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.

◊ References.

1. Brown DL, Robbins R. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999; **39:** 651–60.
2. Shoemaker LR. Expanding role of bisphosphonate therapy in children. *J Pediatr* 1999; **134:** 264–7.
3. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003; **9:** 2643–58.
4. Cohen SB. An update on bisphosphonates. *Curr Rheumatol Rep* 2004; **6:** 59–65.
5. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; **39:** 668–77.
6. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics* 2007; **119** (suppl 2): S150–S162.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res* 2007; **86:** 1022–33.
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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but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.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.

1. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 30/11/06).
2. Aapro M, *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008; **19:** 420–32.
3. Rule S. Managing cancer-related skeletal events with bisphosphonates. *Hosp Med* 2004; **65:** 355–60.
4. Brown JE, *et al.* The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer* 2004; **11:** 207–24.
5. Pavlakis N, *et al.* Bisphosphonates for breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 30/11/06).
6. Saad F, Schulman CC. Role of bisphosphonates in prostate cancer. *Eur Urol* 2004; **45:** 26–34.
7. Djulbegovic B, *et al.* Bisphosphonates in multiple myeloma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/11/06).
8. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005; **23:** 8219–24.
9. Gainford MC, *et al.* Recent developments in bisphosphonates for patients with metastatic breast cancer. *BMJ* 2005; **330:** 769–73.
10. Ross JR, *et al.* Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003; **327:** 469–72. Correction. *ibid.* 2004; **328:** 384.
11. Hillner BE, *et al.* American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003; **21:** 4042–57. Correction. *ibid.* 2004; **22:** 1351.
12. Lacy MQ, *et al.* Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; **81:** 1047–53.
13. Kyle RA, *et al.* American Society of Clinical Oncology. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; **25:** 2464–72.
14. Durie BGM, *et al.*. International Myeloma Working Group. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic consensus statement. *Mayo Clin Proc* 2007; **82:** 516–7; author reply 517–18.

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]

1. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 2003; **19:** 395–414.
2. Masud T, Giannini S. Preventing osteoporotic fractures with bisphosphonates: a review of the efficacy and tolerability. *Aging Clin Exp Res* 2003; **15:** 89–98.
3. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 87 (issued January 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/TA087guidance.pdf (accessed 23/07/08)
4. Dhesi JK, *et al.* The implications of a growing evidence base for drug use in elderly patients. Part 4: vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; **61:** 521–8.
5. Ott S. New treatments for brittle bones. *Ann Intern Med* 2004; **141:** 406–7.
6. Ward L, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/04/08).
7. Homik J, *et al.* Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 22/02/05).
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.

◊ References.

1. Croteau S, *et al.* Bone morphogenetic proteins in orthopedics: from basic science to clinical practice. *Orthopedics* 1999; **22:** 686–95.
2. Groeneveld EH, Burger EH. Bone morphogenetic proteins in human bone regeneration. *Eur J Endocrinol* 2000; **142:** 9–21.
3. Valentin-Opran A, *et al.* Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Orthop* 2002; **395:** 110–20.
4. Govender S, *et al.* Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am* 2002; **84:** 2123–34.
5. Johnsson R, *et al.* Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion. *Spine* 2002; **27:** 2654–61.
6. Khan SN, Lane JM. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in orthopaedic applications. *Expert Opin Biol Ther* 2004; **4:** 741–8.
7. Westerhuis RJ, *et al.* Use of bone morphogenetic proteins in traumatology. *Injury* 2005; **36:** 1405–12.
8. Giannoudis PV, Tzioupis C. Clinical applications of BMP-7: the UK perspective. *Injury* 2005; **36** (suppl 3): S47–S50.
9. Wikesjö UM, *et al.* Tissue engineering with recombinant human bone morphogenetic protein-2 for alveolar augmentation and oral implant osseointegration: experimental observations and clinical perspectives. *Clin Implant Dent Relat Res* 2005; **7:** 112–19.
10. Granjeiro JM, *et al.* Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res* 2005; **38:** 1463–73.
11. Garrison KR, *et al.* Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess* 2007; **11:** 1–150.
12. Mussano F, *et al.* Bone morphogenetic proteins and bone defects: a systematic review. *Spine* 2007; **32:** 824–30.

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-

ports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrollment in approved clinical studies was recommended when treating cervical spine problems.[1]

1. FDA. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. Available at: http://www.fda.gov/cdrh/safety/070108-rhbmp.html (accessed 17/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: InductOs; ***Cz.:*** InductOs; Osigraft; ***Denm.:*** InductOs; Osigraft; ***Fin.:*** InductOs; ***Gr.:*** InductOs; Osigraft; ***Irl.:*** InductOs; ***Ital.:*** Osigraft; ***Neth.:*** Osigraft; ***Norw.:*** InductOs; ***Port.:*** Osigraft; ***Spain:*** InductOs; Osigraft; ***Swed.:*** InductOs; ***UK:*** InductOs; ***USA:*** Infuse Bone Graft.

Calcitonins

Calcitoninas.

ATC — H05BA01 (salmon synthetic); H05BA02 (pork natural); H05BA03 (human synthetic).

ATC Vet — QH05BA01 (salmon synthetic); QH05BA02 (pork natural); QH05BA03 (human synthetic).

Calcitonin (Human)

Calcitonina (humana); Calcitonin-human; Human Calcitonin.

$C_{151}H_{226}N_{40}O_{45}S_3$ = 3417.8.
CAS — 21215-62-3.
ATC — H05BA03 (human synthetic).
ATC Vet — QH05BA03 (human synthetic).

Description. Calcitonin (human) is a synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) *(BANM)*

Calcitonina (cerdo).
CAS — 12321-44-7.
ATC — H05BA02 (pork natural).
ATC Vet — QH05BA02 (pork natural).

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.
Description. Calcitonin (pork) is a polypeptide hormone obtained from pork thyroid.

Calcitonin (Salmon) *(BAN)*

Calcitonina (salmón); Calcitonin-salmon; Calcitoninum salmonis; Kalcitonin lososí; Kalcytonina łososiowa; Kalsitoniini (lohi); Kalsitonin (Somon); Lašišų kalcitoninas; Laxkalcitonin; Lazac-kalcitonin; Salcatonin; Salkatonin; Salmon Calcitonin; SCT-1; SMC-20-051.

$C_{145}H_{240}N_{44}O_{48}S_2$ = 3431.9.
CAS — 47931-85-1.
ATC — H05BA01 (salmon synthetic).
ATC Vet — QH05BA01 (salmon synthetic).

NOTE. There may be some confusion between the terms Salcatonin and Calcitonin (Salmon) (Salmon Calcitonin; Calcitonin-salmon) although in practice these names appear to be used for the same substance.

- The Ph. Eur. 6.2 defines Calcitonin (Salmon) as a polypeptide having the structure determined for salmon calcitonin I. It is available as an acetate.
- Calcitonin (Salmon)/Salcatonin (*BAN*) is defined as a *component* of natural salmon calcitonin. The BP 2008 defines Calcitonin (Salmon)/Salcatonin as a synthetic polypeptide having the structure determined for salmon calcitonin I.
- In the USA, Calcitonin (*USAN*) includes calcitonin (human) and calcitonin (salmon) and there Salcatonin is understood to be a synthetic polypeptide structurally similar to natural salmon calcitonin (Calcitonin Salmon (Synthesis)). The US manufacturers use Calcitonin-salmon for a synthetic polypeptide with the same structure as calcitonin of salmon origin.

Pharmacopoeias. In *Chin*, *Eur.* (see p.vii), and *US.*.
Ph. Eur. 6.2 (Calcitonin (Salmon)). A white or almost white powder. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. Freely soluble in water. Store at 2° to 8°. If the substance is sterile store in a sterile, airtight, tamper-proof container. Protect from light.
USP 31 (Calcitonin Salmon). It is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. One mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP units. Store in airtight containers at a temperature of 2° to 8°, or maintain in a frozen state. Protect from light.

Elcatonin *(rINN)*

[Aminosuberic Acid 1,7]-eel Calcitonin; [Asu^{1,7}]-E-CT; Carbocalcitonin; Elcatonina; Elcatonine; Elcatoninum. 1-Butyric acid-7-(L-2-aminobutyric acid)-26-L-aspartic acid-27-L-valine-29-L-alanine-calcitonin (salmon).

Элькатонин

$C_{148}H_{244}N_{42}O_{47}$ = 3363.8.
CAS — 60731-46-6.
ATC — H05BA04.
ATC Vet — QH05BA04.

Description. Elcatonin is a synthetic analogue of eel calcitonin.

Pharmacopoeias. In *Jpn.*

Incompatibility. Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusion should contain some protein to prevent the sorption and consequent loss of potency (see under Administration, below).

Units

0.8 units of calcitonin, porcine, are contained in one ampoule of the second International Standard Preparation (1991).

128 units of calcitonin, salmon, are contained in approximately 20 micrograms of freeze-dried purified synthetic salmon calcitonin, with mannitol 2 mg in one ampoule of the second International Standard Preparation (1989).

17.5 units of calcitonin, human, are contained in one ampoule of the second International Standard Preparation (1991).

88 units of calcitonin, eel, are contained in one ampoule of the first International Standard Preparation (1989).

Potency of calcitonins is estimated by comparing the hypocalcaemic effect, in *rats*, with that of the standard preparation, and is expressed in international or MRC units which are considered to be equivalent. One manufacturer states that 100 international units by this assay is equivalent to 1 mg of porcine or human calcitonin, and to 25 micrograms of salmon calcitonin although other, slightly different, equivalencies have been cited for other preparations. However, although 1 unit of pork calcitonin, 1 unit of salmon calcitonin, and 1 unit of human calcitonin should give the same response in humans this is not necessarily the case. Doses of calcitonin that have been considered approximately equivalent in practice are:

- 80 units of pork calcitonin
- 50 units of salmon calcitonin
- 500 micrograms of human calcitonin

Clinically, doses of pork and salmon calcitonin are expressed in units whereas those of human calcitonin can be expressed by weight, probably a reflection of its purity.

Adverse Effects, Treatment, and Precautions

Calcitonins may cause nausea, vomiting, diarrhoea, dizziness, flushing, and tingling of the hands. These reactions are dose dependent, usually transient, and occur more often with intravenous doses. Other adverse effects have included skin rash, an unpleasant taste, abdominal pain, urinary frequency, and tremor. A diabetogenic effect has been reported rarely. Inflammatory reactions at the injection site have been reported with some calcitonins, and rhinitis and other local reactions have been reported with nasal formulations. Transient hypocalcaemia may occur after injections of calcitonin, and use is contra-indicated in patients with hypocalcaemia.

Calcitonins should be given with care to patients with renal impairment (see below) or heart failure. If children receive calcitonin it should preferably be for short periods and bone growth should be monitored.

Circulating antibodies may develop after several months of use but resistance does not necessarily follow (see also below). In patients with suspected sensitivity, a skin test has been advised before use as hypersensitivity reactions, including anaphylaxis, have occurred.

Calcitonin has inhibited lactation in *animals*.

Nausea and vomiting may be reduced by giving doses at bedtime or by giving an antiemetic beforehand.

Calcitonin (pork) may contain trace amounts of thyroid hormones, but clinical effects are unlikely in most patients.

Antibody formation. Long-term treatment with heterologous calcitonins may lead to the formation of neutralising antibodies. This appears to be common in patients given calcitonin (pork) or, to a lesser extent, calcitonin (salmon). Calcitonin (human) is less immunogenic than pork or salmon, but a study[1] has also detected antibodies to human calcitonin in 1 of 33 women with postmenopausal osteoporosis after 6 months of therapy.

The degree to which such antibodies affect therapeutic activity is uncertain. Some studies have suggested a significant loss of therapeutic activity in patients who developed neutralising antibodies to calcitonin (salmon),[2] or a restoration in activity after a switch from salmon to human calcitonin in such patients;[3] equally, others have presented evidence that the activity of calcitonin (salmon) was not reduced by the development of antibodies to the drug.[4]

1. Grauer A, *et al.* Formation of neutralizing antibodies after treatment with human calcitonin. *Am J Med* 1993; **95:** 439–42.
2. Grauer A, *et al.* In vitro detection of neutralizing antibodies after treatment of Paget's disease of bone with nasal salmon calcitonin. *J Bone Miner Res* 1990; **5:** 387–91.
3. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; **89:** 181–4.
4. Reginster JY, *et al.* Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheumatol* 1990; **19:** 83–6.

Effect on glucose metabolism. A single subcutaneous injection of calcitonin (salmon) has been reported to increase blood-glucose concentrations,[1] but long-term treatment with calcitonins was considered unlikely to cause diabetes.[2] Nevertheless, deterioration in diabetic control has been noted in a patient given calcitonin (pork)[3] and postprandial release of insulin was abolished by intravenous salmon calcitonin in 8 patients with duodenal ulcers.[4]

1. Gattereau A, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1977; **ii:** 1076–7.
2. Evans IMA, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1978; **i:** 280.
3. Thomas DW, *et al.* Deterioration in diabetic control during calcitonin therapy. *Med J Aust* 1979; **2:** 699–70.
4. Jonderko K. Effect of calcitonin on gastric emptying in patients with an active duodenal ulcer. *Gut* 1989; **30:** 430–5.

Gynaecomastia. A 62-year-old man developed painful gynaecomastia on two occasions after treatment with calcitonin (salmon) given by subcutaneous injection.[1]

1. Vankrunkelsven PJ, Thijs MM. Salcatonin and gynaecomastia. *Lancet* 1994; **344:** 482.

Interactions

There is a theoretical possibility that dosage adjustments of cardiac glycosides or calcium-channel blockers may be required in patients who are given injections of calcitonin, because of the effects of the latter on serum calcium.

Pharmacokinetics

Calcitonins are rapidly inactivated when given orally. After injection, calcitonins are quickly metabolised, primarily in the kidneys but also in blood and peripheral tissues. Bioavailability has been reported to be about 70%; plasma protein binding is about 30 to 40%. The inactive metabolites and a small proportion of unchanged drug are excreted in the urine. The elimination half-life after injection of calcitonin (human) is stated to be 60 minutes and that of calcitonin (salmon) about 70 to 90 minutes.

Calcitonins are also absorbed through the nasal and rectal mucosa. Although figures have varied widely, about 3% of an intranasal dose of calcitonin (salmon) is reported to be bioavailable compared with the same dose given by intramuscular injection, with peak plasma concentrations occurring after about 30 to 40 minutes compared with 15 to 25 minutes after the parenteral dose. Elimination half-life has been reported to be about 16 to 43 minutes.

◊ After the *subcutaneous injection* of 19.9 micrograms of synthetic calcitonin (salmon) in 16 healthy subjects,[1] absorption was rapid with an absorption half-life of 23.4 minutes. The maximum mean plasma concentration was 384 picograms/mL at 60 minutes after which excretion was fairly rapid with an elimination