

THE MANAGEMENT OF PAGET'S DISEASE OF BONE

Background

Paget's disease of bone comprises a marked increase in bone turnover at one or more sites. The disease activity is monitored by measurement of alkaline phosphatase.

The disease may be present in up to 10% of elderly patients in Europe although a much smaller number (perhaps <1%) would have symptomatic disease.

The conventional criteria for treatment of Paget's disease include bone pain and/or deformity, entrapment neuropathy/deafness and the risk of heart failure when the disease is extensive.

Bisphosphonates have been the mainstay of treatment of Paget's disease for many years, initially this was with disodium etidronate, a drug that was associated with the development of osteomalacia if the dose was increased. Subsequent to this the most commonly used bisphosphonate has been Pamidronate which has been given by intravenous infusion, usually as 6 separate infusions of 30mg, either once a week for 6 weeks or for 6 consecutive days. The conventional total dose, therefore, being 180mg. The BNF cost of a 10ml vial of Pamidronate (3mg per ml) is £55 and therefore the cost of the drug for this course of treatment amounts to **£330**.

The duration of treatment effect is variable but anecdotally seems to last in many patients for up to a year. If treatment effect is monitored by the measurement of alkaline phosphatase then it is relatively easy to demonstrate when efficacy is waning.

More recently oral bisphosphonates (Alendronate and Risedronate) have been used in the treatment of Paget's disease with dosages which are significantly larger than those used for osteoporosis (Alendronate 40mg od for 6 months; Risedronate 30mg od for 2 months, repeated for a further 2 months after a rest period of 2 months).

It is not clear what is the most appropriate treatment of this condition and recent policy in the Metabolic Unit at the Western General Hospital has been to continue with pamidronate as outlined above. More recently newer and longer acting bisphosphonates have come on to the market and there is now evidence that Zoledronic acid, given as a single infusion, is at least as efficacious as treatment with 2 months of Risedronate (30mg od). In this study (Reid et al. 2005) the markers of outcome were normalisation of alkaline phosphatase levels or a reduction of at least 75% of the excess level at 6 months.

Zoledronic acid comes in a 5mg vial, which costs **£283.74** (BNF).

A direct cost equivalence, therefore, comparing Zoledronic acid with Pamidronate would indicate that the former is cheaper.

Given that there are no hard end point outcome data for these drugs (and this includes Pamidronate and the oral bisphosphonates) it seems reasonable to use a single intravenous dose of Zoledronic acid 5mg and monitor the response of the alkaline phosphatase at 3 - 6 months. This strategy would become more expensive (cost of drugs) if Zoledronic acid was given at 6 month intervals but if at annual intervals (the most likely outcome) would remain cheaper than Pamidronate.

The difference for the patient would be considerable in that Zoledronic acid would be delivered only once as opposed to 6 separate visits with a larger volume of infusate with Pamidronate. Many of our patients are relatively frail and some require ambulance transport.

The side effect profile is likely to be the same as the flu like symptoms and sometimes bone pain that are often experienced after Pamidronate. The symptoms tend to occur mostly if not exclusively after the first dose and occur with similar frequency with Zoledronic acid.

It is likely that the duration of effect of Zoledronic would exceed one year at a single dose.

The cost in nursing time may be difficult to quantify in financial terms as the nurses would tend to do other things if not infusing Pamidronate but in terms of time this is considerable comparing a 15 minute infusion with 6 separate 2 hour infusions for Pamidronate.

The protocol outlined below, therefore, is extremely simple and as far as one can tell from the literature the **only suggested contraindication to this treatment would be the presence of renal failure.** It is suggested that patients be assessed for evidence of vitamin D deficiency, which should be corrected before treatment as hypocalcaemia is a common sequelae of intravenous bisphosphonates, only tending to be symptomatic in those who are vitamin D deficient.

Protocol for the use of Zoledronic Acid in the Treatment of Paget's Disease

1. Decision to treat Paget's disease is made dependent upon symptomatology and elevation of alkaline phosphatase.
2. Blood is taken to measure 25-hydroxy-vitamin D and plasma calcium.
3. Arrangements are made for patients to attend the metabolic unit (timing unimportant).
4. 5mg of Zoledronic acid is infused over 30 minutes (comes ready to infuse in 100 ml vial).
5. Patients should be advised of the possibility of flu like symptoms and pain in affected bone and take their usual pain relief as required. Symptoms are unlikely to last >24 hours.
6. If there is obvious dental disease discuss patient with consultant. Likely incidence of osteonecrosis of the jaw is extremely low in patients receiving IV bisphosphonate for Paget's disease (see ref below)
7. Patients should return to outpatients at 3 months to identify a biochemical response and again at 6 or 12 months according to clinical need.
8. Further doses are administered, possibly annually, dependent upon symptoms and/or biochemistry.

References

- IR Reid et al. Comparison of a single infusion of zoledronic acid with Risedronate for Paget's disease. N Engl J Med 2005;353:898-908
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