atrophy of the skin leading to striae, poor wound healing, muscle weakness, osteoporosis, hypertension, diabetes mellitus, and depression and other psychological disturbances. Hypokalaemia is rare in Cushing's disease but common in other forms of the syndrome. Women may have hirsutism due to adrenal androgen secretion, and both sexes may develop hypogonadism and loss of libido.

Diagnosis of Cushing's syndrome can be problematic because no test is wholly reliable.[1,3-6] Where there is suspicion, options for initial screening include measurement of urinary cortisol, late-night salivary cortisol, midnight plasma-cortisol, and overnight low-dose dexamethasone suppression testing. A dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism. Once a diagnosis of Cushing's syndrome has been made, plasma-ACTH measurements are used to distinguish between ACTH-dependent and ACTH-independent forms. High-dose dexamethasone suppression testing and corticorelin stimulation testing have been used to differentiate between pituitary and ectopic ACTH-dependent Cushing's syndrome, but they both have disadvantages and their usefulness has been debated. For further discussion of dexamethasone suppression testing, see p.1527, and for corticorelin stimulation testing, see p.1523. Imaging techniques and sampling of central (petrosal) venous blood are additional procedures that may be used for localising tumours.

Appropriate **treatment** depends on accurate identification of the cause of the syndrome.[1] The usual treatment in Cushing's disease is transsphenoidal resection of the tumour, which when carried out by an experienced surgeon produces a successful response in the majority of patients. Pituitary radiotherapy is slower than surgery to take effect, produces a lower remission rate, and is more likely to produce hypopituitarism. It is therefore usually used as second-line therapy when initial surgery has not been curative and a second operation is considered unsuitable. If pituitary surgery or radiotherapy fails, bilateral adrenalectomy may be considered (although this has some risks including that of Nelson's syndrome due to hyperactivity of residual pituitary tumour). Patients who undergo such surgery require glucocorticoid and mineralocorticoid replacement therapy for life. Surgery is also the treatment of choice for a resectable adrenal tumour or ectopic ACTH-secreting tumour; even where there is metastasis it may be useful in moderating symptoms.

A number of drugs have been used in patients with Cushing's disease, but their role appears to be mainly adjuvant.[1,7] Drugs acting at the hypothalamic-pituitary level, aimed at reducing ACTH secretion, do not seem to be of much value; there have been occasional reports of benefit with bromocriptine, cyproheptadine, and sodium valproate. Drugs that inhibit steroid synthesis in the adrenal gland are more effective, and include mitotane, metyrapone, and ketoconazole. These may be used to control severe complications quickly, prepare patients for surgery, or provide cover while radiotherapy takes effect. Mifepristone acts as a glucocorticoid receptor antagonist, and has been used successfully in a few patients with Cushing's syndrome. Etomidate can be useful for acute control of hypercortisolaemia if the oral route is not available.

In patients with the ectopic ACTH syndrome in whom surgery is unsuitable or ineffective, chemotherapy aimed at the primary tumour is the treatment of choice but is likely to be only palliative. Inhibitors of steroid synthesis can be used to control symptoms, and somatostatin analogues such as octreotide may decrease ACTH secretion by ectopic tumours that have somatostatin receptors.[1]

Surgery is the preferred treatment for an adrenal tumour but, although this is usually curative for adrenal adenoma, it is less successful for adrenal carcinoma.[1]

In patients who are successfully treated for Cushing's syndrome adrenocortical replacement therapy (see p.1498) is usually required until the hypothalamic-pituitary-adrenal axis recovers normal function, a process which may take many months.

1. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.
2. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.
3. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
4. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.
5. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab* 2006; **91:** 3746–53.
6. Nieman LK, *et al.* The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93:** 1526–40. Also available at: http://www.endo-society.org/guidelines/final/upload/Cushings_Guideline.pdf (accessed 06/08/08)
7. Nieman LK. Medical therapy of Cushing's disease. *Pituitary* 2002; **5:** 77–82.

Preparations

BP 2008: Metyrapone Capsules;
USP 31: Metyrapone Tablets.

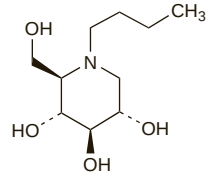
Proprietary Preparations (details are given in Part 3)
Austral.: Metopirone; ***Cz.:*** Metopirone†; ***Fr.:*** Metopirone; ***Gr.:*** Metopirone; ***Irl.:*** Metopirone; ***Israel:*** Metopirone; ***Neth.:*** Metopiron; ***NZ:*** Metopirone; ***Swed.:*** Metopiron; ***Switz.:*** Metopirone; ***UK:*** Metopirone; ***USA:*** Metopirone.

Miglustat *(BAN, USAN, rINN)*

Butyldeoxynojirimycin; *n*-Butyl-deoxynojirimycin; Miglustaatti; Miglustatum; OGT-918; OXAIDS; SC-48334. 1,5-(Butylimino)-1,5-dideoxy-D-glucitol; (2*R*,3*R*,4*R*,5*S*)-1-Butyl-2-(hydroxymethyl)piperidine-3,4,5-triol.

Миглустат

$C_{10}H_{21}NO_4$ = 219.3.
CAS — 72599-27-0.
ATC — A16AX06.
ATC Vet — QA16AX06.



Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances, weight loss, tremor, dizziness, headache, cramps, and visual disturbances are frequent in patients receiving miglustat, and some patients may experience paraesthesias, peripheral neuropathy, or thrombocytopenia. Studies in *animals* have indicated an effect on spermatogenesis; male patients should not attempt conception during, or for 3 months after stopping, treatment. Care is required in renal impairment.

Pharmacokinetics

Miglustat is rapidly absorbed after oral doses with maximum plasma concentrations reached in about 2 hours. It is mainly excreted in the urine with some also excreted in the faeces; the average elimination half-life is 6 to 7 hours.

Food. The average peak plasma concentration was reduced by 37% when miglustat was taken with food by 24 healthy subjects. However, there was no clinically significant effect on the extent of absorption (area under the curve was decreased by 14%).[1] Licensed product information states that miglustat may be taken with or without food.

1. van Giersbergen PLM, Dingemanse J. Influence of food intake on the pharmacokinetics of miglustat, an inhibitor of glucosylceramide synthase. *J Clin Pharmacol* 2007; **47:** 1277–82.

Uses and Administration

Miglustat is an inhibitor of the enzyme glucosylceramide synthase, responsible for the first step in the synthesis of glucosylceramide and most other glycolipids. It is used to help prevent the accumulation of glucosylceramide in patients with mild to moderate type 1 Gaucher disease (p.2249) who cannot be treated with enzyme replacement therapy. The initial dose is 100 mg orally 3 times daily; reduction to 100 mg once or twice daily may be necessary in some patients because of diarrhoea. For details of reduced doses in patients with renal impairment, see below. Miglustat has also been used for the treatment of Niemann-Pick disease, type C.

◊ References.

1. McCormack PL, Goa KL. Miglustat. *Drugs* 2003; **63:** 2427–34.
2. Weinreb NJ, *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80:** 223–9.
3. Giraldo P, *et al.* Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica* 2006; **91:** 703–6.
4. Elstein D, *et al.* Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood* 2007; **110:** 2296–2301.
5. Patterson MC, *et al.* Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007; **6:** 765–72.

Administration in renal impairment. The initial dose of miglustat should be reduced in renal impairment according to the patient's creatinine clearance (CC):

- CC 50 to 70 mL/minute per 1.73 m^2: 100 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Zavesca; ***Canad.:*** Zavesca; ***Cz.:*** Zavesca; ***Denm.:*** Zavesca; ***Fin.:*** Zavesca; ***Fr.:*** Zavesca; ***Ger.:*** Zavesca; ***Gr.:*** Zavesca; ***Hung.:*** Zavesca; ***Israel:*** Zavesca; ***Ital.:*** Zavesca; ***Neth.:*** Zavesca; ***Norw.:*** Zavesca; ***Port.:*** Zavesca; ***Spain:*** Zavesca; ***Swed.:*** Zavesca; ***Switz.:*** Zavesca; ***UK:*** Zavesca; ***USA:*** Zavesca.

Dementholised Mint Oil

Csökkentett mentoltartalmú mezei mentaolaj (partly dementholised mint oil); Menta, aceite esencial desmentolado de; Mentha arvensis, huile essentielle partiellement démentholée de (mint oil, partly dementholised); Menthae arvensis aetheroleum partim mentholum depletum (mint oil, partly dementholised).
CAS — 68917-18-0 (cornmint oil).

Pharmacopoeias. In *Eur.* (see p.vii).
Mentha oil is in *Jpn.*
Ph. Eur. 6.2 (Mint Oil, Partly Dementholised; Menthae Arvensis Aetheroleum Partim Mentholum Depletum; Dementholised Mint Oil BP 2008). The essential oil obtained by steam distillation from the fresh, flowering aerial parts, recently gathered from *Mentha canadensis* (*M. arvensis* var. *glabrata*; *M. arvensis* var. *piperascens*) followed by partial separation of menthol by crystallisation. A colourless or pale yellow to greenish-yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Dementholised mint oil is used as a flavour. *Mentha arvensis* is used in herbal medicine as a febrifuge and for rheumatic disorders. Cornmint oil, obtained from *M. arvensis*, is used in aromatherapy as an adulterant or substitute for peppermint oil. Peppermint oil (p.1761) and spearmint oil (p.2391) are used as carminatives and flavours.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Japanol; JHP Rodler; Retterspitz Muskel- und Nervenol; ***Pol.:*** Migrenol; ***Switz.:*** Carmol; Minthi JHP Huile.

Multi-ingredient: ***Austral.:*** Tiger Balm White; ***Austria:*** Parodontax; ***Chile:*** Astrijesan; Calmatol; ***Ger.:*** Dreierlei; Trachiform†; ***Israel:*** Tiger Balm Red; Tiger Balm White; ***Ital.:*** Broncosedina; Listerine Fresh Citrus; Listerine Tartar Control; Venalta; ***Malaysia:*** Eucarbon†; ***Pol.:*** Argol Essenza Balsamica; Milocardin; Mucosit; Rapacholin C; Rapacholin Forte; Rhin-Bac; Salviasept; ***Switz.:*** GU Eau†; Huile analgesique "Temple of Heaven" contre les maux de tete†; Malveol; Neo-Angin au miel et citron; Neo-Angin sans sucre; Novital; Odontal; Onguent nasal Ruedi; Osa gel dentaire aux plantes; Parodontax F†; Parodontax†; Pastilles pectorales Demo N; Pommade nasale de Nager; Pommade nasale de Ruedi; Pommade Nasale Radix†; Radix; Tyrothricin; Unathene; Unatol; ***Turk.:*** Sandolin; ***UK:*** Olbas; Olbas for Children; Sinose.

Miracle Fruit

Fruta milagrosa.

Profile

Miracle fruit is the fruit of *Synsepalum dulcificum* (*Richardella dulcifica*) (Sapotaceae). It contains a glycoprotein 'miraculin' with no apparent taste of its own but which is able to make sour substances taste sweet and to improve the flavour of foods. Its activity is reduced by heating.

Mistletoe

European Mistletoe; Gui; Mistelkraut; Muérdago; Tallo de Muérdago; Visci Caulis; Visci herba; Viscum; Viscum Album.

Pharmacopoeias. In *Ger.*

Profile

Mistletoe is the dried, evergreen, dioecious semi-parasite, *Viscum album* (Loranthaceae), which grows on the branches of deciduous trees, chiefly apple, poplar, and plum. It occurs as a mixture of broken stems and leaves and occasional fruits. Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders although its activity when taken orally is questionable. It has also been used in nervous disorders.

Mistletoe contains lectins with cytotoxic and immunomodulatory actions *in vitro* and preparations have been given by injection in a number of neoplastic diseases.

Ingestion of the berries and other parts has been reported to cause nausea, vomiting, diarrhoea, and bradycardia.

Homoeopathy. Mistletoe has been used in homoeopathic medicines under the following names: Viscum album; Vis. alb.

◊ A review of mistletoe.[1] There are about 1300 species of mistletoe representing 36 genera of the Loranthaceae, and what is called the "common mistletoe" varies from country to country: in Europe the term describes *Viscum album* while in the USA it describes *Phoradendron flavescens*. The toxicity of aqueous extracts of mistletoe has been found to depend upon the nature of the host plant. Three classes of cytotoxic compounds are present in the leaves and stems of *V. album* although the berries are generally considered to be the most toxic part of the plant. These are alkaloids, viscotoxins, and lectins. The viscotoxins have been shown to cause hypotension, bradycardia, arterial vasoconstriction, and a negative inotropic effect, and may act as acetylcholine agonists. The lectins show toxic effects in *animals* similar to those seen with ricin.

1. Anderson LA, Phillipson JD. Mistletoe—the magic herb. *Pharm J* 1982; **229:** 437–9.

Adverse effects. There have been reports of hepatitis after the ingestion of herbal remedies containing mistletoe.[1,2] Severe delayed hypersensitivity has been reported[3] in a patient given intravenous chemotherapy for breast cancer concurrently with subcutaneous injections of a mistletoe extract. It was thought that mistletoe had stimulated the reaction to methotrexate and gemcitabine.

1. Harvey J, Colin-Jones DG. Mistletoe hepatitis. *BMJ* 1981; **282:** 186–7.