phosphataemia and dyspnoea have been associated with high-dose intravenous bolus therapy.[2] Mecasermin is now given by subcutaneous injection (see Uses and Administration, below).

1. Malozowski S, Stadel B. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 549.
2. Usala A-L. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 550.

Pharmacokinetics

After subcutaneous injection, mecasermin has a bioavailability of almost 100% in healthy subjects. In the circulation it is bound to 6 binding proteins, with more than 80% bound to binding protein 3 (IGFBP-3). However, IGFBP-3 is greatly reduced in patients with severe primary IGF-I deficiency, such that there is an increase in the clearance of mecasermin. Mecasermin is metabolised in the liver and the kidney, and has a terminal half-life of about 6 hours in children with severe primary IGF-I deficiency.

After subcutaneous injection of mecasermin rinfabate in children with severe primary IGF-I deficiency, the half-life of free IGF-I is prolonged to about 13 hours and IGFBP-3 has a half-life of about 54 hours.

Uses and Administration

The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body. Insulin-like growth factor I (IGF-I) is believed to be responsible for many of the anabolic effects of growth hormone. It is secreted primarily by the liver, regulated principally by growth hormone and insulin secretion; IGF-I may also be secreted in other tissues, where it may exert local hormonal (paracrine) effects. In the circulation, IGF-I is almost completely protein bound; 6 binding proteins have been identified and production of some of these is also under the control of growth hormone. In addition to its anabolic effects IGF-I, which is structurally related to insulin, also has potent hypoglycaemic properties.

IGF-I is available as mecasermin, a product of recombinant DNA technology. It is used in the treatment of growth failure in children with severe primary IGF-I deficiency (such as Laron-type dwarfism, in which an abnormality of the growth hormone receptor results in an inability to secrete endogenous IGF-I—see Growth Retardation, below). It may also be used in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone. However, it is not recommended for children less than 2 years of age because of a lack of data. The starting dose of mecasermin is 40 to 80 micrograms/kg twice daily by subcutaneous injection. After 1 week, if this dose is tolerated, it may be increased by 40 micrograms/kg per dose to a maximum of 120 micrograms/kg twice daily. Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia. The dose should be reduced if hypoglycaemia occurs with recommended doses despite adequate food intake. If the patient is unable to eat for any reason, the dose of mecasermin should be withheld.

Mecasermin rinfabate is a recombinant protein complex of IGF-I and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). It is under investigation in the management of amyotrophic lateral sclerosis and myotonic muscular dystrophy.

IGF-II (IGF-2) is thought to play an important role in fetal growth, although its function in adults is uncertain. It is closely related in structure to IGF-I, but is not under the control of growth hormone.

◊ General reviews.

1. Laron Z. Somatomedin-1 (insulin-like growth factor-I) in clinical use: facts and potential. *Drugs* 1993; **45:** 1–8.
2. Bondy CA, *et al.* Clinical uses of insulin-like growth factor I. *Ann Intern Med* 1994; **124:** 593–601.
3. Le Roith D. Insulin-like growth factors. *N Engl J Med* 1997; **336:** 633–40.
4. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol* 2001; **54:** 311–16.
5. Kemp SF, *et al.* Efficacy and safety of mecasermin rinfabate. *Expert Opin Biol Ther* 2006; **6:** 533–8.

Diabetes mellitus. Patients with type 1 diabetes mellitus (p.431) have low circulating levels of insulin-like growth factor I (IGF-I), and there has been considerable interest in the therapeutic potential of mecasermin in these patients.[1] Randomised studies[2,3] have found that mecasermin 40 micrograms/kg once or twice daily by subcutaneous injection improves metabolic control in the short term when added to insulin therapy. Insulin doses can also be reduced in some patients.[3] However, the role of IGF-I in the development of diabetic complications is unclear and there has been some concern about its proliferative effect in diabetic retinopathy.[1] Optic disc swelling and worsening of retinopathy have been reported with higher doses of mecasermin.[3] Mecasermin rinfabate is being studied in an attempt to limit adverse effects such as oedema, jaw pain, headache, Bells' palsy, and retinal oedema.[4]

Mecasermin has also been reported to improve insulin sensitivity and to lower concentrations of insulin, glucose, and C-peptide in patients with syndromes of severe insulin resistance or type 2 diabetes mellitus.[1]

1. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. *Diabetes Technol Ther* 2000; **2:** 69–80.
2. Acerini CL, *et al.* Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350:** 1199–1204.
3. Thrailkill KM, *et al.* Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. *Diabetes Care* 1999; **22:** 585–92.
4. Clemmons DR, *et al.* The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab* 2000; **85:** 1518–24.

Growth retardation. Mecasermin is used in the treatment of Laron-type dwarfism (growth hormone resistance), a form of growth retardation (p.1798). Doses of 150 to 240 micrograms/kg daily, given subcutaneously, have stimulated linear growth and normalised biochemical abnormalities in these patients.[1] During long-term use, growth hormone and insulin are persistently suppressed, preventing hypoglycaemia and stabilising blood-glucose concentrations. There is also an increase in the production of the insulin-like growth factor binding protein-3, which prolongs the half-life of mecasermin so that a progressive dose reduction is needed to avoid overdosage and adverse effects.[2]

1. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; **84:** 4397–4404.
2. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89:** 1031–44.

Motor neurone disease. Mecasermin is under investigation for the management of amyotrophic lateral sclerosis, a form of motor neurone disease (p.2380). Mecasermin may have modest benefits but there is not enough available evidence to assess conclusively.[1]

1. Mitchell JD, *et al.* Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/08/08).

Osteoporosis. Mecasermin[1] and mecasermin rinfabate[2] have been investigated as stimulants of bone formation in osteoporosis (p.1084). Some beneficial effects on bone density have been reported.

1. Grinspoon S, *et al.* Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002; **87:** 2883–91.
2. Boonen S, *et al.* Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002; **87:** 1593–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Increlex; ***Fr.:*** Increlex; ***UK:*** Increlex; ***USA:*** Increlex; Iplex†.

Somatorelin *(rINN)* ⊗

GHRF; GHRH; GRF; GRF-44; Growth Hormone-releasing Factor (Human); Growth Hormone-releasing Hormone; Somatoliberin; Somatoreliini; Somatorelina; Somatoréline; Somatorelinum.

Соматорелин

$C_{215}H_{358}N_{72}O_{66}S$ = 5039.7.

CAS — 83930-13-6.

ATC — V04CD05.

ATC Vet — QV04CD05.

Sermorelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de sermorelina; GRF(1-29)NH_2 (sermorelin); Growth Hormone-releasing Factor (Human)-(1-29)-peptide Amide (sermorelin); Sermoréline, Acétate de; Sermorelini Acetas. Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate hydrate.

Серморелина Ацетат

$C_{149}H_{246}N_{44}O_{42}S.xC_2H_4O_2.yH_2O$ = 3357.9 (sermorelin).

CAS — 86168-78-7 (sermorelin); 114466-38-5 (sermorelin acetate).

ATC — H01AC04; V04CD03.

ATC Vet — QH01AC04; QV04CD03.

Adverse Effects and Precautions

Facial flushing and pain at the injection site may occur after injection of sermorelin acetate. Headache, nausea and vomiting, dysgeusia, and tightness in the chest have also been reported. Antibodies to somatorelin may develop on repeated use.

Sermorelin should be used with care in patients with epilepsy. Uncontrolled hypothyroidism, obesity, hyperglycaemia, or elevated plasma fatty acids may impair response to sermorelin. Sermorelin should not be used to treat growth retardation in children whose growth hormone response to stimulation tests is inadequate. Treatment should cease once the epiphyses have closed.

Interactions

Drugs that affect the secretion of growth hormone may interfere with the diagnostic efficacy of somatorelin or sermorelin; these include growth hormone itself, somatostatin, insulin, corticosteroids, and cyclo-oxygenase inhibitors such as aspirin and indometacin. Growth hormone concentrations may be raised by clonidine and levodopa. The response to somatorelin or sermorelin may also be reduced by antimuscarinic drugs such as atropine, and by antithyroid drugs such as propylthiouracil.

Uses and Administration

Somatorelin is a peptide, secreted by the hypothalamus, that promotes the release of growth hormone from the anterior pituitary. It exists as 44-, 40-, and 37-amino acid peptides; the 44-amino acid form may possibly be converted to the smaller forms but all are reported to be active, the activity residing in the first 29 amino acid residues. Sermorelin is a synthetic peptide corresponding to the 1–29 amino acid sequence of somatorelin.

Sermorelin acetate is used for the diagnosis of growth hormone deficiency. The usual dose is the equivalent of sermorelin 1 microgram/kg by intravenous injection in the morning after an overnight fast. A normal response to sermorelin indicates that the somatotrophs are functional, but does not exclude growth hormone deficiency due to hypothalamic dysfunction; to establish a diagnosis it must be used with other tests. Somatorelin acetate is used similarly.

Sermorelin has also been used for the treatment of growth hormone deficiency in children; doses equivalent to 30 micrograms/kg, as the acetate, may be given once daily at bedtime by subcutaneous injection.

Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation and has been investigated in the treatment of HIV-associated wasting.

Diagnostic use. Somatorelin (in its 40- or 44-amino acid forms) has been used in the assessment of growth hormone deficiency.[1-3] It has usually been given as a single intravenous injection in doses of 1 microgram/kg or total doses of up to 200 micrograms. Subsequent normal or exaggerated increases in serum-growth hormone concentrations have occurred in healthy subjects,[1,2] and in patients with hypothalamic tumours[3] or acromegaly,[2] but not in patients with hypopituitarism.[2] A synthetic 29-amino-acid sequence of somatorelin, sermorelin acetate is now available for the diagnosis of growth hormone deficiency. However, it has been suggested that the test is not useful for screening as it does not test the hypothalamic-pituitary axis, and that it should not be used in routine clinical practice.[4] The use of