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Aminoglutethimide and warfarin

A new important drug interaction

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Summary. *Aminoglutethimide (AG) has recently been introduced for endocrine therapy in patients with advanced breast and endometrial cancer. In this study two patients being treated with both AG and the anticoagulant agent warfarin are described. An important drug interaction was observed, resulting in a decrease in the anticoagulant effect of warfarin. This was shown by means of thrombotest measurements and pharmacokinetic evaluation of warfarin. A 3- to 5-fold increase in warfarin clearance was found.*

This interaction is probably due to an AG-promoted induction of hepatic microsomal enzymes accelerating warfarin metabolism.

Introduction

Aminoglutethimide (AG) in combination with a glucocorticoid has recently been used for the treatment of advanced breast cancer [18]. AG, being a derivative of the hypnotic agent glutethimide, was soon found to be an inducer of hepatic drug-metabolizing enzymes [11, 17]. Warfarin is a commonly used coumarin anticoagulant. Different types of interactions between warfarin and several other drugs have been described [10]. Increased warfarin requirement may result from an induction of liver microsomal enzymes increasing the metabolic inactivation of the drug. Alterations in oral anticoagulant requirement during AG treatment have been described [6, 12], but have not been accompanied by pharmacokinetic studies.

In this report we describe two patients to whom both AG and warfarin were given. AG seems to antagonize the anticoagulant effect of warfarin, possibly by the induction of metabolizing microsomal enzymes in liver.

Patients and methods

Patient characteristics. Patient no. 1, a 79-year-old female, was initially treated for an endometrial carcinoma in 1964. In 1977 she developed lung metastases and later a local recurrence, both of which were successfully treated with endocrine therapy (gestagens, tamoxifen) and radiation. In December 1981 a local recurrence was again discovered, and treatment with AG (Elipten, Ciba-Geigy) was started [14]. The drug schedule was AG 250 mg q.i.d. and cortisone acetate 25 mg b.i.d. In January 1982 she was hospitalized due to a deep venous thrombosis. Heparin treatment IV was started immediately, and from day 4 warfarin was administered as an oral anticoagulant. After 4 months AG treatment had to be stopped due to a persistent rash. Warfarin treatment continued.

Patient no. 2 was a 71-year-old female. In July 1981 she had a mastectomy for a locally advanced breast cancer. In the postoperative period both a deep venous thrombosis and lung embolism occurred, which were treated with heparin and warfarin. In June 1982 AG treatment was started for lung metastases, after progression on tamoxifen medication. The dose schedule was as for patient no. 1. At this time patient no. 2 had been using warfarin for 9 months due to recurrent episodes of phlebitis. AG treatment was stopped after 6 weeks due to rapidly progressing disease. In both patients the anticoagulant effect of warfarin was evaluated by thrombotest.

Methods. Both patients gave their informed consent to the study. Blood for warfarin measurements was obtained by venous puncture at 0, 1, 2, 3, 6, 12, and 24 h after drug intake. The blood samples were allowed to coagulate for 1 h at 4° C before centrifugation (10 min at 3,000 rpm, 4° C). Serum obtained was kept frozen (−20° C) until analysis. Warfarin was quantified using a high-performance liquid chromatographic (HPLC) method [21]. The detection limit of the method is 0.2 mg/l. The average standard deviation was found to be 6%. Serum blanks were not available. Each sample was analyzed twice, and the mean value was used as the result. Samples frozen for 2 months gave the same results as were obtained in fresh samples.

Results

Daily warfarin doses given and thrombotest values in relation to AG treatment are illustrated in Fig. 1. In patient no. 1 (Fig. 1a), who had been treated with AG for several weeks, warfarin resistance was observed during the first 2 weeks of treatment. A steady-state clearance was performed after daily dose of 12.5 mg for 6 days. Thereafter the amount of warfarin given was increased until acceptable thrombotest values were obtained (8%–15%), reaching between 17.5 and 20 mg per day. After AG had been stopped the increased warfarin requirement persisted for 2 weeks and then declined. From the 12th week daily doses of 3.75 and 5 mg on alternate days were

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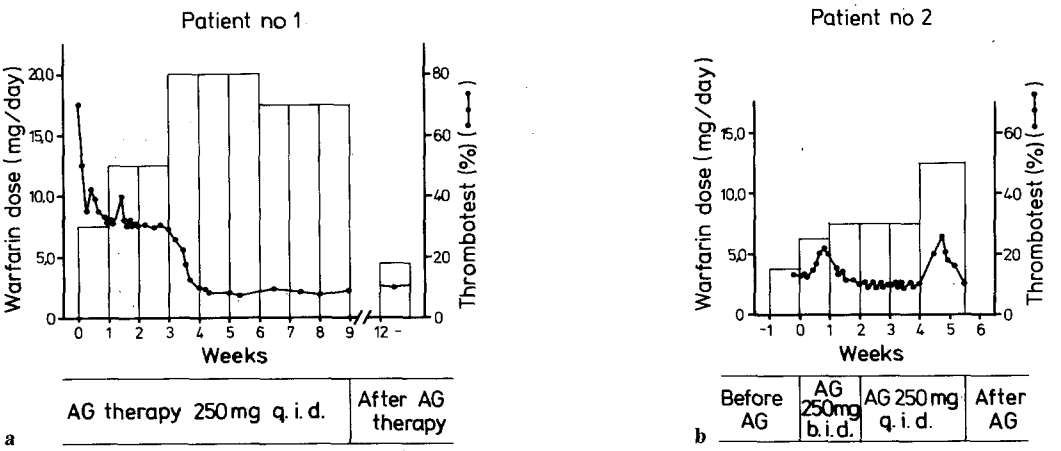

Fig. 1a and b. Mean warfarin dose (mg/day) during each week of treatment *(bars)* and thrombotest values (●–●–●) related to time (weeks) and AG therapy in patients 1 (**a**) and 2 (**b**)

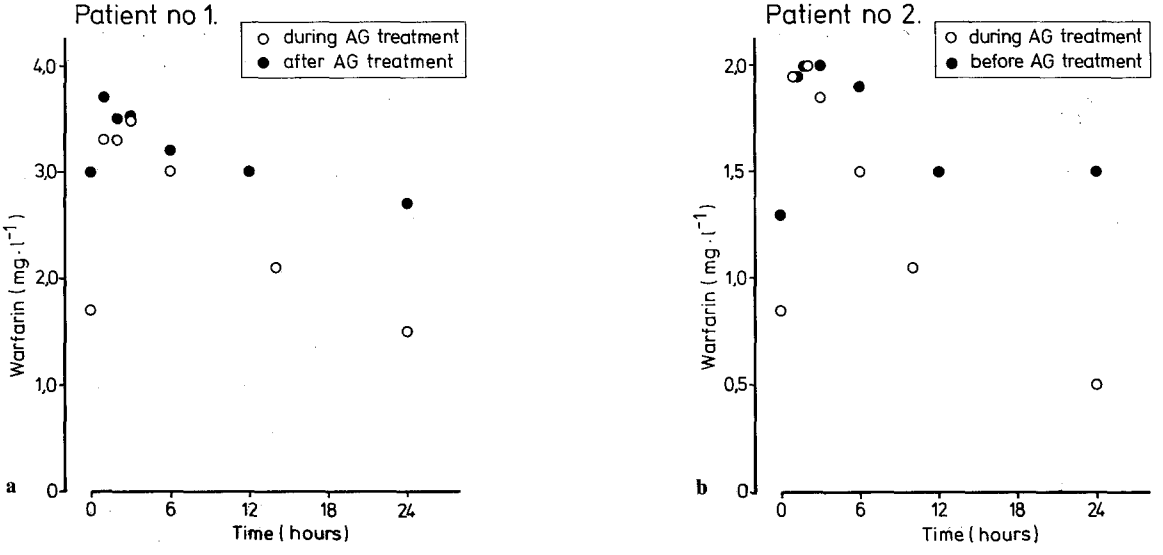

Fig. 2a and b. Serum warfarin concentrations (mg/l) as a function of time (h) after last dose of warfarin **a** in patient 1 after (●) and during (○) AG therapy, and **b** in patient 2 before (●) and during (○) AG therapy

given. A new steady-state clearance evaluation was performed on a day with a 3.75 mg dose, using the same procedure as already described.

Patient no. 2 had been treated with warfarin for 9 months when AG therapy was initiated. An increase in the dose needed to maintain acceptable thrombotest values was observed (Fig. 1b). A steady-state clearance evaluation was performed before and after 6 weeks with AG treatment. Warfarin absorption has been shown to be almost complete [4], and there is no detectable first-pass phenomenon [1]. Clearance was calculated according to the equation

$$Cl = FD/AUC_n^{n+1},$$

where AUC_n^{n+1} is area under curve in a steady-state situation calculated by the trapezoidal rule; D is dose of drug; and F is fraction of drug available (= 1). These concentration curves are shown in Fig. 2. In patient no. 1 (Fig. 2a) the dose was approximated to 4.5 mg daily when used in the calculation of clearance after AG treatment. Clearance values obtained in patient no. 1 were 0.22 l per hour (0.0037 l/kg per hour; 0,13 l/m^2 per hour) during AG treatment and 0.067 l per hour (0.0011 l/kg per hour; 0.040 l/m^2 per hour) after cessation of therapy; the corresponding values in patient no. 2 were 0.47 l per hour (0.0067 l/kg per hour; 0.26 l/m^2 per hour) during AG therapy and 0.09 l per hour (0.0013 l/kg per hour; 0.050 l/m^2 per hour before the start of AG treatment (Fig. 2b).

Discussion

The HPLC method used in this work is based upon similar methods described by others [3, 20]. The method is rapid and sensitive, and known metabolites of warfarin do not interfere with the analysis. Warfarin is very well absorbed [4], and similar kinetics have been found after administration PO and IV. It therefore seemed justified in this study to administer the drug PO only.

In our two patients, when no AG therapy was given clearance calculations yielded values in the lower part of the normal range reported [5]. Values given in the literature have usually been obtained from studies in young, healthy volun-

teers, and these values may not necessarily by applicable in our elderly patients with disseminated malignancies.

Warfarin is highly protein bound (97%–99% [2]); virtually all binding is to albumin, which is reflected in distribution volumes similar to the albumin space [13]. Albumin is considered to be a storage depot for warfarin [8], i.e., both hepatic clearance and anticoagulant effect are related to unbound fraction. Assuming a constant albumin concentration, an increase in the free fraction would usually be due to either displacement of warfarin or a decrease in its affinity to albumin. AG has been shown to bind only 20%–25% to serum protein [19]. Evidence has been provided that an increase in the free fraction of warfarin results in an increase in its hepatic clearance, maintaining the mean free drug concentration. A displacement of warfarin by AG, although of minor importance for the reasons given, should result in an unchanged or even increased warfarin effect in our patients and not the opposite, as was observed. Neither hyperbilirubinemia nor uremia, both of which are known to decrease the binding affinity of warfarin to albumin [2] was found in our patients.

A moderate decrease (from 37 to 29 g/l) in albumin concentration was observed in patient no. 2 during AG treatment. Again due to a restrictive type of hepatic clearance [22] it has been found that the mean free drug steady-state clearance remains unchanged [2]. As a decrease in albumin concentration will result in an increase in the free fraction of warfarin and thereby in an increase in elimination kinetics [23], a small contribution to the increase in clearance could be explained by the observed fall in albumin concentration.

Glutethimide, from which AG is derived, has been shown to shorten the half-life of warfarin [7] by the induction of hepatic microsomal enzymes [9]. The most plausible explanation for the drug interaction seen in our patients and suggested in the earlier reports [6, 12] is that warfarin metabolism is increased due to an AG-promoted increase in hepatic microsomal enzymes [11, 17]. AG, being a so-called type-II inhibitor [15], is both an aromatase inhibitor and a blocker of several enzymes in the steroidogenic pathway, giving marked alterations in blood levels of hormones [16]. Although probably of lesser importance, an indirect effect of AG on coagulation due to these changes in endocrine profile therefore cannot be excluded. An initial AG $t_{1/2}$ of 14.5 h in patient no. 2 during continuous warfarin treatment does not suggest any major influence of warfarin on AG elimination kinetics (unpublished observations). Furthermore, blood hormone levels did not change.

With increased use of AG for endocrine treatment of advanced breast cancer [15] the problem of AG and warfarin interaction described in this study will occur more frequently.

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