Short Communication

Agranulocytosis associated with aminoglutethimide: Pharmacological and marrow studies

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Aminoglutethimide (AG) inhibits steroid biosynthesis and the peripheral conversion of androgens to oestrogens (Santen et al., 1978; Dexter et al., 1967). Aminoglutethimide has proved to be an effective therapy in advanced breast cancer with response rates of 37.5-50% (Wells et al., 1978; Harris et al., 1983) and duration of response similar to adrenalectomy. However, blood dyscrasias have been reported in ~1% of patients. We have seen two patients who developed severe agranulocytosis while taking aminoglutethimide and we describe possible mechanisms and predisposing factors.

A 62-year old woman presented with local recurrence of breast cancer and bone pain 2 years after primary treatment. She started treatment with aminoglutethimide 250 mg three times a day and hydrocortisone 20 mg twice a day and 10 days afterwards she developed a skin rash. The rash faded after 5 days. A full blood count on the 28th day after starting showed agranulocytosis and no granulocytes were visible on a peripheral blood film. She developed a sore mouth and mouth ulcers which improved after 2 weeks. She continued aminoglutethimide and hydrocortisone and 3 weeks after the episode of agranulocytosis her peripheral blood film was normal. Marrow aspirated at the same time showed normal haemopoiesis and marrow infiltration with malignant cells. An abnormal alkaline phosphatase and γGT became transiently worse during the episode of agranulocytosis.

She continued on aminoglutethimide and hydrocortisone and had a complete regression of skin nodules and sclerosis of her lytic bone secondaries. Her remission lasted for 18 months.

A 50-year old woman was treated by radical mastectomy and adjuvant radiotherapy to the right chest wall and right supraclavicular fossa. She was started on adjuvant endocrine therapy with aminoglutethimide 250 mg three times a day and hydrocortisone 20 mg twice a day. Seven weeks later she had a fever, sore throat, felt generally unwell and had mild nausea. She was treated with cephalixin by her general practitioner with no improvement. A week later she had a low white cell count, total 0.8×10⁹ l⁻¹; 34% granulocytes. She was seen in clinic after a further week and aminoglutethimide was stopped. The white cell count had started to improve while on aminoglutethimide (total count, 1.1×10⁹ l⁻¹; 40% granulocytes). Marrow aspirate showed a hypocellular marrow with normal erythroid cells and normal megakaryocytes. There were some large early granulocytic cells present. Repeat marrow aspiration 3 weeks after recovery showed a cellular marrow with normal development of all cell lines.

Marrow was assayed for granulocyte/macrophage precursors (CFUc) in a semi solid colony assay (Barrett et al., 1976). Normal marrow and marrow from patient 2 was preincubated with plasma from patient 2 taken before starting aminoglutethimide, during and after the episode of agranulocytosis. The effects of a final concentration of 10% and 50% patient’s plasma were studied on normal marrow and 50% patient’s plasma on autologous marrow. The preincubation was for 1.5 h at 37°C and cells were washed and then plated. Colonies and clusters were read after 10 days incubation. All assays were performed in triplicate.

Colony formation in marrow aspirated from patient 2 after recovery from agranulocytosis was very poor. Plasma containing aminoglutethimide suppressed colony formation further (Table I). There was a suppressive effect also on normal marrow, with 50% patient’s plasma, while on aminoglutethimide.

Plasma levels were measured by reverse phase high pressure liquid chromatography after dichloromethane extraction, using 2 internal standards.

The levels for patient 1 were 0.4 µg ml⁻¹ aminoglutethimide and 4.2 µg ml⁻¹ N acetyl aminoglutethimide and for patient 2, 3.2 µg ml⁻¹

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aminogluthethimide and 4.0 μg ml⁻¹ N acetyl aminogluthethimide. These concentrations are in the range found in 49 other patients taking aminogluthethimide (aminogluthethimide mean 4.8 ± 5.1 s.d., range 0.4–24.4 μg ml⁻¹; N acetyl aminogluthethimide mean 1.9 ± 1.3 s.d., range 0.3–5.4 μg ml⁻¹). The ratio of N acetyl aminogluthethimide to aminogluthethimide was higher in patient 2 than in any other patient (10.5) (patient 1, 1.25; other patients mean 0.83 ± 1.59 s.d., range 0.5–8.77).

Oestrone, oestradiol, testosterone and dehydroepiandrosterone sulphate (DHAS) were measured by radioimmunoassay using reagents in the WHO matched reagents scheme. The methods and assays have been described in detail (Harris et al., 1982; Harris et al., 1983).

Table I - Effects of patient plasma on normal and patient’s own marrow

|                  | Normal bone marrow | Patient bone marrow |
|------------------|--------------------|---------------------|
|                  | Colonies | Total groups | Colonies | Total groups |
| Normal plasma    |          |             |          |             |
| 0%               | 13 ± 2   | 44 ± 6      | 0        | 2.6 ± 0.6   |
| 10%              | 12 ± 2   | 51 ± 7      | 0        | 2.6 ± 0.6   |
| 50%              | 18 ± 2   | 56 ± 2      | 0        | 2.6 ± 0.6   |
| Pretreatment plasma |        |             |          |             |
| 10%              | 10 ± 0   | 45 ± 6      | 2.6 ± 0.6 | 25 ± 5      |
| 50%              | 17.7 ± 6 | 50 ± 11     | 2.6 ± 0.6 | 25 ± 5      |
| Plasma during treatment |        |             |          |             |
| 10%              | 13.5 ± 5 | 39 ± 2      | 0        | 13 ± 6      |
| 50%              | 13 ± 5   | 38 ± 2      | 0        | 13 ± 6      |
| Convalescent plasma |        |             |          |             |
| 10%              | 14 ± 3   | 45.5 ± 8    | 0.6 ± 0.6 | 20 ± 10     |
| 50%              | 17.3 ± 3 | 69 ± 9      | 0.6 ± 0.6 | 20 ± 10     |

Bone marrow cells were incubated for 1½ hours with patient’s plasma at a final concentration of 10% or 50% before being plated on agar feeder layers. Colony growth was counted on day 10.

In other cases with quinine, amiodaquine and phenytoin, there was an increased sensitivity of the marrow to normal therapeutic plasma levels (Young & Vincent, 1980; Lind et al., 1973; Sutherland et al., 1977; Smith et al., 1977).

One detailed case of pancytopenia due to aminogluthethimide has been reported (Lawrence et al., 1978), 4 cases of agranulocytosis (Austerlitz, 1982; Kampel & Kurman, 1984; Young et al., 1984; Gez & Sulkes, 1984) and 2 of thrombocytopenia (Ragaz et al., 1984; Ardman & Rudders, 1982). In the majority of cases, there have been predisposing factors present likely to compromise marrow reserve. These include recent prior extensive radiotherapy (Austerlitz, 1982; Young et al., 1984; Ragaz et al., 1984; Ardman & Rudders, 1982), combination chemotherapy (Young et al., 1984; Gez & Sulkes, 1984; Ragaz et al., 1984; Ardman & Rudders, 1982), marrow infiltration with carcinoma (Austerlitz, 1982; Ragaz et al., 1984; Ardman & Rudders, 1982) or recent adjuvant chemotherapy (Lawrence et al., 1978). In two cases of thrombocytopenia, rechallenge with aminogluthethimide produced thrombocytopenia again (Ragaz et al., 1984; Ardman & Rudders, 1982). Our 2 cases also had predisposing factors likely to deplete bone marrow stem cell reserve, or had intrinsically poor CFUc forming capacity (case 2). Some patients who have recovered from drug induced agranulocytosis have poor CFUc growth, and it is suggested that this predisposed them to drug induced agranulocytosis (Parmentier et al., 1978).

The most likely reason for the agranulocytosis from aminogluthethimide is a direct toxic effect on
marrow with poor stem cell reserve. In a normal marrow, the effect could easily be compensated (Table I).

Pharmacokinetic differences were not evident in our patients, since plasma levels of aminoglutethimide and its acetylated metabolite were similar to levels in other patients, although the ratio of acetylated to parent compound was high in patient 2.

An unusual feature of both patients is that the granulocyte count had started to rise again while on the drug. This again suggests a direct effect that could be compensated by an increase in stem cell numbers. Gez and Sulkes (1984) re instituted aminoglutethimide after agranulocytosis recovered and there was no repeated suppression of granulocyte count.

Another possible site of the adverse effect of aminoglutethimide might be the marrow fat cell. The growth of mammalian marrow in long-term continuous culture requires the presence of fat cells (Dexter et al., 1977). One of the effects of aminoglutethimide is to inhibit the aromatase enzymes that convert androgens to oestrogens in peripheral fat (Santen et al., 1978). Aromatisation activity is present in normal human marrow fat cells and is inhibited by aminoglutethimide in vitro (Frisch et al., 1980).

The incidence of blood dyscrasias due to aminoglutethimide is ~1%, since we have treated 228 patients with aminoglutethimide and only observed agranulocytosis in 2 patients. Lawrence et al. (1978) described one case of pancytopenia and they have treated 153 patients. Ragaz et al. (1984) found one severe case of thrombocytopenia and 2 mild cases (platelets $> 60 \times 10^9$ $^{-1}$ ) in 141 patients (2%). However, compared to chemotherapy this risk is small and recovery is very rapid. The onset of agranulocytosis has been within 10 weeks of starting therapy, and it seems unlikely that routine blood counts would detect a trend in falling white count. Patients should be advised to report to their doctors if they develop sore throats, mouth ulcers or influenza-like symptoms.

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