Cancer Chemother Pharmacol (1990) 26: 241–244

Cancer Chemotherapy and Pharmacology

Review

Aminoglutethimide enzyme induction: pharmacological and endocrinological implications

Per Eystein Lønning

Department of Therapeutic Oncology and Radiophysics, Haukeland University Hospital, N-5021 Bergen, Norway

Received 28 August 1989/Accepted 8 February 1990

Summary. Aminoglutethimide is an aromatase inhibitor that is successfully used for endocrine treatment of advanced breast cancer. This drug also stimulates the activity of hepatic mixed-function oxidases, increasing the metabolism of several drugs, including warfarin, digitoxin, antipyrine and theophylline. It also increases the plasma clearance rate of oestrone sulphate. As this oestrogen may be an important substrate for tumour cells, stimulation of oestrone sulphate metabolism may be a component of the mechanism of action of aminoglutethimide.

Introduction

Aminoglutethimide is a drug that is successfully used in the endocrine treatment of advanced breast cancer. The drug was initially introduced for treatment of breast cancer in an attempt to achieve a "medical adrenalectomy" [3]. More recent studies have shown adrenal steroid output to remain stable [25, 30, 32]; however, aminoglutethimide inhibits postmenopausal oestrogen production by blocking the main pathway of oestrogen synthesis, aromatisation of androstenedione into oestrone [26]. Whereas in vivo isotope tracer studies have reported aromatisation to be inhibited by 92%–98% [6, 26], plasma oestrogens are usually suppressed by only about 50% [5, 27, 32]. Aminoglutethimide causes a response rate of about 30% among unselected postmenopausal breast cancer patients [12].

Another aromatase inhibitor, testololactone, was found to inhibit in vivo aromatisation by about 90% [2]. However, testololactone treatment causes a response rate of only 10%–14% in postmenopausal breast cancer [33]. It is tempting to speculate that the different response rates for aminoglutethimide and testololactone could be related to biochemical effects other than aromatase inhibition.

Aminoglutethimide may induce drug metabolism [14, 15, 17]. Many drugs and steroids are metabolized by similar hepatic enzyme systems [4]. For this reason, we have studied the influence of aminoglutethimide on oestrogen metabolism. The findings that aminoglutethimide increases the oestrone sulphate clearance rate [18] and changes the urinary oestrogen metabolite profile [13] suggest that this drug could influence oestrogen disposition by mechanisms unrelated to aromatase inhibition.

This paper summarizes the results of our studies on the influence of aminoglutethimide on drug and oestrogen metabolism. Several important drug interactions and the possible implications of aminoglutethimide stimulation of oestrogen metabolism are discussed.

Patients and methods

Patients. During the period between 1983 and 1988, a total of 65 patients were studied for a possible influence of aminoglutethimide on drug or oestrogen metabolism. All of these patients received aminoglutethimide therapy for advanced breast cancer. One patient had two possible drug interactions evaluated. Many patients who took part in the oestrogen tracer studies had more than one parameter evaluated on each occasion. Each patient was studied in a control situation (either before or 3–4 weeks following cessation of aminoglutethimide treatment) and during steady-state aminoglutethimide therapy.

The possible influence of aminoglutethimide on digitoxin or theophylline (and, in two patients, warfarin) disposition was examined in patients receiving these drugs therapeutically. Otherwise, the patients received a single test dose of the drug to be investigated (antipyrine or warfarin) or an oestrogen tracer (oestradiol or oestrone labelled with carbon 14 and/or tritium-labelled oestrone sulphate) before and during chronic aminoglutethimide therapy.

Methods. Plasma levels of aminoglutethimide, warfarin and theophylline were determined by HPLC methods as described elsewhere [24, 29, 31]. Antipyrine concentrations were determined by a gas chromatographic method [7], whereas digitoxin levels were measured by a commercial radioimmunoassay kit. The coefficient of variation was <5% for all analytical procedures. Plasma oestrone, plasma oestrone sulphate and plasma tracer oestrogen concentrations were measured by methods described elsewhere [18, 21]. The coefficients of variation were between 5% and 10% for all methods. Urinary tracer oestriol was isolated by the use of an LH20 Sephadex column system [21] or by HPLC [22].

The metabolic clearance rate for different drugs and tracer oestrogens was calculated from the equation Cl = dose/AUC. As all drugs were given by the oral route, the AUC was calculated by use of the trapezoidal

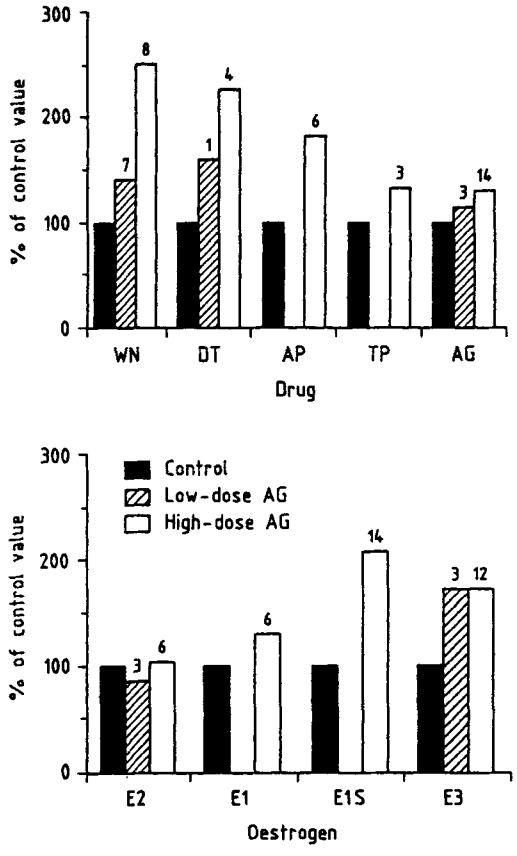

Fig. 1. Alterations in plasma clearance rate for certain drugs and oestrogens caused by chronic treatment with aminoglutethimide (*AG*) on a "low-dose" (250 mg/day) or "high-dose" (1,000 mg/day) drug schedule *WN*, warfarin; *DT*, digitoxin; *AP*, antipyrine; *T*, theophylline; *AG*, aminoglutethimide; E_2, oestradiol; E_1, oestrone; E_1S, oestrone sulphate; E_3, oestriol. Note that the diagram for E_3 shows an alteration in the urinary excretion rate of this oestrogen

rule, adding the residual by extrapolation to infinity. Radiolabelled oestrogens were always given by the intravenous route. The pharmacokinetics of tracer oestrone and oestradiol fitted to a three-compartment model (Statgraphics on an IBM 5060). In contrast, the plasma kinetics of oestrone sulphate did not fit into a simple two- or three-compartment open model, most probably because of its enterohepatic circulation. Therefore, the AUC for oestrone sulphate was determined by the trapezoidal rule. Statistical comparison between values obtained before and during treatment in individual patients was done by the Wilcoxon matched-pair signed-rank test, with probability being expressed as two-tailed values.

Results

The influence of aminoglutethimide on the disposition of different drugs and oestrogens is illustrated in Fig. 1. The results may be summarized as follows:

1. Aminoglutethimide given at its conventional dose (1,000 mg daily) increased the plasma clearance rates of warfarin ($n = 8$, $P < 0.01$), digitoxin ($n = 5$, $0.05 < P < 0.10$) and antipyrine ($n = 6$, $P < 0.05$) by mean values of 81%–152%. Plasma clearance rates for theophylline and aminoglutethimide itself were moderately increased, by 32% ($n = 3$, $P > 0.2$) and 29% ($n = 14$, $P < 0.025$), respectively.

2. This enzyme induction appears to be dose-dependent, as treatment with aminoglutethimide at 250 mg/day seemed to cause smaller alterations in drug metabolism than did a dose of 1,000 mg/day.

3. Aminoglutethimide seems to have no influence on the clearance rate of oestradiol. The oestrone clearance rate was moderately increased by a mean value of 30% ($n = 6$, $P < 0.05$). In contrast, the clearance rate of oestrone sulphate was increased by a mean of 112% ($n = 14$, $P < 0.0005$) and the urinary excretion of labelled oestriol following tracer injections of oestrone or oestradiol was increased by a mean of 63% ($n = 12$, $P < 0.0025$).

Clinical implications

Aminoglutethimide is a potent enzyme inducer in man. Possible drug interactions should be considered whenever aminoglutethimide is given in concert with drugs that are metabolized by hepatic mixed-function oxidases.

Our study, similar to that of Adam et al. [1], found aminoglutethimide to increase its own clearance rate by a mean value of 30%–35%. Murray et al. [23] reported that it caused a 100% increase in its own metabolism during steady-state treatment, but in their study [23] the clearance rate was calculated from the half-life under the assumption that the volume of distribution remained unchanged during treatment. This concept has been challenged [16].

The influence of aminoglutethimide treatment on oestrone clearance has been examined by one other group [26], but no additional studies of the drug's influence on the oestradiol or oestrone sulphate clearance rate have been conducted. Santen's group [26] found no influence of aminoglutethimide treatment on the metabolism of oestrone. In contrast, we found the oestrone clearance rate to be moderately increased by a mean of 30% [20]. Both of these studies involved a limited number of patients, and such a difference might occur by chance; however, it could also be related to different investigation protocols. In their study, Santen et al. gave a priming bolus dose one-sixth of the total dose) followed by a 4-h steady-state infusion. The validity of short-term steady-state infusions for the investigation of oestrogen kinetics has been challenged [9]. In all, 50%–90% of a tracer dose of oestrone is converted into oestrone sulphate, and 15%–45% of the oestrone sulphate reappears in plasma as unconjugated oestrone [20]. Thus, to reach oestrone steady state it is necessary that equilibrium with the oestrone sulphate pool be obtained. Oestrone sulphate has a half-life of 3–10 h in untreated patients and 2–4 h in patients on aminoglutethimide treatment [15]. This suggests that oestrone infusion times of between 24 and 48 h may be required to obtain oestrone steady-state plasma levels. A possible explanation as to why the clearance rate of oestrone but not of oestradiol could be increased during aminoglutethimide treatment is given elsewhere [20].

Although aminoglutethimide seems to have only a modest influence on the metabolism of unconjugated oestrogens, it stimulates oestrone sulphate metabolism. Accordingly, a selective suppression of plasma oestrone sulphate as compared with plasma oestrone is seen [21].

A significant increase in the urinary excretion of oestrogen metabolites produced by hydroxylation of oestrone in the 16α-position suggests that aminoglutethimide stimulates oestrone sulphate metabolism by enhancing this particular mixed-function oxidase. This could occur either by direct hydroxylation of oestrone sulphate [10] or after intracellular oestrone sulphate solvolysis [12]. Interestingly, a reduction in the plasma oestrone sulphate : oestrone ratio similar to that caused by treatment with aminoglutethimide is also seen in patients treated with the enzyme inducer rifampicin [19]. This finding indirectly suggests that aminoglutethimide may stimulate oestrone sulphate metabolism by inducing certain mixed-function oxidases.

It is difficult to assess the importance of aminoglutethimide stimulation of oestrone sulphate metabolism. However, the following evidence suggests that this mechanism could be beneficial for the activity of aminoglutethimide against breast cancer:

1. There are theoretical reasons suggesting that oestrone sulphate may be an important oestrogen source for the tumour cell [28].

2. Testololactone, a drug found to inhibit aromatisation in vivo by about 90%, has a response rate of 10%–14% [33]. This contrasts with a response rate of 29% following treatment with aminoglutethimide at 1,000 mg/day [12]. Although most patients on aminoglutethimide also receive glucocorticoids, there is no direct evidence suggesting that a difference in the response rates for aminoglutethimide and testololactone may be caused by glucocorticoid administration. Recent results [8] suggest a similar response rate for patients treated with aminoglutethimide with or without glucocorticoids [11]. Accordingly, the difference in the response rates for aminoglutethimide and testololactone suggests that mechanisms unrelated to aromatase inhibition could partly be responsible for the action of aminoglutethimide.

3. Although aminoglutethimide given at a low dose of 250 mg/day causes an inhibition of aromatisation amounting to >90% in vivo [6], the response rate to this dose was 19% among patients with advanced disease, regardless of whether they received glucocorticoids [8, 11]. This response rate seems to be inferior to that of 29% seen among patients treated with aminoglutethimide at 1,000 mg/day [12]. Although aminoglutethimide doses of 250 and 1,000 mg/day caused similar aromatase inhibition, aminoglutethimide enzyme induction seems to be dose-dependent in the dose range of 250–1,000 mg/day. Thus, dose-dependent alterations in oestrone sulphate metabolism could be responsible for a difference in the response rates obtained using different aminoglutethimide dose schedules.

Considering the new aromatase inhibitors that have been introduced for treatment of breast cancer, the finding that aminoglutethimide influences oestrogen disposition by mechanisms unrelated to aromatase inhibition may have important clinical implications. Enzyme-inducer compounds could be added to endocrine treatment schedules in breast cancer.

Acknowledgements. These investigations were supported by grants from The Norwegian Cancer Society. Special thanks are due all of my co-workers who have contributed to these investigations over the past years. I am most grateful to Prof. R. Scheline, Department of Pharmacology, Medical Faculty, University of Bergen, for valuable criticism during the preparation of this manuscript.

References

1. Adam AM, Rogers HJ, Amiel SA, Rubens RD (1984) The effect of acetylator phenotype on the disposition of aminoglutethimide. Br J Clin Pharmacol 18: 495
2. Barone RM, Shamonki IM, Siiteri PK, Judd HL (1979) Inhibition of peripheral aromatization of androstenedione to estrone in postmenopausal women with breast cancer using Δ^1-testololactone. J Clin Endocrinol Metab 49: 672
3. Cash R, Brough AJ, Cohen MNP, Satoh PS (1967) Aminoglutethimide (Elipten-Ciba) as an inhibitor of adrenal steroidogenesis: mechanism of action and therapeutic trial. J Clin Endocrinol 27: 1239
4. Conney AH, Levin W, Jacobsen M, Kuntzman R (1973) Effects of drugs and environmental chemicals on steroid metabolism. Clin Pharmacol Ther 14: 727
5. Dowsett M, Harris AL, Stuart-Harris R, Hill M, Cantwell BMJ, Smith IE, Jeffcoate SL (1985) A comparison of the endocrine effects of low dose aminoglutethimide with and without hydrocortisone in postmenopausal breast cancer patients. Br J Cancer 52: 525
6. Dowsett M, Santner SJ, Santen RJ, Jeffcoate SL, Smith IE (1985) Effective inhibition by low-dose aminoglutethimide of peripheral aromatization in postmenopausal breast cancer patients. Br J Cancer 52: 31
7. Fraser HS, Muclow JC, Murray S, Davies DS (1976) Assessment of antipyrine kinetics by measurement in saliva. Br J Clin Pharmacol 3: 321
8. Harris AL, Cantwell BMJ, Carmichael J, Dawes P, Robinson A, Farndon J, Wilson R (1989) Phase II study of low dose aminoglutethimide 250 mg/day plus hydrocortisone in advanced postmenopausal breast cancer. Eur J Cancer Clin Oncol 25: 1105
9. Hembree WC, Bardin CW, Lipsett MB (1969) A study of estrogen metabolic clearance rates and transfer factors. J Clin Invest 48: 1809
10. Hobkirk R, Nilsen M, Mori J (1978) 16-Hydroxylation of estrone-3-sulfate and estrone in the guinea-pig in vivo. Endocrinology 103: 1227
11. Lønning PE (1990) New endocrine drugs for treatment of advanced breast cancer. Acta Oncol (in press)
12. Lønning PE, Kvinnsland S (1988) Mechanisms of action of aminoglutethimide as endocrine therapy of breast cancer. Drugs 35: 685
13. Lønning PE, Skulstad P (1989) Alterations in the urine excretion of estrogen metabolites in breast cancer women treated with aminoglutethimide. J Steroid Biochem 33: 565
14. Lønning PE, Kvinnsland S, Bakke OM (1984) Effects of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. Clin Pharmacol Ther 36: 796
15. Lønning PE, Kvinnsland S, Jahren G (1984) Aminoglutethimide and warfarin. A new important drug interaction. Cancer Chemother Pharmacol 12: 10
16. Lønning PE, Schanche JS, Kvinnsland S, Ueland PM (1985) Single-dose and steady-state pharmacokinetics of aminoglutethimide. Clin Pharmacokinet 10: 353
17. Lønning PE, Ueland PM, Kvinnsland S (1986) The influence of a graded dose schedule of aminoglutethimide on the disposition of the optical enantiomers of warfarin in patients with breast cancer. Cancer Chemother Pharmacol 17: 177
18. Lønning PE, Kvinnsland S, Thorsen T, Ueland PM (1987) Alterations in the metabolism of oestrogens during treatment with aminoglutethimide in breast cancer patients. Preliminary findings. Clin Pharmacokinet 13: 393
19. Lønning PE, Bakke P, Thorsen T, Olsen B, Gulsvik A (1989) Plasma levels of estradiol, estrone, estrone sulfate and sex hormone binding globulin in patients receiving rifampicin. J Steroid Biochem 33: 631

20. Lønning PE, Johannessen DC, Thorsen T (1989) Alterations in the production rate and the metabolism of oestrone and oestrone sulphate in breast cancer patients treated with aminoglutethimide. Br J Cancer 60: 107
21. Lønning PE, Johannessen DC, Thorsen T, Ekse D (1989) Effects of aminoglutethimide on plasma estrone sulfate not caused by aromatase inhibition. J Steroid Biochem 33: 541
22. Lønning PE, Skulstad P, Sunde A, Thorsen T (1989) Separation of urinary metabolites of radiolabelled estrogens in man by HPLC. J Steroid Biochem 32: 91
23. Murray FT, Santner S, Samojlik E, Santen RJ (1979) Serum aminoglutethimide levels: studies of serum half-life, clearance, and patient compliance. J Clin Pharmacol 19: 704
24. Orcutt JJ, Kozak PP, Gillman SA, Cummins LH (1977) Micro-scale method for theophylline in body fluids by reversed-phase, high-pressure liquid chromatography. Clin Chem 23: 599
25. Samojlik E, Santen RJ (1980) Potency of the effect of D-steroisomer of aminoglutethimide on adrenal and extra-adrenal steroido-genesis. J Clin Endocrinol Metab 51: 462
26. Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E (1978) Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. J Clin Endocrinol Metab 47: 1257
27. Santen RJ, Worgul TJ, Lipton A, Harvey H, Boucher A, Samojlik E, Wells SA (1982) Aminoglutethimide as treatment of postmenopausal women with advanced breast carcinoma. Ann Intern Med 96: 94
28. Santner SJ, Feil PD, Santen RJ (1984) In situ estrogen production via the estrone sulfatase pathway in breast tumours: relative importance versus the aromatase pathway. J Clin Endocrinol Metab 59: 29
29. Schanche JS, Lønning PE, Ueland PM, Kvinnsland S (1984) Determination of aminoglutethimide and *N*-acetylaminoglutethimide in human plasma by reversed-phase liquid chromatography. Ther Drug Monit 6: 221
30. Stuart-Harris R, Dowsett M, D'Souza A, Donaldson A, Harris AL, Jeffcoate SL, Smith IE (1985) Endocrine effects of low-dose aminoglutethimide as an aromatase inhibitor in the treatment of breast cancer. Clin Endocrinol 22: 219
31. Ueland PM, Kvalheim G, Lønning PE, Kvinnsland S (1985) Determination of warfarin in human plasma by reversed-phase liquid chromatography. Ther Drug Monit 7: 329
32. Vermeulen A, Paridaens R, Heusen JC (1983) Effects of aminoglutethimide on adrenal steroid secretion. Clin Endocrinol 19: 673
33. Volk H, Deupree RH, Goldenberg IS, Wilde RC, Carabasi RA, Escher GC (1974) A dose response evaluation of delta-1-testololactone in advanced breast cancer. Cancer 33: 9