METHAEMOGLOBIN INDUCTION BY AMINOGLUTETHIMIDE AND SOME OF ITS METABOLITES IN MOUSE BLOOD

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Several aromatic amines are capable of producing methaemoglobin (Kiese 1966) and there is evidence that this occurs via their N-hydroxyl metabolites (Cucinell et al 1972). In man, aminoglutethimide (AG; 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione) is oxidized to N-hydroxyl AG (HAG; Jarman et al 1983). This, and the importance of AG in the management of breast cancer in post-menopausal women, prompted a study of the methaemoglobin-inducing activity of the drug and some of its metabolites. AG was administered orally to female albino mice (25g) and blood, collected under ether anaesthesia, was assayed for methaemoglobin by the method described by Fairbanks (1976). Following AG (500mg/kg), methaemoglobin was detected reaching a max (8.5±0.9% of total haem pigments (THP)) at 45 min. Subsequently, methaemoglobin returned to baseline levels within 50 min. A well-defined dose/response relationship was observed over the range 200-500mg/kg (0.5-8.5% THP) for blood collected at 45 min. A major metabolite of AG, N-acetyl AG (AcAG; 590mg/kg orally) showed a similar time-course of methaemoglobinaemia but with a lower peak value (1.2±0.3% THP).

In vitro experiments were performed with heparinized mouse blood (0.5ml) incubated at 37°C for 45 min with a solution of either AG, AcAG or HAG in 0.06M phosphate buffer pH 7.4 (0.1ml) in the presence and absence of the 10,000 x g supernatant of a 20% (w/v) homogenate of mouse liver in 1.15% (w/v) KCl/0.1M Tris buffer pH 7.4 (0.2ml) and a solution containing 0.2µmole NADP, 4µmole glucose-6-phosphate and 4µmole Mg^{2+} (0.2ml). Methaemoglobin was determined at the end of incubation.

Table 1. Methaemoglobin (MH) formation in mouse blood in vitro

Compound (final concn. 5µg/ml)	MH(% THP) (- liver)	(+ liver)
AG	0	8.0 ± 1.3
HAG	6.0 ± 0.8	-
AcAG	0	2.8 ± 0.7

(results are means ± s.d. n=6)

The results (Table 1) showed that HAG was a directly-acting methaemoglobin-inducer while AG and AcAG required the presence of liver for methaemoglobin formation. Methaemoglobinaemia has not been reported during AG therapy in daily dose up to 1g, and as yet there is no information on plasma levels of HAG in man or the mouse. The methaemoglobin-producing potential of AG is only slightly less than that of dapsone (Ali et al 1985), a drug giving rise to clinically-significant side-effects related to this phenomenon (Cucinell et al 1972). Thus if methaemoglobinaemia does arise during AG therapy it is likely to be clinically-important. Based on the data reported here and on the pharmacokinetics of the drug (Nicholls 1984), a combination of high dose, extensive metabolism to HAG, low erythrocyte methaemoglobin reductase activity and compromised renal function may predispose patients to this blood dyscrasia.

We thank CIBA-Geigy, Horsham, for a gift of AG and for financial assistance.

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