INTERACTIONS OF AMINOGLUTETHIMIDE WITH ANALGESICS IN THE MOUSE

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Aminoglutethimide (AG) is a non-steroidal agent effective in the treatment of oestrogen-dependent breast cancers in post-menopausal women by inhibition of peripheral aromatase. These tumours frequently metastasise to the bone, resulting in an intense pain which is traditionally treated by non-steroidal anti-inflammatory drugs (NSAIDs) (Powles et al 1980) believed to act by inhibiting cyclooxygenase enzymes and prostaglandin (PG) synthesis. It has been reported that institution of therapy with AG results in a decrease of pain suffered by patients with the metastatic disease (Harris et al 1983) who are already taking NSAIDs. Inhibition of aromatase cannot explain this effect as AG also alleviates the bone pain suffered by men with advanced prostatic cancer (Rostom et al 1982).

Using a conventional antinociceptive test the possible interaction of AG with several commonly used analgesics has been studied in mice. The abdominal constriction test employed (Koster et al 1959) involved injecting acetic acid (3% v/v, 0.1ml/10g body weight) intraperitoneally (i.p.) and counting the total number of abdominal constrictions elicited in the 30 minute period following the injection of the irritant. Dose-response curves to standard analgesics, given orally as a suspension (in 0.1% w/v carboxymethylcellulose/0.1% v/v Tween 80, 0.1ml/10g body weight) 45 minutes before the i.p. irritant, were established to select an effective sub-maximal dose that could be given in combination with AG. The dose of AG chosen (10mg/kg) did not exhibit marked antinociceptive activity; however, higher doses (25-100mg/kg) had a more pronounced protective effect. The results are given in the table.

Table: Antinociceptive Effect of Standard Analgesics ± AG

Drug	Dose mg/kg	Antinociceptive Effect (%) -AG	+AG
NSAIDs			
Aspirin	100	31	56.3
Ibuprofen	20	46	62
Indomethacin	20	29.5	54.6
Mefenamic Acid	50	50.3	63.4
OTHERS			
Dextromoramide	5	42	38
Dihydrocodeine	5	63	59
Morphine	2	39.5	41.6
Paracetamol	200	28.2	25.1

$$\text{Antinociceptive Effect} = \frac{a-b}{a} \times 100\%$$

a = score of control group
b = score of drug treated group
All S.E.M.s < 1.5
Dose of AG 10mg/kg

Analysis of the data using a linear model (GLIM) indicates that AG significantly enhanced ($P<0.02$) the effects of the NSAIDs at plasma levels (2µg/ml one hour after 10mg/kg AG) which is within the therapeutic range for man. This synergism together with reports that AG lowers PG metabolite levels (Harris et al 1983) suggests AG may act in a manner similar to that of NSAIDs.

Harris et al (1983) Br. J. Cancer 48: 595-598
Koster et al (1959) Fed. Proc. 18: 412
Powles et al (1980) Advances in Prostaglandin and Thromboxane Research 6: 511-516
Rostom et al (1982) Br. J. Urol. 54: 552-555