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INTESTINAL ABSORPTION OF SYNTHETIC STEROIDS

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SUMMARY

The absorption of 17α-ethynylsteroids was studied by an *in situ* procedure in the rat and *in vivo* in the rat, guinea-pig and rabbit. Absorption of ethynyloestradiol and norethisterone from rat intestinal loops *in situ* was rapid, more than 90% being absorbed within 1 h. Most of the absorbed steroid could be recovered in the bile showing an entero-hepatic circulation of both steroids. Whereas derivatives of norethisterone were absorbed as rapidly as norethisterone, ethynyloestradiol-3-sulphate was only slowly absorbed. The steroids in bile were present predominantly in a conjugated form and those present in intestinal washings, the gut wall and portal plasma were present mainly in a free state. Only small amounts of norethisterone were absorbed from the stomach but absorption from the large intestine was rapid. Absorption of norethisterone from oily solutions was slower than when administered in ethanol–saline using the *in situ* technique but *in vivo* there was no difference between the two formulations in the rat, guinea-pig and rabbit. Both ethynyloestradiol and its sulphate were rapidly absorbed by the guinea pig *in vivo*.

INTRODUCTION

Although oral administration of steroids is common, few studies on the absorption of steroids from the gastro-intestinal tract have been carried out. Absorption of many steroids has been measured indirectly by estimating plasma, urinary or faecal concentrations of the administered steroid and its metabolites. Everted sacs of rat intestine [1] and *in situ* perfusion [2] have been used to study the absorption of steroids by direct techniques. In the present study a rat *in situ* preparation similar to that described by Pelzmann[3] was used to study the absorption of two widely used synthetic steroids, ethynyloestradiol and norethisterone (17α-ethynyl-19-nortesterone). In addition the absorption of the major circulating form of ethynyloestradiol in humans, ethynyloestradiol-3-sulphate [4, 5] and some derivatives of norethisterone, also in use for fertility control, were investigated. As it has been reported that administration of steroids in oily solution not only enhances their biological activity in animals [6] and man [7] but also alters their rate of absorption [8] the absorption of norethisterone from oil-based solutions was compared to that from aqueous solutions. A preliminary account of some of this work has been previously published [9].

MATERIALS AND METHODS

Ethynyloestradiol and norethisterone were obtained from Sigma and used without further purification. [4-^{14}C]-Ethynyloestradiol (S.A. 12 Ci/mmol) and [6,7-^{3}H]-norethisterone (S.A. 57 Ci/mmol) were purified by paper chromatography using the solvent system light petroleum (boiling range 40–60°C) toluene–methanol–water (5:5:4:1, by vol.). Ethynyloestradiol-3-sulphate and [6,7,-^{3}H]-ethynyloestradiol-3-sulphate (S.A. 40 Ci/mmol) were prepared according to Fex, Lundvall and Olsson[10]. [^{3}H]-Ethynyloestradiol-3-sulphate was purified by paper chromatography using the solvent system *t*-butanol–dipropylether–methanol–water (6:2:1:2, by vol.).

Measurement of absorption from the ligated intestine in situ. Mature female rats of the Wistar strain (wt. 190–250 g) were used. Anaesthesia was induced with Nembutal (sodium phenobarbitone, Abbott Laboratories, Kent: 50 mg/kg), the abdomen opened and a 10 cm loop of small intestine was ligated just below the point of entry of the bile duct [3]. The bile duct was then cannulated with 10 cm polyethylene tubing (PE 50). Lymph was collected as described by Bollman, Cain and Grindlay[11]. The steroid under investigation (0.5–1 μCi labelled and 10 μg unlabelled steroid) was injected into the loop in 1 ml 10% ethanolic-saline and in some cases in oil solutions. The oil solutions contained 10 μg norethisterone/ml. The vehicles for the solutions were:

Solution 1—acetoglyceride
Solution 2—a 4:1(w/w) mixture of acetoglyceride and 'fat-mix' (beeswax, lecithin and hydrogenated coconut oil; 1:4:1 by wt.)
Solution 3—acetoglyceride and glycerylmonostearate, 11:1 (by wt.)

Groups of animals were killed 7½, 15, 30 and 60 min after injection of the steroid. Bile was collected for the duration of the experiment. At the end of the experiment the loop of intestine was removed, the contents were collected and the loop was flushed

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twice with saline and the washings from the small intestine were added to the loop contents. The radioactivity in samples of this solution was measured to determine the total amount of the dose remaining in the small intestine. The amount of the dose associated with the gut wall was measured after homogenisation of the intestinal loop in ethanol with an Ultra-Turrax tissue disintegrator. After centrifugation of the homogenate at 800 *g* for 10 min a sample of the ethanol supernatant was taken to determine the total radioactivity present. A similar technique was used to study absorption from the stomach and large intestine. After injection of norethisterone in oil solutions it was not feasible to determine the amount of dose remaining in the small intestine and gut wall separately. In these studies the contents of the small intestine and gut wall were homogenized in ethanol and the radioactivity determined as described above.

Bile collected for the duration of each experiment was diluted to 5 ml with water and the content of radioactivity determined. In some cases, samples of blood were obtained from the hepatic portal vein.

Determination of radioactivity in plasma samples and other details of the counting procedures have been described previously [4].

Measurement of absorption in vivo. Rats (Wistar strain, body weight 200–250 g), guinea-pigs (Dunkin-Hartley strain, wt. 230–850 g) and rabbits (New Zealand Whites, wt. 2.2–3.0 Kg) were used. The animals were kept in metabolic cages for the duration of the experiment and had free access to food and water. The dose (0.5–1.0 μCi labelled and 10 μg unlabelled steroid) was administered orally in 1 ml ethanol in saline or in oil solution. Urine and faeces were collected separately at 4 hourly intervals up to 12 h after administration of the dose and thereafter at 24, 48 and 72 h. In addition to the collection of urine and faeces from rabbits, blood samples were also obtained from the marginal ear vein at 1, 4, 8 and 24 h after administration of the dose. The total radioactivity and amounts present in a freely extractable and conjugated form in plasma, urine and faeces were determined as described previously [12].

RESULTS

Absorption from intestinal loops in situ

The amounts of ethynyloestradiol, its sulphate and norethisterone remaining in the rat small intestine, between 7½ and 60 min after injection are shown in Table 1. Absorption of ethynyloestradiol was rapid and by 7½ min after the injection less than 40% remained in the small intestine and by 1 h this value had decreased to less than 10%. The amount of the dose in the gut wall also decreased markedly with time. That absorption of ethynyloestradiol had taken place was shown by the excretion of increasing amounts of radioactivity in bile. Only small amounts were excreted by 7½ min but by 1 h over 80% of the radioactivity associated with the administered dose had been eliminated in bile. Absorption of norethisterone from the small intestine was also rapid, only about 2% remaining in the loop after 1 h, but elimination in bile was slower than that of ethynyloestradiol. Less than 1% was collected from the lymph. Absorption of derivatives of norethisterone was similar to that of norethisterone itself with less than 10% of the dose remaining in the intestine after 30 min (Table 1).

In contrast with the absorption of these unconjugated steroids absorption of ethynyloestradiol-3-sulphate was slow. More than 60% of the dose remained in the small intestine after 1 h and less than 25% had been excreted in bile.

The amounts of radioactivity present in washings from the small intestine, gut wall, bile and samples of portal vein plasma in a freely extractable and in a conjugated form, released by acid hydrolysis, are shown in Table 2. Large amounts of freely extractable radioactivity were present in portal vein plasma, gut

Table 1. Absorption of ethynyloestradiol, its 3-sulphate and norethisterone and derivatives from a loop of rat small intestine

Steroid administered	Time (min)	Intestinal loop	% dose in intestinal wall	Bile
Ethynyloestradiol	7½	38.0, 22.0	28.4, 30.3	1.8, 0.1
	15	11.0, 10.1	10.3, 8.2	30.0, 29.8
	30	12.1, 14.3	1.4, 3.7	53.5, 67.5
	60	4.0, 10.8	1.7, 2.4	83.3, 78.4
Ethynylyoestradiol-3-sulphate	7½	68.6, 77.4	0.3, 0.3	0.2, 0.3
	60	70.1, 60.6	1.2, 1.5	11.9, 22.8
Norethisterone	7½	19.9, 13.8	11.8, 12.7	1.7, 0.8
	15	10.9, 1.6	5.9 ± 3.0	4.0 ± 0.8
	30	15.5, 9.4	2.9, 2.5	20.3, 14.2
	60	2.0 ± 0.4	0.9 ± 0.5	31.0 ± 12.8
Norethisterone acetate	30	4.5, 3.8	4.4, 3.8	9.8, 10.4
Norethisterone oenanthate	30	5.5, 3.5	9.1, 7.2	10.2, 4.3
Norethisterone oxime	30	6.9, 5.8	1.3, 1.1	11.0, 11.4

Steroids injected into loop in ethanol–saline. Values are for two separate experiments except for norethisterone at 15 and 60 min where values represent mean ± SD for three experiments.

Table 2. Radioactivity in small intestine, bile and portal plasma in a freely extractable or conjugated form after administration of ethynyloestradiol and norethisterone

		Ethynyloestradiol			Norethisterone		
Time (min)		7½	15	30	7½	15	30
Tissue or fluid							
Small intestine	F	92.7, 87.9	47.5, 44.2	48.4, 23.6	30.7, 30.5	56.4, 41.9	41.5, 36.6
	C	7.3, 12.1	52.3, 55.8	51.6, 76.4	69.3, 69.5	43.6, 58.1	58.5, 63.4
Intestinal wall	F	96.7, 95.3	—	41.2, 70.3	96.6, 95.8	89.8, 87.9	51.3, 72.3
	C	3.3, 4.7	—	58.8, 29.7	3.4, 4.2	10.2, 12.1	48.7, 27.7
Bile	F	—	0.6, 0.5	1.2, 2.0	—	9.4, 8.4	2.8, 3.3
	C	—	99.4, 99.5	98.8, 98.0	—	90.6, 91.6	97.2, 96.7
Portal vein plasma	F	76.3	30.3	49.7	76.5	57.2	33.0
	C	23.7	19.7	50.3	23.5	42.8	67.0

Values are % radioactivity in a freely extractable (F) or conjugated (C) form for separate experiments. Values for portal vein plasma refer to pooled samples.

wall and washings from the small intestine after injection of ethynyloestradiol, the amount decreasing with increase in time. Similarly, large amounts of radioactivity were freely extractable from portal plasma and gut wall after injection of norethisterone, the amounts decreasing with time, but only about one-third of the radioactivity in the washings from the small intestine was freely extractable at any time. Only very small amounts of the radioactivity excreted in bile were in a freely extractable form at any of the time intervals studied after injection of ethynyloestradiol or norethisterone and most of the radioactivity was present in a conjugated form. After injection of ethynyloestradiol-3-sulphate no freely extractable radioactivity was detected in any of the fractions at the two times (7½ and 30 min) studied and all the radioactivity was present in a conjugated state. The radioactivity present in portal plasma in a conjugated form after injection of the sulphate was shown by chromatographic analysis to be mainly associated with the unaltered compound.

Thin-layer chromatography on silica gel using the solvent system toluene–ethanol (4:1, v/v) of the freely extractable fractions obtained 7½ min after injection of ethynyloestradiol or norethisterone showed that most of the radioactivity in portal plasma and gut wall was associated with the unaltered steroid. However, in the washings from the small intestine although most of the radioactivity was associated with ethynyloestradiol after administration of this steroid, for norethisterone only 20% was associated with the unaltered steroid. Analysis by thin-layer chromatography [13] of the conjugated material present in the washings from the small intestine 7½ min after injection of norethisterone showed that sulphate conjugates were predominant.

Since absorption of steroids can also occur from other parts of the gastrointestinal tract, the absorption of norethisterone from the stomach and norethisterone and ethynyloestradiol from the large intestine was studied (Table 3). Only small amounts of norethisterone were absorbed from the stomach and almost 80% of the dose remained after 1 h. However, absorption of both ethynyloestradiol and norethisterone from the large intestine was rapid as shown by the large amounts of the dose (56.3% and 34.0% for ethynyloestradiol and norethisterone respectively) recovered in bile. Less than 2% was present in the wall of the large intestine.

When norethisterone was injected into the small intestine in oil solution (Table 4) absorption was delayed with over 60% of the dose remaining after 1 h and only small amounts being excreted in bile. In two animals where absorption was allowed to continue for 2 h, more than 50% of the dose still remained in the small intestine after injection of norethisterone in solution 1. By collecting bile and preventing its secretion into the intestine, absorption of the oil or release of the steroid from the oil might have been affected. Accordingly in one experiment the whole of the small intestine was ligated and bile allowed to enter the intestine but 60% of the dose

Table 3. Absorption of ethynyloestradiol and norethisterone from stomach and large intestine of the rat

		% Dose at 1 h		
Tissue	Steroid	Remaining in lumen	In tissue wall	In bile
Stomach	Norethisterone	77.8, 79.2	5.1, 12.7	1.2, 1.7
Large intestine	Norethisterone	0.3, 6.4	0.4, 0.3	41.4, 71.1
	Ethynyloestradiol	6.6, 13.4	1.6, 0.6	37.7, 28.4

Values are for two separate experiments.

Table 4. Absorption of norethisterone from rat small intestine after administration in ethanol–saline and oily solutions

Vehicle	% Dose remaining in intestine at 1 h	% In bile at 1 h
Ethanol–saline	2.0 ± 0.8 (3)	31.0 ± 12.8 (3)
Solution 1	67.4 ± 5.1 (5)	3.0, 9.7
Solution 2	62.7 ± 3.9 (5)	2.0, 2.7
Solution 3	65.6 ± 6.4 (4)	1.7, 2.7

Values are mean ± SD except where values for individual experiments are given. Figures in parentheses denotes number of estimations. For composition of vehicles see Methods Section.

still remained after 1 h. Since it was possible that some of the material in the small intestine could result from the enterohepatic circulation of norethisterone and its metabolites, a further experiment was carried out in which bile from one animal was transferred directly into the small intestine of the animal under investigation with the bile duct ligated but most of the dose still remained in the small intestine.

Absorption of steroids in vivo

The apparent delay in the absorption of norethisterone when injected in oil solution appeared to be an artefact of the *in situ* technique. Accordingly the absorption of norethisterone when given in an oil solution was studied under *in vivo* conditions. The results (Table 5) showed that there was no difference in the rate at which the dose was excreted after administration of norethisterone in ethanol–saline or in oil solution to the rat and values for recovery over a three period are shown in Table 5. These findings were confirmed in the guinea-pig and rabbit. Surprisingly in the rabbit the amount of the dose excreted over a three day period was significantly greater ($P < 0.01$) when norethisterone was administered in oil solution than in ethanol–saline. No difference in plasma levels was detected during the first 24 h after administration of norethisterone in ethanol–saline or in solution 2 although a difference might have been expected if absorption of norethisterone from oil solution were delayed.

It was previously shown in the guinea-pig [12] that ethynyloestradiol was readily absorbed after oral administration and similar results were obtained in the present work with the sulphate conjugate (Table 5). However the recovery of the dose was lower, particularly in faeces ($P < 0.01$), after administration of the conjugate. As found after the administration of ethynyloestradiol, most of the radioactivity (90%) in faeces after administration of the sulphate was present in an unconjugated state.

DISCUSSION

The rapid absorption of ethynyloestradiol or norethisterone introduced directly into the small intestine of the rat in ethanol–saline in the present work confirms the findings previously reported for ethynyloestradiol [8, 14] and for norethisterone [3]. Although the direct absorption of ethynyloestradiol-3-sulphate has not been investigated previously its slower rate of absorption compared with the non-esterified steroid is consistent with the theory that lipid solubility is an important determinant for intestinal absorption of drugs [2]. As ethynyloestradiol-3-sulphate is more polar and hydrophylic than the unconjugated steroid, its rate of absorption would be

Table 5. % Dose excreted in urine (U) and faeces (F) after oral administration of steroids

Steroid administered	Vehicle		% Dose excreted over 3 day period		
			Rat	Guinea-pig	Rabbit
Norethisterone	Ethanol–saline	U	18.1, 18.6	22.7, 36.6	44.9 ± 5.9 (4)
		F	19.5, 18.2	11.9, 5.2	7.7 ± 9.1 (4)
	Solution 1	U	10.3, 28.4	58.2, 14.3	—
		F	25.9, 16.0	17.7, 27.4	—
	Solution 3	U	7.6, 20.6	36.7, 24.8	69.7 ± 10.2 (4)
		F	12.0, 9.6	11.0, 11.6	11.5 ± 1.0 (4)
Ethynyloestradiol-3-sulphate	Ethanol–saline	U	—	11.9 ± 3.6 (4)	—
		F	—	31.7 ± 4.3 (4)	—
Ethynyloestradiol*	Ethanol–saline	U	—	20.0 ± 6.9 (4)	—
		F	—	46.4 ± 6.0 (4)	—

* Values from Reed and Fotherby[12].

Individual values are given for the separate experiments, other values are mean ± SD with no. of estimations in parentheses.

expected to be slower. The finding of a much lower amount of the administered dose in the gut wall 7½ min after injection of the sulphate (0.3%) compared to the amount present 7½ min after injection of ethynyloestradiol (30%) would support this conclusion.

Chromatographic analysis of the radioactivity present in portal plasma and intestinal washings after injection of ethynyloestradiol-3-sulphate showed that the conjugate was present in an unaltered form. Thus the conjugate appeared to be absorbed without prior hydrolysis. Ethynyloestradiol and norethisterone were also largely absorbed in an unaltered form; over 75% of the radioactivity in portal plasma was in a freely extractable form and chromatographic analysis showed that most of the radioactivity was associated with the injected steroids. However, some radioactivity was present in portal plasma in a conjugated form. Preliminary investigations suggested that whereas radioactivity associated with ethynyloestradiol was conjugated mainly as a glucuronide, radioactivity associated with norethisterone was present mainly as a sulphate. These findings for ethynyloestradiol are similar to those of Meli *et al.*[14]. Unaltered ethynyloestradiol and norethisterone were also found in the freely extractable fractions from the washings of the small intestine and gut wall 7½ min after injection of the dose. As the amount of radioactivity present in portal plasma and intestinal wall in a freely extractable form was considerably greater than in the small intestine 7½ min after injection of norethisterone it seems likely that hydrolysis of material conjugated in the intestine occurred during its passage through the gut wall.

Analysis of the radioactivity in bile showed that at all times studied only insignificant amounts of radioactivity were excreted in an unconjugated form. Excretion of radioactivity associated with ethynyloestradiol was more rapid than that associated with norethisterone although these steroids were absorbed at a comparable rate. Conjugated metabolites were also found to account for most of the dose excreted in bile after injection of ethynyloestradiol into the small intestine [15] and after intravenous administration of norethisterone to rats [16].

Absorption of the derivatives of norethisterone from the small intestine of the rat was also rapid with less than 10% of the dose remaining 30 min after injection. Elimination of radioactivity in bile was at a rate similar to that found for norethisterone. Only one-third of the radioactivity in bile after administration of norethisterone and its derivatives was extractable after enzymic hydrolysis with a β-glucuronidase preparation. Thin layer chromatography of radioactivity extractable after enzymic hydrolysis suggested that norethisterone and norethisterone acetate were metabolised to polar compounds to a greater extent than norethisterone oxime. After administration of norethisterone oxime to the rabbit the unchanged oxime was the major urinary metabolite detected in the enzyme hydrolysed fraction [17]. It would therefore appear that norethisterone oxime is more resistant to metabolism than norethisterone or its acetate.

The portal circulation was the major pathway for the absorption of the steroids under study. Less than 1% of the dose was recovered when lymph from the thoracic lymph duct was collected for 3 h after the injection of norethisterone into the small intestine. Similar small amounts of the dose were collected in lymph over a 24 h period after the oral administration of ethynyloestradiol to rats [18].

Development of a slow release formulation for oral administration of contraceptive steroids might result in a beneficial reduction of the dose required. However, although results of the *in situ* experiments suggested that compared to the absorption from ethanol–saline, absorption from oil based solutions was reduced, *in vivo* studies in the rat, guinea-pig and rabbit showed that no significant difference existed between the two vehicles. No delay in the absorption of ethynyloestradiol or norethisterone when given to humans in the oil-based vehicles used for this study was found compared to administration of the steroids in a tablet formulation [19].

From the studies in which ethynyloestradiol-3-sulphate was administered to guinea-pigs, it would appear that metabolism of this compound differed from that previously reported for ethynyloestradiol by this species [12]. After administration of the sulphate only 30% of the urinary radioactivity could be accounted for as unconjugated, glucuronide or sulphate metabolites compared with more than 80% of urinary radioactivity which could be accounted for after the administration of ethynyloestradiol. Differences occur in the rate and pathway of metabolism of oestrone and oestrone sulphate in humans [20] and ethynyloestradiol and its sulphate are probably treated similarly.

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