(mean maximum delta SBP: 0.4 ± 9.4 mm Hg; $P < 0.01$ vs group I). There was no significant change in SBP following saline injection in groups II and IV. When the renin-angiotensin system is suppressed, captopril significantly reduces blood pressure by a mechanism that is inhibited by indomethacin.

References

MURTHY, V.S., WALDRON, T.L. & GOLDBERG, M.E. (1978). The mechanism of bradykinin potentiation after inhibition of angiotensin converting enzyme by SQ 14,225 in conscious rabbits. *Circ. Res.*, Suppl. 1, **43**, 40–44.

ONDETTI, M.A., CUSHMAN, D.W. & BURIN, B. (1977). Design of specific inhibitors of angiotensin converting enzyme: A new class of orally active antihypertensive agents. *Science*, **196**, 441–444.

WANG, P.Y., TALAMO, R.C., WILLIAMS, G.H. & COLMAN, R.W. (1975). Response of the kallikrein-kinin and renin-angiotensin systems to saline infusion and upright posture. *J. Clin. Invest.*, **55**, 691–698.

The interaction of antibiotics with ethinyloestradiol in the rat and rabbit

D.J. BACK, A.M. BRECKENRIDGE, FRANCESCA E. CRAWFORD, KAREN J. CROSS, M.L'E. ORME & P.H. ROWE

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

Conjugation is a major route of metabolism of the synthetic oestrogen ethinyloestradiol (EE_2). Conjugates formed in the liver and gut wall may be subsequently available for enterohepatic circulation (EHC). Tritiated EE_2 conjugates were obtained from the bile of 'donor' rats and were then infused into the caecum of 'recipient' rats. Bile was collected from the 'recipient' rats over a period of 6 hours. Radioactivity appearing in the bile of 'recipient' rats is a measure of the extent of deconjugation in the gastrointestinal tract, since only unconjugated steroid can be reabsorbed across the intestinal mucosa. The influence of various antibiotics on the EHC of EE_2 was then studied following pretreatment of 'recipient' animals with ampicillin, a combination of neomycin + lincomycin, or cefoxitin. There was a reduction in the biliary excretion of the radiolabelled drug of 83%, 79% and 81% respectively, with a concomitant supression of the gut microflora (Table 1).

Following the intravenous administration of EE_2 to rabbits, a biphasic decline in plasma concentration of the steroid was found. However, after 7 h a secondary peak was observed in all animals. Pretreatment with the antibiotic combination of neomycin + lincomycin ($100 + 100$ mg kg^{-1} day^{-1} for 4 days) resulted in a significant decrease ($P < 0.01$) in the area under the plasma concentration time curve ($AUC_{control}$ 61.3 ± 6.2; $AUC_{antibiotic}$ 37.4 ± 5.3 ng ml^{-1} h). Not only was there a reduction in the secondary peak consistent with a reduced EHC, but also a change in the initial disposition of EE_2.

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Table 1 Effect of chronic antibiotic treatment on the EHC of EE_2 and the gut microflora

Treatment	*% excretion in bile*	*Caecal flora*
Control	32.6 ± 2.3	LFC + + + ; M.An. + + +
Ampicillin (200 mg kg^{-1} day^{-1} for 4 days)	***8.1 ± 2.6	LFC +*; M.An. ±
Neo + Linco ($100 + 100$ mg kg^{-1} day^{-1} for 4 days)	***6.9 ± 1.7	No LFC; M. An. ±
Cefoxitin (100 mg kg^{-1} day^{-1} for 4 days)	***6.2 ± 1.3	—

LFC—Lactose fermenting coliforms (e.g. E. Coli; Strep. faecalis) M.An.—Mixed Anaerobes (e.g. Clostridia spp., Bacteroides spp.) ± < 10^3/ml; + 10^3–10^5/ml; + + + 10^7–10^{10}/ml.

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

* Emergence of ampicillin resistant microflora.