AMINOGLUTETHIMIDE INHIBITS BOTH ADP- AND ARACHIDONIC ACID-INDUCED PLATELET AGGREGATION IN RABBIT BLOOD

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Aminoglutethimide is a non-steroidal inhibitor of several cytochrome P-450-dependent systems and is used in the therapy of oestrogen-dependent breast cancers in postmenopausal women, where it acts as an inhibitor of aromatase. The drug has been reported to alleviate bone pain in patients suffering from the primary metastatic disease (Harris et al. 1983) and also to relieve the bone pain in men suffering from advanced prostatic cancer (Rostom et al. 1982). Aminoglutethimide has also been reported to be comparable to flurbiprofen in lowering prostaglandin metabolite levels in breast cancer patients (Harris et al. 1983).

Using platelet aggregation as a model for studying the arachidonic acid cascade (Longenecker et al. 1985), we have investigated the effect of aminoglutethimide and the positive control substance indomethacin on this process.

Male New Zealand White rabbits (2.5kg) were fasted overnight prior to being bled by cardiac puncture under anaesthesia (N_2O/O_2, 1:4; induced by halothane). Blood was collected into tri-sodium citrate (1 volume citrate: 9 volumes blood). Platelet rich plasma (PRP) containing approximately $3x10^{-5}$ platelets mm^{-3} was prepared from the citrated blood. Platelet aggregation was induced by adenosine diphosphate (ADP) or arachidonic acid and the effects of incubating PRP with aminoglutethimide or indomethacin investigated.

With control platelets, ADP (10μM) and arachidonic acid (1.67mM) induced 77 and 67% aggregation respectively. From the results in the Table, it may be observed that both aminoglutethimide and indomethacin inhibited platelet aggregation induced by either agent. In the case of ADP-induced aggregation the inhibition appeared dose-dependent. It is also apparent that aminoglutethimide has a comparable activity to indomethacin.

Table: Inhibition of platelet aggregation by aminoglutethimide (AG) and indomethacin (IND) (% mean ± sem)

Drug*	Concn (μM)	Inhibition of aggregation (% mean + sem, n=6) induced by: ADP	Arachidonic acid
AG	20	21 ± 9	-
	50	39 ± 6	100
IND	20	32 ±11	-
	50	46 ± 8	100

*incubated with platelets for 15 min before addition of aggregating agent.

The results indicate that aminoglutethimide interferes with the arachidonic acid cascade and this may be relevant to the drug's ability to relieve bone pain. As metastasis of some breast tumours has been linked to their synthesis of prostaglandins (Bennett, 1985), it is possible that the latter pathway may be an additional site for the action of aminoglutethimide.

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