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

BLOGG, C.E., SIMPSON, B.R., MARTIN, L.E. & BELL, J.A. (1973). Metabolism of ^{3}HAH 8165 in man. *Br. J. Anaesth.*, **45**, 1233–1234.

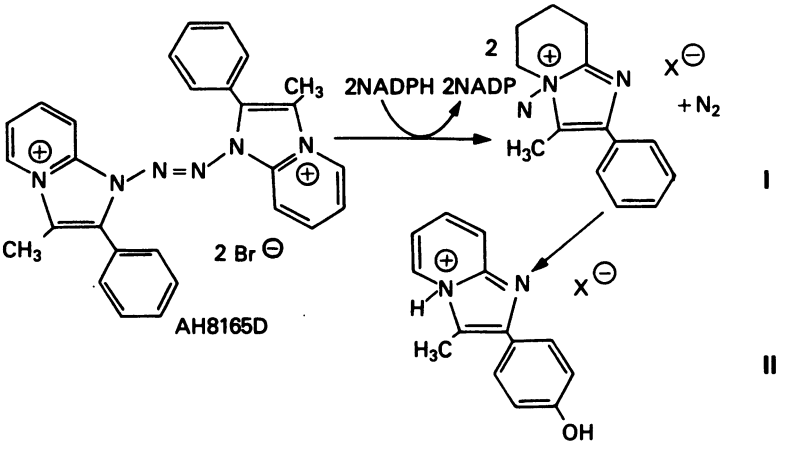

Figure 1 Metabolism of Fazadinium Bromide *in vitro*

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