Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism

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Summary: We report a case of idiopathic hypoparathyroidism, maintained on alphacalcidol who developed hypercalcaemia during treatment with danazol for endometriosis.

Introduction

Alphacalcidol and danazol are established treatments for idiopathic hypoparathyroidism and endometriosis respectively. We report a case of idiopathic hypoparathyroidism maintained on alphacalcidol who developed hypercalcaemia following the introduction of danazol. She was subsequently stabilized on a smaller dose of alphacalcidol while danazol treatment continued but required an increase back to the original level when danazol was withdrawn. This drug interaction is previously unreported.

Case report

This 30 year old premenopausal Caucasian first presented in 1967 with epilepsy, bilateral ptosis, a right convergent squint, dry skin and bilateral cataracts. Investigation revealed a low uncorrected serum calcium (1.15 mmol/l), a high inorganic phosphate (4.04 mmol/l), a high alkaline phosphatase (430 IU/l) associated with a very low urinary calcium excretion. The urinary cyclic adenosine monophosphate response to injected parathyroid extract was normal. A diagnosis of idiopathic hypoparathyroidism was made and treatment commenced with calciferol (60,000–90,000 U/day) plus calcium lactate (6 g/day). In 1982 her treatment was changed to alphacalcidol ('one Alpha', Leo Laboratories, Aylesbury) 4 µg/day, which produced satisfactory control.

She was then lost to follow-up but presented again in June 1987 for investigation of infertility during which a laparoscopy revealed endometriosis. Her uncorrected serum calcium was low at 1.6 mmol/l despite alphacalcidol 4 µg/day. Danazol ('Danol', Winthrop, Guildford) 200 mg twice daily and calcium

lactate gluconate ('Sandocal', Sandoz, Basel) were added to her treatment with alphacalcidol.

Her serum calcium gradually increased reaching 4.6 mmol/l after 9 weeks which necessitated inpatient rehydration. All medication was withdrawn for one week. She was then discharged on the same doses of alphacalcidol and danazol but calcium lactate gluconate was omitted. A resurgence of her serum calcium was noted and a second admission for inpatient rehydration occurred following which reduction in her maintenance dose of alphacalcidol was made. A daily dose of 0.75 µg alphacalcidol was found ideal (Figure 1).

After completion of the 6 month course of danazol an increase in the maintenance requirement of alphacalcidol back to 4 µg/day was documented. She remained normocalcaemic on this dose during the following 6 months.

Discussion

Alphacalcidol is an established treatment for idiopathic hypoparathyroidism. In this patient a dose of 4 µg/day maintained her serum calcium within the normal range. The introduction of danazol appeared to reduce the maintenance requirement for alphacalcidol; its introduction was followed by a rise in serum calcium until the maintenance dose was reduced. This suspicion was confirmed by a fall in serum calcium when danazol was withdrawn and a return to normal when alphacalcidol was increased to its original level.

It is likely that the low serum calcium recorded when she presented in 1987 was due to erratic compliance; however, the increase in her serum calcium following administration of danazol cannot be dismissed on this basis as she remained stable on 4 µg/day alphacalcidol following the withdrawal of danazol.

Martino¹ reported a 75 year old woman with metastatic carcinoma of the breast who developed hypercalcaemia when danazol 200 mg twice daily was

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Figure 1 The effect of danazol on the serum uncorrected calcium in a patient with idiopathic hypoparathyroidism maintained on alphacalcidol; ① and ② represent hospital admissions for rehydration to lower the serum calcium.

administered but reverted to normal each time the danazol was stopped.

In contrast, Purdie *et al.*² reported that danazol 800 mg/day given to 14 healthy post-menopausal women produced a significant fall in plasma ionized calcium (but not total calcium). This finding was associated with a reduction in both the fasting urinary calcium/creatinine ratio (indicating a decrease in calcium excretion) and alkaline phosphatase (indicating a reduction in the rate of bone formation and possibly also of bone resorption with which it is usually closely coupled). A role for danazol in the prevention of

post-menopausal osteoporosis has been postulated by these workers.

A mechanism for the action of danazol on calcium homeostasis remains unclear and merits further study to determine whether it acts primarily on the skeletal or the renal handling of calcium.

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References

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