Acenatal administration of aminopropylene diphosphate

Sir: Diphosphonates are now commonly prescribed drugs in the treatment of a variety of conditions, including the hypercalcaemia of malignancy. 1,2 Aminopropylene diphosphate 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 aminopropylene diphosphate 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 adverse effect to either 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 abdominal pain and right upper chest pain. Clinical and radiological examination showed bilateral pleural effusions, which were tapped and found to contain malignant cells consistent with breast from her original primary malignancy. She was also diagnosed as having lytic bone metastases. At that time her corrected serum calcium was normal, but her alkaline phosphatase was raised at 495 U/l (range reference at our laboratory 8-230 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 of chemotherapy, she was advised not to continue 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 phosphorus 0.8 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 aminopropylene diphosphate 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 supplementations and the mother'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 1-2.1 pmol/l). The child's total plasma calcium was normal 10 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 aminopropylene diphosphate 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 animals exposed to aminopropylene diphosphate. 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. Zell, 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. Aminopropylene diphosphate has very few side effects. In the extremely rare situation in which one might envisage giving this drug to a pregnant mother we suggest careful monitoring of serum calcium for at least a week after delivery. In conclusion, aminopropylene diphosphate 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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Fetal 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 showed an erythrocyte sedimentation rate of 96 mm/h, white cell count 7×10⁹/l, 80% granulocytes, urine analysis negative for protein, blood, and glucose, and mid-stream urine culture negative with all cultures on microscopy and culture.

On the day of her admission she was given the first of three alternate daily doses of 1 g methylprednisolone succinate (250 mg intramuscularly every 8 h). 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 16·3×10⁹/l, 89% neutrophils, 5·1×10⁹/l lymphocytes, and 1·1×10⁹/l monocytes. On the following day she remained febrile, developed left iliac fossa pain, and became confused. The azathioprine was discontinued after a cumulative dose of 600 mg and the amoxicillin was withdrawn in view of the development of 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. The pregnant rats given methylprednisolone showed no signs of acute 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 arthritis, 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 steroid treatment, including the very rapid development of infections. 4 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 Grant and Paulus (nine of 21 rheumatoid patients) may be that it was the purpose of their investigation to highlight such events. 5,6 The benefit 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. 7 Erosions have been shown to progress despite methylprednisolone treatment. 8 Controlled studies of such treatment have failed to show any improvement in response rates or risks of adverse reactions to slow acting antirheumatic agents compared with pulse methylprednisolone therapy. 9

The benefit, then, of a short term anti-inflammatory effect of pulse methylprednisolone therapy should be weighed carefully against the risks of adverse reactions, some of which may be extremely serious. We agree with Smith et al that pulse methylprednisolone may be useful in selected patients, particularly "between initiation and titration of treatment with disease modifying agents, but would be extremely wary of 'allowing pulse therapy to become an outpatient procedure'. 10 Used cautiously and in the lowest effective
Response criteria for slow acting antirheumatic drugs

Sir: With great interest we read the recent article by Scott et al on response criteria for slow acting antirheumatic drugs. The authors emphasise the development of a simple index and its relation to clinical practice. The basis for this index was a consensus meeting of 16 rheumatologists. Later the response index was used in the evaluation of penicillamine and sulphasalazine. As the authors explained, however, the index has not been validated.

We have attempted to determine which variables are most useful for measuring disease activity. We evaluated, therefore, the judgment of doctors in clinical practice for high and low disease activity. The study group comprised 113 patients with recently diagnosed rheumatoid arthritis who were studied prospectively. The follow up ranged from two to 39 months (1816 check ups). We thus obtained a disease activity score (DAS) composed of the Ritchie articular index, the number of swollen joints, erythrocyte sedimentation rate, and general health on a 100 mm scale. Subsequently, the DAS was validated by comparison with various single and composite indices used to measure disease activity, with attention to their correlation with radiographic damage and functional incapacity (in preparation). This validation was made with an extended group of patients from the same prospective study (follow up range eight to 58 months, 6011 check ups). The DAS and the Mallya index were found to be the most valid variables for measuring disease activity.

In comparison with the response index proposed by Scott et al, the DAS has several advantages and one disadvantage. The disadvantage is that the DAS is not as simple to compute as the response index; a calculator is needed. To overcome this problem we have constructed a nomogram, making it easy to determine the DAS in little time without a calculator. The advantages are threefold: first of all the DAS is a reflection of the decision making of doctors in clinical practice. What happens in practice has been expressed in facts and numbers. Hence there is little distance between clinical practice and the outcome variable in evaluation of clinical trials with slow acting antirheumatic drugs. Secondly, the DAS has been shown to be a valid measurement. Last but not least, the DAS is a variable with a continuous scale. Therefore no arbitrary division of the grades of response has been made. The mean DAS in our large database was 3.25 (range 0-30-8). The 'sensitivity to change' was 1.0-89 - that is, the difference which can be considered to reflect the minimum of measurement error and biological variation.

In conclusion, the DAS is a valid measurement for evaluation of clinical trials. Its advantage over Dr Scott's proposed response index and other existing indices is that it needs no further validation and is ready to use.

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Correlation of iron exchange between the oral iron chelator 1,2-dimethyl-3-hydroxypropyrid-4-one (L1) and transferrin and possible antiaemic effects of L1 in rheumatoid arthritis

Sir: Iron and ferritin are probably able to stimulate local free radical damage in joints of patients with rheumatoid arthritis (RA) by forming hydroxyl radicals and in this way contribute to the persistence of synovitis. In the anaemia of chronic disease in RA iron stores are increased, but they are probably less available for erythropoiesis. Owing to the possible deleterious effects of iron stores on RA activity the treatment of RA with desferrioxamine has been studied. 7 The results were controversial. In addition to the possible beneficial effects of iron chelators on RA activity, it is claimed that iron chelation might improve bone marrow iron availability and hence erythropoiesis. Giordano et al found a haemoglobin increase after treatment with desferrioxamine. 8 We confirmed their findings using a new oral iron chelator, 1,2-dimethyl-3-hydroxypropyrid-4-one (L1). 9 L1 has been shown to be an effective iron chelator 10 with promising potential in the treatment of haemosiderosis and, possibly, RA. If increased bone marrow iron availability is the mechanism through which a haemoglobin increase occurs after iron chelation it can be assumed that this takes place through a higher iron saturation of transferrin, which indeed was the case in our study. 6

Hewitt et al found that L1 released 90% of iron-59 (59Fe) bound to transferrin. 11 This implies that after L1 iron chelation a high proportion of iron may be bound to L1, instead of transferrin, suggesting a decrease rather than an increased amount of iron bound to transferrin available for bone marrow. We therefore examined both the ability of L1 to chelate iron from human transferrin and of human transferrin to remove iron from L1.

The following method was used: 388 µl of L1 (0-1 mg/ml) was added to 100 µl of 59Fe-transferrin (97 mg/ml). After incubation the iron chelator was carried out by red blood cell 3-5-permeation chromatography (Sephadex G 50; pH 7-4 with an elution velocity of 32 ml/h, recovery 76-6%). In the second experiment 20 µl (272 µg) of 59FeCl4 and 148 µl (2 mg/ml) of FeCl3 were added to 300 µl of L1. Human apotransferrin (3 mg) was added to 1 ml of the Fe-L1 solution, after which fractionation was performed similarly (Sephadex G 50; pH 7-4; velocity of 32 ml/h; recovery 75-8%). The table shows the results obtained. Activity was measured with a Packard-autogamma 500 C.

The results obtained indicate that L1 is able to remove a substantial amount of iron from transferrin, confirming findings of Hewitt et al, 11 depending on the time of incubation and the amounts of L1 and transferrin added. It was also found, however, that apotransferrin can release iron from L1, depending on the same factors. Thus, possibly, in a patient treated with L1, the iron saturation of transferrin and L1, determines the direction of iron exchange between them. In the anaemia of chronic disease in RA iron saturation of transferrin generally is low 12 so it is possible that iron exchange between ferritin and transferrin mediated by L1 takes place, explaining the haemoglobin increase after iron chelation in these patients. 8 13 It has also been found that L1 diffuses easily through the erythroblast membrane and thus it may incorporate iron into erythroblasts and hence...