this level *in vitro* produced 77 ± 3% inhibition of DNA synthesis. The duration of greater than 50% inhibition of DNA synthesis *in vivo* would be expected to be 5 h based on plasma Ara-C levels. However, based on intracellular Ara-CTP levels, DNA synthesis would be inhibited by more than 50% for 11 h, at which time plasma Ara-C would be expected to have no effect on DNA synthesis. It is apparent when considering dosage schedules of Ara-C in the treatment of leukaemia, the cellular pharmacokinetics and pharmacodynamics of Ara-CTP may be more important determinants than plasma Ara-C levels.

References

ARMENTROUT, S.A. & BURNS, C.P. (1974). Cytosine arabinoside as a single agent in the therapy of adult acute leukaemia. *Am. J. Med. Sci.*, **268**, 163–168.

MOMPARLER, R.L. (1974). A model for the chemotherapy of leukaemia with 1-β-D-arabinofuranosylcytosine (Ara-C). *Cancer Res.*, **34**, 1775–1787.

FURTH, J.J. & COHEN, S.S. (1968). Inhibition of mammalian DNA polymerase by the 5'-triphosphate of 1-β-D arabinofuranosylcytosine and the 5'-triphosphate of 9-β-D-arabinofuranosyladenine. *Cancer Res.*, **28**, 2061–2067.

The interaction of antibiotics with synthetic steroids in the rat

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Norethisterone and ethinyloestradiol are the synthetic steroids present in many combination type oral contraceptive preparations. Animal studies have established that both steroids undergo extensive biliary excretion, principally as glucuronides, and enterohepatic circulation (Steinetz, Meli, Giannina & Beach, 1967; Hanasono & Fischer, 1974; Smith, 1974). Neomycin has previously been reported to interfere with the enterohepatic circulation of radioactivity associated with the synthetic oestrogen mestranol, by affecting the viability of the gut microflora which are partly responsible for deconjugation (Brewster, Jones & Symons, 1977).

We have investigated the biliary excretion of labelled ethinyloestradiol and norethisterone both quantitatively and qualitatively. In addition, the effect of ampicillin and neomycin on the enterohepatic circulation has been studied using the 'linked rat' preparation previously described by Ladomery, Ryan & Wright (1967).

When administered intravenously (i.v.), 71.1% of a dose of [^{3}H]-ethinyloestradiol ([^{3}H]-EE_2; 10 μCi/kg; 10 μg/kg) and 76.0% of an i.v. dose of [^{3}H]-norethisterone ([^{3}H]-N; 10 μCi/kg; 125 μg/kg) were excreted in the bile of anaesthetized female rats in 4 hours. The majority of radioactivity appeared in the glucuronide fraction. Characterization (by thin layer chromatography, chemical transformation and recrystallization to a constant specific activity) of the hydrolysed glucuronide fraction obtained after giving [^{3}H]-EE_2 showed that approximately 10% of the administered dose was excreted as EE_2-glucuronide; the remainder of the glucuronide fraction contained conjugates of metabolites of EE_2. In contrast, the hydrolysed glucuronide fraction obtained after giving [^{3}H]-N contained only conjugates of metabolites of norethisterone and there was no evidence of direct conjugation of the steroid.

In the 'linked rat' preparation the bile duct cannula from a 'donor' rat is inserted into the duodenum of a 'recipient' rat. Of a dose of [^{3}H]-EE_2 administered to donor rats (i.v.), 15.4% was excreted in the bile of control recipient rats in 7 hours. When recipient rats were pretreated with either neomycin or ampicillin (100 mg body weight^{-1} day^{-1} for 5 days; orally), 5.2% and 6.0% of the dose appeared in bile respectively. With [^{3}H]-N, 13.2% of the dose was excreted in the bile of control recipient rats in 7 h and this was reduced to 3.6% in neomycin pretreated and 3.9% in ampicillin pretreated animals.

References

BREWSTER, D., JONES, R.S. & SYMONS, A.M. (1977). Effects of neomycin on the biliary excretion and enterohepatic circulation of mestranol and 17β-oestradiol. *Biochem. Pharmac.*, **26**, 943–946.

HANASONO, G.K. & FISCHER, L.J. (1974). The excretion of tritium-labelled chlormadinone acetate, mestranol, norethindrone and norethynodrel in rats and the enterohepatic circulation of metabolites. *Drug Metabolism and Disposition*, **2**, 159–168.

LADOMERY, L.G., RYAN, A.J. & WRIGHT, S.E. (1967). The excretion of [^{14}C]-butylated hydroxytoluene in the rat. *J. Pharm. Pharmac.*, **19**, 383–387.

SMITH, R.L. (1974). Biliary excretion and hepatotoxicity of contraceptive steroids. In: *Pharmacological models in contraceptive development* (edited by M.H. Briggs & E. Diczfalusy). W.H.O., Stockholm, pp. 149–168.

STEINETZ, B.G., MELI, A., GIANNINA, T. & BEACH, V.L. (1967). Studies on biliary metabolites of orally administered ethinyloestradiol (EE) and its 3-cyclopentyl ether (EECPE-Quinestrol). *Proc. Soc. exp. Biol. Med.*, **124**, 1283–1289.