The pharmacokinetics of norethisterone in the rabbit and rat after systemic and oral administration: Effect of phenobarbitone

D.J. BACK, A.M. BRECKENRIDGE, FRANCESCA E. GAY, M.L'E. ORME, P.H. ROWE & EILEEN SMITH

Department of Pharmacology and Therapeutics, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

Norethisterone is a synthetic progestogenic component of many oral contraceptive preparations. We have investigated the pharmacokinetics of norethisterone after intravenous (i.v.) and oral administration (85 μg/kg) to unanaesthetized female rabbits and i.v. and portal administration (50 μg/kg) to anaesthetized female rats. Blood samples were collected over 24 h from the marginal ear vein of the rabbit and over 2 h from the carotid artery of the rat.

Norethisterone was measured in plasma by radioimmunoassay using an antiserum raised in rabbits against norethisterone 3-(O-carboxymethyl) oxime bovine serum albumin. The antiserum was used at a dilution of 1 in 25,000.

In all experiments the plasma concentration-time curve was resolved into two exponential components. The values for the 'fast disposition' half life, the 'slow disposition' half life and the area under the curve (AUC) are listed in Table 1.

Norethisterone showed a marked first pass effect in both the rabbit and rat (Table 1). In the rabbit the AUC after oral administration was 53% of that after i.v. administration, whilst in the rat the AUC after portal administration was 32% of that after i.v. administration.

There is increasing evidence that enzyme induction may influence the efficacy of oral contraceptives. The effect of phenobarbitone on the previously determined pharmacokinetic parameters was therefore determined. Phenobarbitone was administered either in drinking water (1 mg/ml for 6 days) to rabbits or intraperitoneally (40 mg/kg twice daily for 4 days) to rats. Induction was indicated from a decrease in pentobarbitone sleeping time in treated rabbits from 3.6 to 1.1 h and from an increase (76%) of cytochrome P-450 in treated rats (0.43 ± 0.02 nmol/mg protein in controls; 0.75 ± 0.12 nmol/mg protein in treated rats). In the rabbit phenobarbitone had no significant effect on plasma norethisterone concentrations after i.v. administration but significantly reduced the plasma concentration after oral administration. In contrast, in the rat, phenobarbitone had little effect on plasma norethisterone concentrations despite the clear evidence of enzyme induction.

F.E.G. is supported by a grant from G.D. Searle & Co. Ltd.

Table 1 Pharmacokinetic parameters of norethisterone in the rabbit and rat

	Intravenous	*Oral*
Rabbit		
'Fast disposition' half life (h)	0.4 ± 0.1	0.7 ± 0.1
'Slow disposition' half life (h)	7.4 ± 2.1	12.5 ± 1.2
AUC (h ng ml^{-1})	56.0 ± 2.9	30.9 ± 8.3
Rat		
'Fast disposition' half life (min)	5.1 ± 1.2	10.1 ± 2.3
'Slow disposition' half life (min)	44.7 ± 6.6	72.0 ± 12.0
AUC (min ng ml^{-1})	672 ± 129	223 ± 56

Each result is the mean ±s.e. mean of 5 experiments.