

The reduction of the enterohepatic circulation of norethisterone by antibiotics in the rat

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We have previously established, using a 'linked rat' preparation that certain antibiotics will reduce the enterohepatic circulation (EHC) of the synthetic steroids norethisterone and ethinyloestradiol (Back, Breckenridge, Challiner, Crawford, Orme, Rowe & Smith, 1978). The aim of the present work was to examine whether or not the antibiotic induced reduction in norethisterone EHC correlated with changes in the gut flora. To show this we have used a different model in which bile, containing tritiated conjugates of norethisterone collected from 'donor' rats, was infused into the caecum of anaesthetized male ('recipient') rats. Bile was subsequently collected from the 'recipient' rats for 6 hours. Since only unconjugated steroid is absorbed, any radioactivity appearing in the bile of these 'recipient' rats is the result of deconjugation in the gut.

'Recipient' rats were pretreated with ampicillin or neomycin or rifampicin (all 200 mg kg⁻¹ day⁻¹ for 4 days) or neomycin + lincomycin (100 + 100 mg kg⁻¹ day⁻¹ for 4 days). Experiments were performed on the 5th day. The percentage recovery of radioactivity in bile in 6 hours is shown in Table 1. Ampicillin, neomycin and neomycin + lincomycin pretreatment all caused a reduction in the biliary excretion of radiolabelled drug. Following treatment with rifampicin (4 days) there was no significant change in excretion. At the termination of each investigation *in vivo*, a semiquantitative analysis of the gut flora was made. The main findings are summarised in Table 1. Marked rifampicin resistance was found after 4 days of treatment. To investigate the onset of this resistance, 'recipient' rats were treated with rifampicin (200 mg/kg) for 1, 2 or 3 days and the Table shows both the graded effect on the EHC of the steroid and the incidence of resistant organisms.

Reference

BACK, D.J., BRECKENRIDGE, A.M., CHALLINER, M., CRAWFORD, F.E., ORME, M.L.E., ROWE, P.H. & SMITH, E. (1978). The interaction of antibiotics with synthetic steroids in the rat. *Br. J. Pharmac.*, **62**, 441P.

Table 1 Percentage excretion of radioactivity in bile, and bacteriological analysis of gut flora, of recipient rats following intracaecal infusion of labelled conjugates of norethisterone

<i>Treatment</i>	<i>% Excretion</i>	<i>Bacteriological comment</i>
Control	42.4 ± 2.6	
Ampicillin (200 mg/kg/day for 4 days)	4.2* ± 0.8	Suppression of anaerobes; partial suppression of aerobes.
Neomycin (200 mg/kg/day for 4 days)	13.6* ± 3.3	Slight suppression of anaerobes; marked suppression of aerobes.
Neo. + Linco. (100 + 100 mg/kg/day for 4 days)	4.9* ± 0.33	Marked suppression of anaerobes and aerobes
Rifampicin (200 mg/kg/day for 1 day)	8.7* ± 2.0	No effect on anaerobes; marked suppression of aerobes.
Rifampicin (200 mg/kg/day for 2 days)	10.3* ± 1.3	No effect on anaerobes; some rifampicin resistant aerobes.
Rifampicin (200 mg/kg/day for 3 days)	22.2* ± 1.8	No effect on anaerobes; increased rifampicin resistant aerobes.
Rifampicin (200 mg/kg/day for 4 days)	47.5 ± 5.7	No effect on anaerobes; marked rifampicin resistant aerobes.

* Significantly different from controls, *P* < 0.001.