primarily hydroxylated at the 2 position but a wide variety of hydroxylated and methylated metabolites are formed and these are present both free and as glucuronide and sulphate conjugates. Ethinyloestradiol is conjugated directly at the 3 position (unlike the progestagens) and thus is liable to enterohepatic recirculation. Ethinyloestradiol sulphate concentrations in plasma are many times higher than that of the unchanged drug.
The oral contraceptive steroids are involved in drug interactions of clinical significance. While the effect of contraceptive steroids on other drugs is small and unlikely to be of clinical significance, failure of contraception often occurs if enzyme-inducing agents such as rifampicin, phenobarbitone or carbamazepine are coadministered. Oral antibiotics do not seem to cause a significant loss of contraception in the large majority of women. Vitamin C will enhance the effect of contraceptive steroids by competing for sulphate conjugation in the gut wall, thus leading to increased bioavailability of ethinyloestradiol.

Oral contraceptive steroids have been in widespread use for more than 15 years and it is estimated that they are used by at least 50 million women throughout the world. Despite this extensive use, there has been a paucity of information about the clinical pharmacology of these drugs, until the last few years. This lack of knowledge may have arisen for a number of reasons. Firstly, oral contraceptive steroids are predominantly taken by women who are in good health, rather than being prescribed to women with disease, and they therefore present a unique group of drugs in therapeutics. Secondly, until recently, oral contraceptive steroids have been given in supratherapeutic doses, thus minimising any problems from interindividual variation in their elimination. Thirdly, oral contraceptive steroids are taken in small doses and, in the case of the oestrogens, the daily dose is very small indeed. This has undoubtedly led to problems with the chemical assay of these drugs, and it is only in the last few years that assay methods have been both specific and sensitive.

The first combination preparation to undergo large-scale clinical trials was 'Enovid', which contained 10mg of a progestagen (norethynodrel) and 150μg of an oestrogen (mestranol). Most contraceptive preparations now contain 1mg of progestagen or less and between 20 and 50μg of oestrogen. Thus, any factor which reduces the bioavailability of the lower dose preparations will become very important. This article will describe the pharmacokinetics of the commonly used oral contraceptive steroids and the interactions which may occur with other drugs. The oestrogens that are considered are ethinyloestradiol, mestranol and to a lesser extent quinestrenol; the progestagens discussed include norethisterone, norethynodrel, lynoestrenol, ethynodiol diacetate and levonorgestrel [d-(−)-norgestrel]; quingestanol acetate is considered briefly. The structures of the commonly used oral contraceptive steroids are shown in figure 1. Those steroids usually administered by the parenteral route are not discussed.

Oral contraceptive steroids exert their main pharmacological effect through a suppression of the pituitary output of luteinising hormone and follicle-stimulating hormone. (Diczfalusy, 1968; Swerdloff and Odell, 1969). This action is usually taken to be more usual with the combined type of oral contraceptive steroid preparation but suppression of the pituitary hormones is also seen with progestagen-only preparations such as levonorgestrel (Weiner et al., 1976a). Daily doses of ethinyloestradiol as low as 20μg will produce effective contraception in most women, although the more usual daily dose is 30 to 35μg.

I. Analytical Methods

A wide variety of methods of analysis is now available for the assay of the common contraceptive steroids. Some of the earlier assay methods were either colorimetric (Rizk et al., 1973; Smith et al., 1970) or spectrophotometric (Keay, 1968) but these analytical systems are not sufficiently sensitive to measure contraceptive steroid concentrations in plasma; their main use now is for pharmaceutical purposes in order to check the content of drug in various formulations. Similarly, high-