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