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HAEMATOLOGICAL EFFECTS OF AMINOGLUTETHIMIDE IN THE MOUSE

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The aromatase inhibitor, aminoglutethimide (AG), is an effective agent in the hormonal therapy of metastatic breast cancer. In addition to the usually-transient side-effects of the drug e.g., lethargy, ataxia and dizziness, haematological effects have occasionally been observed. Of 1333 patients treated with AG, a 0.9% incidence of marked leukopaenia and/or thrombocytopaenia has been found to occur (Messeih et al 1985) and a single case of pancytopaenia has also been described in a patient receiving this drug (Lawrence et al 1978). In these cases blood cell counts recovered quickly on cessation of therapy with AG. Currently, there is uncertainty whether this effect of AG occurs by an immunological or a direct toxic mechanism (Messeih et al 1985; Vincent et al 1985). To provide further information about this phenomenon the effects of AG upon the blood picture of mice were examined.

Female albino mice (20-35 g) in groups of 20 received either AG (50 mg/kg suspended in 0.5% w/v sodium carboxymethyl cellulose plus 0.1% v/v Tween 80) or dosing vehicle by intraperitoneal injection daily. Blood samples for haematological examination, by conventional techniques, were collected from the tail vein at various times during the course of treatment.

At the end of the first week of dosing, most animals receiving AG showed evidence of a slight fall in white blood cells. The effect was progressive because by the end of the third week of treatment there was a pronounced leukopaenia (Table). At this time there was also a marked thrombocytopaenia (Table). While in the AG-treated group the mean erythrocyte count was not significantly altered, in comparison with controls, in about 20% of the mice the red blood cell counts were lowered and this was associated with lowered haemoglobin levels in blood. However, in all AG-treated animals examination of the blood film revealed the presence of polychromatophilia and a toxic granulation was observed in white blood cells. On cessation of dosing, the haematological parameters returned to normal within one week. Re-institution of the dosing schedule caused the re-appearance of the haematological effects by the end of one week.

Thus the haematological effects of AG in the mouse appear to be similar to those described in man. The occurrence of this toxic action in the mouse and its high incidence argue strongly in favour of a direct toxic effect of AG on the bone marrow. However, AG inhibits the organification of iodine by the thyroid (Hughes & Burley 1970) and the possibility that the haematological effects observed in the mouse may be related to an antithyroid effect of the drug cannot be excluded at present. The rapid return of haematoxicity on restarting AG administration is an important indication that in patients, where AG has been discontinued because of leukopaenia or thrombocytopaenia, the resumption of therapy with this drug may not be possible. Together with the clinical experience of AG, the present results indicate the need for monitoring the complete blood count and platelet count during the first few weeks after starting AG therapy.

Table. Haematological effects of AG (50 mg/kg) administered i.p. daily for 3 weeks to female mice.

	rbc	haemoglobin	wbc	platelets
	(10^6/cmm)	(g/100ml)	(10^3/cmm)	(10^6/cmm)
Controls	9.32±0.08	14.3±0.2	8.80±0.78*	1.17±0.39*
AG-treated	8.80±0.20	14.2±0.3	4.23±0.46*	0.60±0.22*

values are means ± sem (n=20); * P<0.001

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