

LETTERS TO THE EDITOR

Antenatal administration of aminopropylidene diphosphonate

Sir: Diphosphonates are now commonly prescribed drugs in the treatment of a variety of conditions, including the management of hypercalcaemia of malignancy.^{1,2} Aminopropylidene diphosphonate has been shown to be one of the most effective of this group of drugs for this condition.³

We would like to report a case in which aminopropylidene diphosphonate was given to a woman for malignant hypercalcaemia two weeks before she gave birth. We, and the manufacturers of this product, believe this to be the first report of such treatment. More importantly, the drug was given safely and without any major adverse effect to mother or child. A 24 year old woman underwent lumpectomy and received local radiotherapy in 1984 for a scirrhous carcinoma of the breast. In August 1988 she attended an antenatal clinic, eight weeks' pregnant with her second child. At that time, she seemed perfectly well and the fetal ultrasound was normal. At 27 weeks' gestation she was admitted as an emergency to the obstetric unit with acute breathlessness and pleuritic chest pain. Clinical and radiological examination showed bilateral pleural effusions, which were tapped and found to contain malignant cells consistent with spread from her original primary malignancy. She was also diagnosed as having lytic bony metastases. At that time her corrected serum calcium was normal, but her alkaline phosphatase was raised at 495 U/l (reference range at our laboratory 8-280 U/l). Treatment was started with epirubicin 90 mg/m² and prednisolone 40 mg for five days, every three weeks. Careful monitoring of the fetus showed normal development. After three courses her effusions had not reaccumulated and her symptoms improved. A biochemical screen done one week later showed a serum calcium concentration of 3.75 mmol/l, corrected for a serum albumin of 31 g/l, serum phosphate 0.78 mmol/l, and alkaline phosphatase 506 U/l. Her parathormone level was <0.8 pmol/l (reference at our laboratory 1-5 pmol/l). At 34 weeks' gestation she was treated initially with frusemide and with saline intravenously. After much deliberation and discussion with the medical advisers of the manufacturing company we gave 30 mg of aminopropylidene diphosphonate as a four hour infusion. Her serum calcium concentration fell gradually over the next two weeks. At 36 weeks, with a corrected serum calcium of 3.15 mmol/l, she gave birth to a healthy male child weighing 3.06 kg by spontaneous vertex delivery. The child's total plasma calcium was 2.05 mmol/l (reference range 2.2-2.4 mmol/l) at birth but gradually, over the next five days, fell to 1.65 mmol/l, despite calcium supplementation of the child's feeds and intravenous calcium gluconate. Serum albumin at that time was 33 g/l. Four days after birth, the infant's parathormone level was 2.01 pmol/l (reference range for neonates 1-7 pmol/l). The child's total plasma calcium was normal five days after birth. One week after delivery the mother's serum calcium was 2.50 mmol/l.

Subsequently, the child has had normal

growth and development and, with further chemotherapy, the mother is alive with stable disease 10 months after the delivery of her child. It is difficult for us to assess whether the transient hypocalcaemia noted in the infant was due to fetal parathyroid suppression by maternal hypercalcaemia or whether it was an effect of aminopropylidene diphosphonate crossing the placental barrier and exerting a direct effect on the fetus.

Ciba-Geigy have informed us that no teratogenic effects were observed in the fetuses of pregnant rats given aminopropylidene diphosphonate. Animal reproductive studies were only performed with the oral preparation, however. They have no data as yet for the long term effects on the progeny of the animals tested (P Graepel, R Zeil, personal communication). We suggest that the parathormone level measured in the child four days after birth, in the face of significantly low total plasma calcium, is inappropriately low. Thus it seems more likely that the maternal hypercalcaemia caused parathyroid suppression in the neonate. Aminopropylidene diphosphonate has very few side effects. In the extremely rare situation in which one might envisage giving this agent to a pregnant mother we suggest careful monitoring of serum calcium for at least a week after delivery. In conclusion, aminopropylidene diphosphonate was given to a mother in the third trimester with no adverse effects on the delivery of the fetus or on the fetus itself.

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- 2 Ralston S H, Dryburgh F J, Cowan R A, Gardner M D, Jenkins A S, Boyle I T. Comparison of APD, Mithramycin and corticosteroids/calcitonin in the treatment of cancer-associated hypercalcaemia. *Lancet* 1985; ii: 907-10.
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Fatal acute pyelonephritis following pulsed methylprednisolone for rheumatoid arthritis

Sir: We read with interest your two recent articles on pulse methylprednisolone therapy in rheumatoid arthritis.^{1,2} Although the evidence is strong that such treatment can induce rapid relief of inflammatory joint symptoms, we fear that the risk:benefit ratio may not be as favourable as suggested. We report here a fatal case of acute pyelonephritis following pulse methylprednisolone therapy for rheumatoid arthritis.

A 71 year old woman with a six year history of seronegative rheumatoid arthritis (American Rheumatism Association criteria, 1987) was admitted with a recent deterioration of her arthritis. She denied recent urinary symptoms and denied any recent infection. She had had a total hysterectomy with bilateral oophorectomy at the age of 47. There was no history of hypertension or diabetes mellitus. Examination

confirmed an active, symmetrical polyarticular inflammatory joint disease, but was otherwise unremarkable. Investigations on admission showed an erythrocyte sedimentation rate of 96 mm/h, white cell count $7.4 \times 10^9/l$, 80% granulocytes, urine analysis negative for protein, blood, and glucose, and mid-stream urine negative for white cells and organisms on microscopy and culture.

On the day of her admission she was given the first of three alternate day doses of 1 g methylprednisolone succinate in 100 ml normal saline intravenously over 30 minutes. On day 2 treatment was started with azathioprine 50 mg/day. During the following week her joint symptoms improved and on day 8 the azathioprine was increased to 50 mg twice daily.

On day 10 she developed a fever of 39.3°C and urinary incontinence. Blood and mid-stream urine were collected and treatment with oral amoxicillin 500 mg eight hourly started immediately. Microscopy and cultures were subsequently found to be negative. Her blood count at that stage included a total white cell count of $16.3 \times 10^9/l$, 89% neutrophils, haemoglobin 101 g/l, platelets $266 \times 10^9/l$. The following day she remained feverish, developed left iliac fossa pain, and became confused. The azathioprine was discontinued after a cumulative dose of 600 mg and the amoxicillin replaced by intravenous cefuroxime 750 mg eight hourly and rectal metronidazole 1 g eight hourly. Fluids were given intravenously.

Subsequent deterioration was rapid and she died on the 12th day of her admission. Necropsy showed macroscopic appearances of bilateral acute pyelonephritis, confirmed on histological examination, with microabscess formation.

Uncontrollable infection in this patient might have been in part due to pulse methylprednisolone therapy, azathioprine, the underlying rheumatoid disease, or a combination of all three. There was, however, no evidence of marrow suppression attributable to azathioprine. Fatal infections following pulse methylprednisolone therapy have been reported in renal transplant recipients.³ Other fatalities have been attributed to this form of treatment, including sudden death.⁴⁻⁶ It is difficult to assess the risk of serious adverse reactions from published data as most studies were not designed specifically to consider this question. One reason for the relatively high incidence of adverse reactions noted by Garrett and Paulus (nine of 21 rheumatoid patients) may be that it was the purpose of their investigation to highlight such events.⁷

The benefits of pulse methylprednisolone therapy should also not be overstated. Most studies indicate a return to baseline of indices of response within eight weeks of methylprednisolone alone.¹ Erosions have been shown to progress despite methylprednisolone treatment.⁸ Controlled studies of combination treatment have failed to show any improvement in response rates or risks of adverse reactions to slow acting antirheumatic agents when combined with pulse methylprednisolone therapy.^{2,9}

The benefits, then, of a short term anti-inflammatory effect of pulse methylprednisolone therapy should be weighed carefully against the risks of adverse reactions, sometimes fatal. We agree with Smith *et al* that pulse methylprednisolone may be useful in selected patients, particularly 'between initiation and response' with slow acting agents, but would be extremely wary of 'allowing pulse therapy to become an outpatient procedure'.¹ Used cautiously and in the lowest effective