sorption and turnover, such as Paget's disease of bone and osteoporosis, as well as in the management of bone metastases. Etidronate has been used in the prevention and treatment of ectopic ossification.

The affinity of bisphosphonates for bone allows complexes labelled with radioactive technetium-99m (see p.2055) to be used diagnostically as bone scanning agents.

Bisphosphonates have been given by intravenous infusion or orally. In the latter case food should be avoided for a suitable period before and after a dose, especially foods with a high calcium content such as milk.

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Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients.

Ectopic ossification. Bisphosphonates that are potent inhibitors of mineralisation such as etidronate have been advocated for prevention of ectopic ossification (p.100), but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.

Hypercalcaemia. In patients with severe symptomatic hypercalcaemia restoration and maintenance of adequate hydration and urine flow is essential, and helps to reduce plasma-calcium concentrations by promoting calcium diuresis. In hypercalcaemia of malignancy (p.1083) therapy with inhibitors of bone resorption such as the bisphosphonates is used. Although sustained, the action of bisphosphonates is not particularly rapid; they may be used with a calcitonin where both rapid and prolonged diminution of plasma-calcium concentration is desired.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p.1087), but seem to be of little benefit for long-term treatment.

Juvenile idiopathic arthritis. Bisphosphonates may have a role[1] in preventing low bone mineral density and fragility fractures in children with juvenile idiopathic arthritis (p.10).

1. Thornton J, *et al.* Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; **91:** 753–61.

Malignant neoplasms of the bone. There is good evidence that some bisphosphonates are of benefit in **treatment** of patients with metastatic bone disease (p.660) not only to control bone pain[1,2] and to manage the attendant hypercalcaemia, but also to reduce skeletal complications such as fractures.[2-8] Maximum benefit in terms of skeletal events occurs only after 6 months of treatment.[9] It has been suggested that given the strength of the evidence, treatment with bisphosphonates should be begun at first diagnosis of bone metastases, and continued until no longer clinically relevant.[2,10] While some continue treatment despite disease progression, others advocate changing to a more potent bisphosphonate, or stopping treatment altogether.[9] Starting bisphosphonates in women with breast cancer without evidence of bone metastases is not recommended.[11]

There are concerns over the development of osteonecrosis of the jaw with bisphosphonate treatment (see Effects on the Musculoskeletal System, under Adverse Effects, above), and a possibly increased incidence in patients with multiple myeloma. Some have recommended[12,13] that monthly intravenous bisphosphonate therapy continue for 2 years in myeloma patients. After 2 years, therapy can be stopped in those who have achieved a complete response or who are in a stable plateau phase. If disease is still active, frequency of infusion can be decreased to once every 3 months. However, others recommend stopping therapy after 1 year in those with a complete response or very good partial response. For those with a poorer response and ongoing active bone disease, bisphosphonates may be continued for up to 2 years.[14] In newly diagnosed patients, pamidronate is favoured over zoledronate as data suggest the risk of osteonecrosis may be higher with the latter.[12-14] However, routinely switching patients from zoledronate to pamidronate is not recommended, as no data suggest that this will prevent osteonecrosis. Multiple myeloma patients without evidence of skeletal involvement should not routinely be given bisphosphonates.[12]

There is also much interest in the use of bisphosphonates to **prevent** the development of bone metastases;[2,4,5,8] however, preliminary evidence of their efficacy is conflicting. Specific references may be found under the individual drugs.

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Osteogenesis imperfecta. Bisphosphonates have been tried in osteogenesis imperfecta (p.1083), but orthopaedic treatment and physical activity programmes form the basis of therapy.

Osteoporosis. Bisphosphonates are used first-line in the prevention and treatment of osteoporosis (p.1084). Alendronate, risedronate and cyclical etidronate are used orally; clodronate and ibandronate have been used both orally and parenterally, and ibandronate, pamidronate, and zoledronate by intermittent intravenous infusion. Generally, in the management of **postmenopausal** osteoporosis, bisphosphonates increase bone mineral density (BMD) at both the spine and hip and reduce vertebral fractures; effect on non-vertebral fractures varies.[1,2] Treatment in women at highest risk, with prevalent fractures or low BMD, is considered most effective.[2] In the UK, NICE[3] recommends the use of bisphosphonates for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Alendronate, etidronate, or risedronate may be given to all women aged 75 years and older, to women aged between 65 and 74 years with confirmed osteoporosis, and to postmenopausal women younger than 65 with very low BMD or with confirmed osteoporosis and one or more additional age-independent risk factors. Data also suggest that the more severe the osteoporosis, the greater the benefit, and since bone density continues to decline with age, and vertebral fracture incidence rises after age 75, some consider it more beneficial in older women.[4] However, others have expressed concern about a possible increase in brittleness of bones with long-term bisphosphonate treatment.[5]

Although there is less evidence for the efficacy of bisphosphonates for the treatment of idiopathic osteoporosis in **men**, some consider them the treatment of choice. A systematic review[6] stated that, while further evaluation of bisphosphonate therapy in **children** with secondary osteoporosis is warranted, evidence does not support their use as standard therapy.

Bisphosphonates are also considered effective at prevention and treatment of **corticosteroid-induced** osteoporosis.[7] Fracture risk (see p.1491) may also be reduced although a systematic review was inconclusive in this respect.[7]

A meta-analysis of bisphosphonate use in the early **post-transplant** period found that they were effective in reducing BMD decline at the lumbar spine; however, prolonged and more intensive treatment may increase the risk of adynamic or low bone turnover disease.[8]

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8. Mitterbauer C, *et al.* Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21:** 2275–81.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease.

Bone Morphogenetic Proteins

BMP; Proteínas morfogenéticamente óseas.

Костные Морфогенетические Белки

ATC — M05BC01 (BMP-2); M05BC02 (BMP-7).

Dibotermin Alfa *(BAN, USAN, rINN)*

Dibotermina alfa; Dibotermine Alfa; Diboterminum Alfa; hrBMP-2; rhBMP-2. Human recombinant bone morphogenetic protein 2.

Диботермин Альфа

CAS — 246539-15-1.

ATC Vet — QM05BC01.

Eptotermin Alfa *(rINN)*

Eptotermina alfa; Eptotermine Alfa; Eptoterminum Alfa; hrBMP-7; OP-1; Osteogenic Protein-1. Human recombinant bone morphogenetic protein 7.

Эптотермин Альфа

CAS — 129805-33-0.

ATC Vet — QM05BC02.

Profile

Bone morphogenetic proteins (BMPs) are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix. Several have been identified and developed for use in orthopaedic and reconstructive surgery; some have been produced by recombinant technology.

Eptotermin alfa is a recombinant form used in adults for the treatment of non-union of tibia of at least 9 months duration in cases where autograft has failed or is unfeasible. Dibotermin alfa, another recombinant form, is used as an adjunct to standard care for the treatment of acute tibia fractures in adults, as an implant containing 12 mg. The implant is also indicated for anterior lumbar spine fusion, as a substitute for bone grafting, in adults with degenerative disc disease who have had at least 6 months of non-operative treatment. Dibotermin alfa is also used as an alternative to bone grafting for sinus augmentation, and for localised alveolar ridge augmentations for defects associated with extraction sockets. Osteogenin (BMP-3) is under investigation.

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Adverse effects. The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products in cervical spine fusion had been associated with at least 38 re-