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Aminoglutethimide as an inducer of microsomal enzymes Part 1: pharmacological aspects

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Introduction

Aminoglutethimide (AG) [3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione] has come into regular use for treatment of advanced breast cancer, as 1. line endocrine therapy (1), but more often as 2. line therapy in tamoxifen-resistant patients (1,2,3). This drug is regarded as an inhibitor of the non-glandular steroid aromatase and several enzymes involved in the steroidogenic pathways in the adrenal cortex (4), causing a reduction of estrogen production in the postmenopausal woman.

The pharmacology of AG has recently received considerable interest, and several aspects related to drug scheduling, side-effects, drug interaction and mechanism of action have been focused. Detailed knowledge of the pharmacological properties of AG may be critical for an optimal therapy with this drug, since AG gives transient side effects in about ⅓ of the patients (1,3), is polymorphically acetylated (5), undergoes complex metabolic transformations (5–8) and is a potent inducer of hepatic metabolizing enzymes (9,10).

The following will focus on two aspects related to AG-induced metabolism, 1; the importance of induction for the understanding of AG pharmacokinetics, and thereby drug scheduling, and 2; the importance of induction related to drug interaction.

AG and induction: autoinduction

A substantial change in AG half-life (from about 15 h to 9 h) with continuous treatment was soon realized (11), and later confirmed in several studies (12,13,14), see Fig. 1. This prompted a dose escalating schedule of AG to avoid initial side effects (5,11).

However, this pronounced effect of AG on it's half-life was not found to be parallelled by a similar increase in clearance, being in the order of 30% only (13,14). We have shown that the discrepancy between the large reduction in half-life and the more modest increase in clearance is at least partly due to a reduction in volume of distribution during AG therapy (14). A similar, but smaller change in volume of distribution was reported by Adam et al. (13) after 1 week of AG treatment. Because half-life is a distribution of volume dependent parameter (15), the change in half-life, consistently observed, might mainly be attributed to the reduction in volume of distribution.

Indirect evidence supports the moderate, 30% increase in AG clearance found during multiple-dose therapy. Recently, several hydroxylated metabolites of AG have been isolated and identified from human urine (7,8), one of which, hydroxylaminoglutethimide (HxAG, see Fig. 2) might be of quantitative importance (16). HxAG

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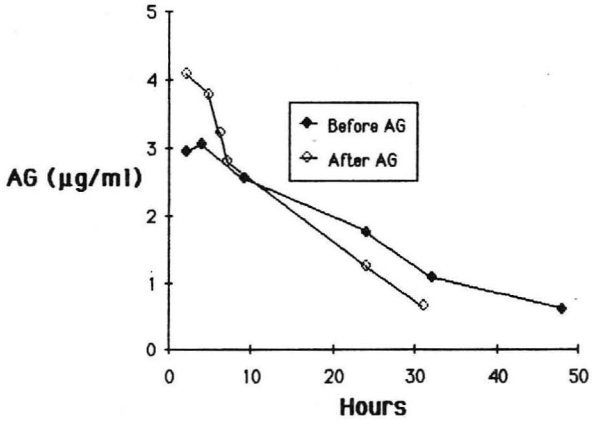

Fig. 1. Elimination of AG from blood, before and during chronic treatment with AG, after one oral dose of AG (250 mg). In patients on continuous treatment therapy was stopped for 48 hours before giving the test dose. AG was assayed by the method of Schanche et al. (28).

was found in urine from all patients tested, treated with AG, while this metabolite was not seen in patients after a single dose of AG. When HxAG was quantified in a patient on AG therapy, it was shown that the amount of the induced metabolite in 24h urine collections was about 25% of the oral dose (16). Assuming that other metabolic pathways are unchanged and that HxAG was excreted by the urinary pathway only, this might correspond to a 35% increase in clearance. Furthermore, it was reported recently (17) that a linear relationship was found between AG dose and serum concentration from 62.5 mg to 500 mg b.i.d. in a dose escalating study. On the other hand, we have found that there is a dose-

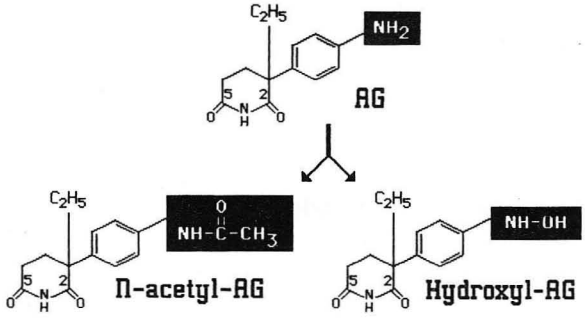

Fig. 2. The main metabolites of AG are shown, N-acetylaminoglutethimide (N-acetyl-AG) and N-hydroxyaminoglutethimide (hydroxyl-AG).

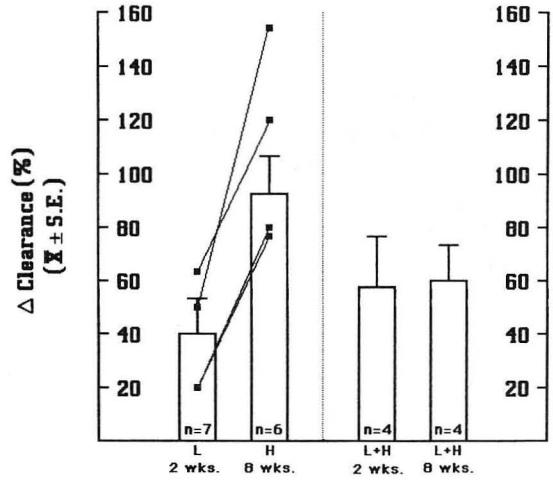

Fig. 3. The change in warfarin clearance (△clearance (%)) after low (L) dose (125 mg bid) and high (H) dose AG. To the left, the relative change in warfarin clearance after both low (4 weeks treatment) and high dose (8 weeks treatment) is shown. In 4 patients (shown with lines) AG was given first in low dose for 4 weeks and thereafter changed to high dose (250 mg qid and hydrocortison 25 mg bid). To the right the influence of 2 and 8 weeks of low *or* high dose of AG was compared. No further increase in △clearance with time after the first 2 weeks was observed. For further details, see (18).

dependent induction of warfarin by AG from 125 mg b.i.d. to 250 mg q.i.d. (18), see Fig 3. These results indicate that the autoinduction of AG metabolism is of a rather small magnitude. In conclusion we suggest that there is no data in favour of using a dose escalating schedule for AG treatment. Our findings indicate that the reduction of side effects seen with a modification of the conventional dosage schedule (i.e. aminogluthethimide at half dosage, double dose of glucocorticoids (3,11)) probably results from the increased dose of glucocorticoid administered.

AG and induction: drug interaction

Dexamethasone was originally used for adrenal substitution in the conventional AG schedule (250 mg q.i.d.). However, it was soon realized that AG promoted an increased metabolism of dexamethasone (9), which was not found to the same degree with cortisone. This finding probably reflects a lower affinity of cortisol than dexa-

methasone for the 6ß-hydroxylase, an enzyme known to be inducible with drugs like diphenylhydantoin (19), and rifampicin (20), both well-known stimulators of hepatic microsomal enzymes.

As has been noted above, AG also seemed to enhance its own metabolism, although not to the extent (14), originally suggested (11).

Later, alterations in oral anticoagulant requirement during AG therapy were described (21,22) and pharmacokinetically investigated (10). It was shown that AG induced a 3 to 5 fold increase in warfarin clearance (10). The increase in warfarin clearance is related to the AG dose (18), see Fig 3.

Other important drug interactions have recently been described (23). Theophylline and digitoxin, important drugs with a narrow therapeutic index, both show an increase in clearance during AG therapy (23). This implicates that the dose given of theophylline and digitoxin may have to be adjusted to maintain the blood levels within therapeutic limits. Antipyrine has been used as a test substance to assess drug metabolism, showing an increase in drug clearance during use of enzyme inducers like barbiturates (24). We observed a substantial and consistent increase in antipyrine clearance (80%) in patients receiving chronic AG therapy (23), see Fig. 4.

Oral high dose medroxyprogesterone acetate (MPA) has been shown to be an effective treatment in advanced breast cancer (25). It has been combined with AG to exploit 2 different mechanisms of action, and using MPA as a glucocorticoid substitute (26). In 41 evaluable women there were 7 objective responders (17%) (26). It has been shown, however, that the serum concentration of MPA when used in this combination, is less than one half the expected concentration (27). Again the most plausible explanation is an increase in hydroxylating, microsomal enzymes, accelerating the metabolism of MPA. An overview of the interactions described so far, is given in Table 1.

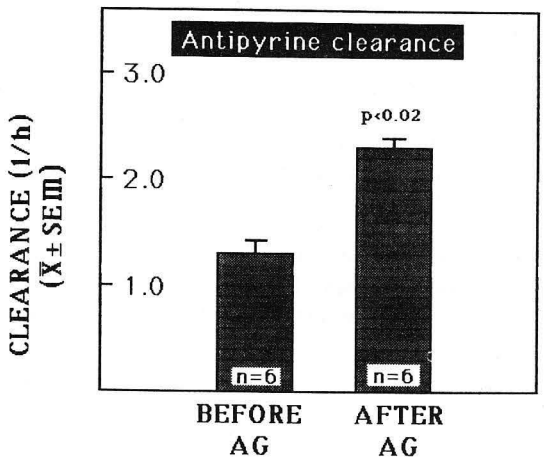

Fig. 4. Antipyrine clearance before and after AG treatment for 12 weeks.

In conclusion, several important drug interactions have been described with AG, probably reflecting an AG promoted, dose dependent induction of microsomal, drug metabolizing enzymes. With the increasing use of AG in the treatment of advanced brast cancer, further interactions should be expected.

Table 1. AG promoted changes in drug clearance (△C1(%)).

Drug	△C1 (%)	Range	Time on AG treatment (weeks).	Ref.
AG	+ 26.7 (n=17)	15.0- 91.1	9	13,14
Antipyrine	+ 81.1 (n=6)	28.3-154.0	12	23
Theophylline	+ 32.0 (n=3)	18.0- 43.0	8	23
Digitoxine	+109.0 (n=5)	25.0-244.0	5	23
Warfarin	+149.9 (n=8)	56.2-422.2	8	10, 18
Dexamethasone	+292.0 (n=7)	—	2	9
Medroxyprogesterone acetate	+ 15.4 (n=4)	–	—	29

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