The metabolism of fazadinium bromide

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Fazadinium bromide (AH 8165D) is a new short-acting competitive neuromuscular blocking agent. Its duration of action in rat, rabbit and dog is <4 min and in man, about 20 min.

AH 8165D is anaerobically reduced by rat liver microsomes to I and N_2 (Figure 1). The reaction is NADPH and flavin dependent. Aerobically, I is hydroxylated to II.

Since neither I nor II possess neuromuscular blocking activity, it is possible that the metabolism of AH 8165D may control its duration of action. The metabolism of either [^{3}H]- or [^{14}C]-AH 8165D was studied in rat, rabbit, dog and man following intravenous administration in doses of 0.5–10 mg/kg. In rat, AH 8165D was extensively metabolised, <5% being excreted as unchanged drug in urine. The principal route for excretion of radioactivity was bile. High voltage paper electrophoresis (HVPE), pH 2–10, showed that the biliary metabolite was neutral. The metabolite was reduced by $TiCl_3$ to I. Polarography of bile showed that the —N—N=N—N—linkage of AH 8165D was absent.

In rabbit <5% dose was excreted unchanged in urine together with a metabolite which on acid hydrolysis gave II.

In dog, 60% of the radioactivity excreted in bile and urine during 0–6 h was present as AH 8165D.

Studies in man (Blogg, Simpson, Martin & Bell, 1973) have shown that 70–80% of radioactivity is excreted in 0–48 h urine. HVPE showed that only AH 8165D was present in 0–4 h urine. In later samples a neutral metabolite was detected.

These results show that AH 8165D is extensively metabolised by rat and rabbit but not by dog and man. The duration of action of AH 8165D, therefore, cannot be predicted from metabolism studies. It is likely that the pharmacokinetics of AH 8165D play a larger part than metabolism in determining its duration of action.

Reference

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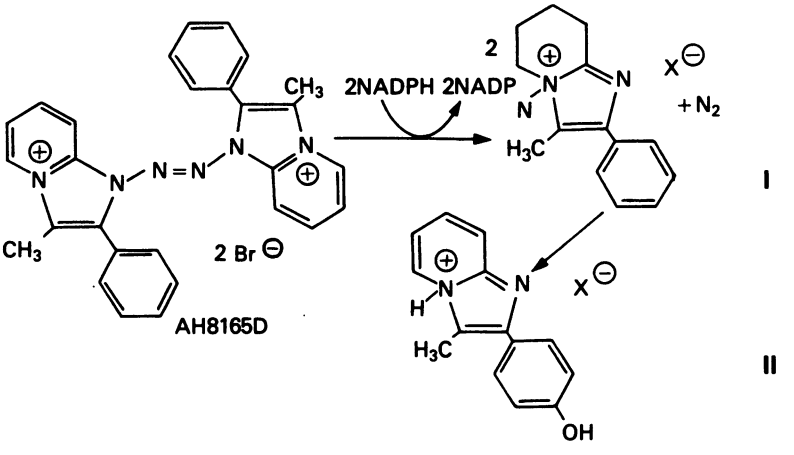

Figure 1 Metabolism of Fazadinium Bromide *in vitro*

Drug metabolism interactions with cytotoxic agents in mice

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In anticancer chemotherapy the functional integrity of the mixed function oxidase enzyme system in the liver is essential as many cytotoxic drugs exert their activity only after metabolic activation by these enzymes. Inhibitory drug metabolism interactions involving anticancer drugs may therefore have clinical consequences. It has been reported that several antitumour drugs, e.g. cyclophosphamide (Donelli & Garrattini, 1971), 5-fluoro-uracil (Klubes & Cerna, 1974) and procarbazine (Lee & Lucier, 1976) given in high doses appreciably inhibit oxidative drug metabolism.

In this study the effects on hepatic drug metabolism

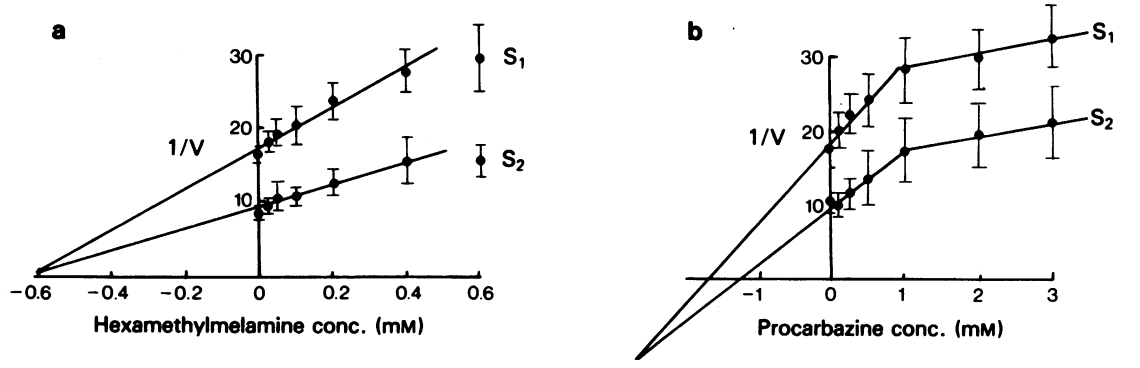

Figure 1 Inhibition of p-nitroanisole O-demethylase by (a) hexamethylmelamine and (b) procarbazine. S1 and S2 represent respectively p-nitroanisole substrate concentrations of 0.03 mM and 0.1 mM. Velocities (V) are given as nmoles of p-nitrophenol formed per 80 mg of liver during a 30 min incubation period. Each point shows the mean of at least four experiments.

of administration of seven antineoplastic agents given in doses which cause inhibition of tumour growth in mice were investigated. The drugs were administered i.p. to CBA lac mice (3 weeks old) as a single dose of 40 mg/kg (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, carmustine, chlorozotocine) or five daily doses of 40 mg/kg (procarbazine, hexamethylmelamine, dacarbazine, p-carbmethoxyphenyldimethyltriazene). Two days later hepatic N-demethylase activity was measured as an index of metabolic drug oxidation using a crude 9000 *g* liver preparation. The experiments indicated that the drugs exert only weak to negligible inhibition of drug metabolism at these dose levels.

In order to investigate interference by the cytotoxic drugs with oxidative drug metabolism at the enzymic site their ability to inhibit p-nitroanisole-O-demethylation *in vitro* was measured. The nature of the inhibition was characterised by plotting the reciprocal of the rate of O-demethylation against inhibitor concentration according to Dixon (1952) (Figure 1). The resulting inhibition profiles showed that high concentrations (>0.1 mM) of most drugs or their metabolites are required to exhibit appreciable inhibition. It is therefore possible that inhibitory drug metabolism interactions involving these drugs are not of major importance in the treatment of malignancies with drug combinations.

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In vitro biotransformation of carbinolamine metabolites of cytotoxic dimethyltriazenes

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N-demethylation reactions are major metabolic pathways of most tertiary amine xenobiotics with N-dimethyl moieties. The products of the reactions, the secondary amine and formaldehyde, are thought to be formed by the non-enzymatic breakdown of an intermediate carbinolamine (Figure 1). Carbinolamines are in most cases highly transient species and have been rarely isolated because of their chemical instability (Testa & Jenner, 1976).

Antineoplastic dimethyltriazenes (Figure 1*a*) belong to a group of cytotoxic agents for which it has been ascertained that an N-methyl group is crucial for activity (Connors, Goddard, Merai, Ross & Wilman, 1976). Dimethyltriazenes are not cytotoxic *in vitro* and it is generally considered that they are metabolically N-demethylated to form active cytotoxic agents *in vivo* (Connors, Goddard, Merai, Ross & Wilman, 1976). We have recently reported the chemical synthesis of the carbinolamine triazenes (Figure 1*b*),