First generation aromatase inhibitors — aminoglutethimide and testololactone

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Summary

Aminoglutethimide and testololactone may be considered the first generation aromatase inhibitors for the endocrine treatment of breast carcinoma. Initially, both of these agents were designed and used clinically based on different concepts of their mechanisms of action. Only later were they both demonstrated to inhibit aromatase.

Curiously, testololactone was earlier and more widely used than aminoglutethimide in treating advanced breast carcinoma. The discovery of the peripheral aromatase inhibition as the proper mechanism of action was delayed for both the agents but was relatively more timely for aminoglutethimide. Paradoxically, the clinical use of testololactone has become already obsolete since its true mechanism of action was discovered.

Aminoglutethimide is still the most widely used aromatase inhibitor in treating advanced breast carcinoma. Due to the initial misinterpretation of its mechanism of action, aminoglutethimide was used for a long time at a relative high daily dose, always combined with hydrocortisone. Subsequent phase II and then randomized phase III studies demonstrated an equivalent efficacy using half (500 mg) of the previous conventional daily dose (1000 mg), with hydrocortisone. Very recently, a randomized clinical trial demonstrated that administering this lower dose without hydrocortisone did not significantly decrease the clinical efficacy.

By decreasing the dose of aminoglutethimide, the incidence of side effects has been reduced. So, the last paradoxical aspect of the aminoglutethimide story is that this agent seemed initially very toxic but finally, with the new schedules, shows a very low toxicity profile, especially after the first few weeks of treatment.

AMINOGLUTETHIMIDE

The most widely studied aromatase inhibitor is aminoglutethimide. However, the drug had a rather long history before its clinical efficacy by this mechanism of action was completely accepted. For a rather long period of time, it was considered as inducing a medical adrenalectomy and was combined with corticosteroids. Because of that, the problems of the optimal dose and of the indispensability of the addition of hydrocortisone have only recently been elucidated.
History of the mechanisms of action

Aminoglutethimide, the amino derivative of the hypnotic glutethimide, was introduced as an anticonvulsant in the United States in 1960. Nearly half of the treated patients experienced side effects, including drowsiness, dizziness and ataxia. Clinical studies demonstrated a relatively weak anticonvulsant activity [1] and, in 1966, adrenal insufficiency was noted in two children on treatment with the drug [2]. Aminoglutethimide was withdrawn by the FDA in 1966.

Experimental studies in rats and in man indicated that the drug blocked adrenal steroidogenesis by inhibiting desmolase conversion of cholesterol to pregnenolone [3,4]. In 1967, Cash et al [5] reported the first dramatic relief of bone pain in a single postmenopausal woman with metastatic breast cancer given aminoglutethimide at a dose of 1000 mg daily for 4 days, in lieu of adrenalectomy. Griffith et al in 1973 [6] and Lipton and Santen in 1974 [7] published the results of the first two clinical studies. The first authors treated 9 patients with a daily aminoglutethimide dose of 1000 to 2500 mg, plus dexamethasone and fludrocortisone acetate replacement. Three of these patients experienced objective regression of metastases. The latter authors treated 12 women with increasing daily doses of aminoglutethimide until toxicity was observed or with 1000 mg daily dose, plus dexamethasone in order to block release of ACTH. A therapeutic effect was observed in 6 patients.

Medical adrenalectomy

The term medical adrenalectomy had already been introduced before aminoglutethimide was available to indicate an alternative means to surgical adrenalectomy. It was originally achieved through the administration of cortisone or another corticosteroid in an amount sufficient to inhibit ACTH release and to produce adrenal atrophy.

In both of the above mentioned first clinical studies [6,7], the administration of aminoglutethimide with corticosteroid replacement was considered as another, possibly more effective medical adrenalectomy compared to corticosteroids alone. Indeed, at that time, the clinical need for an effective nonsurgical adrenalectomy together with the known inhibition of desmolase by aminoglutethimide in experimental studies seemed to support medical adrenalectomy for explaining the positive results achieved. Another additional mechanism of action of aminoglutethimide was nevertheless also hypothesized based on the first pioneering study by Griffith et al [6]. In fact, they suggested that activity of aminoglutethimide might result "from a peripheral effect of the drug or from suppression of an unidentified steroid". Indeed, hormonal measurements in their patients did not always demonstrate a suppression of adrenal corticoid excretion.

In 1977, Santen et al [8] demonstrated a negative interaction between aminoglutethimide and dexamethasone, in that the first drug accelerated the metabolism and reduced the bioavailability of the second. They proposed the new aminoglutethimide (1000 mg) and hydrocortisone (40 mg) regimen, which became the conventional regimen. Santen et al considered this regimen as a method of adrenal suppression. However, they also postulated that the reduction of estrone and the increase of androstenedione (observed when a patient received a low dose of dexamethasone) were due to extra-adrenal effects of aminoglutethimide on estrogen production. This mechanism of action was thought to be occurring in addition to the blocking effects on the cholesterol-to-pregnenolone conversion. On the other hand, in 1973 Grodin et al [9] had shown that the major source of estrone (and estradiol) in postmenopausal women was a transformation of androstenedione into estrone in the peripheral tissues, and Thompson and Siiteri in 1974 [10,11] had demonstrated that aminoglutethimide was a potent inhibitor of the aromatase in placental microsomal preparations.

Surprisingly, several papers, until about 1982, continued to consider, even in the title, medical adrenalectomy as an important mechanism of