

**Hydrocortisone Sodium Succinate**(BANM, rINN)  $\otimes$ 

Cortisol Sodium Succinate; Hydrocortisone, Succinate Sodique d'; Hydrocortisoni Natrii Succinas; Hydrokortyzonu bursztynianu sól sodowa; Succinato sódico de hidrocortisona. Hydrocortisone 21-(sodium succinate).

Гидрокортизона Натрия Суццинат

 $C_{25}H_{33}NaO_8 = 484.5$ 

CAS — 125-04-2.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

**Pharmacopoeias.** In *Chin., Int., It., Jpn., Pol., and US.*

**USP 31** (Hydrocortisone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform. Store in airtight containers. Protect from light.

**Hydrocortisone Valerate** (BANM, USAN, rINN)  $\otimes$ 

Cortisol Valerate; Hydrocortisone, Valérate d'; Hydrocortisoni Valeras; Valerato de hidrocortisona. Hydrocortisone 17-valerate.

Гидрокортизона Валерат

 $C_{26}H_{38}O_6 = 446.6$ 

CAS — 57524-89-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

**Pharmacopoeias.** In *US.***Adverse Effects, Treatment, Withdrawal, and Precautions**

As for corticosteroids in general (see p.1490).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

**Effects on fluid and electrolyte balance.** A report of marked hypokalaemia and hypomagnesaemia associated with high-dose intravenous hydrocortisone therapy in an alcoholic patient with suspected immune thrombocytopenia.<sup>1</sup> Cardiac arrhythmias developed, and prolonged infusion of magnesium and potassium was required to restore normal plasma concentrations.

1. Ramsahoye BH, *et al.* The mineralocorticoid effects of high dose hydrocortisone. *BMJ* 1995; **310**: 656–7.

**Effects on the nervous system.** For reports and comments on paraesthesia or perineal irritation associated with hydrocortisone sodium phosphate given intravenously, see p.1492.

**Hypersensitivity and anaphylaxis.** References to hypersensitivity reactions and anaphylaxis associated with the intravenous use of hydrocortisone;<sup>1–7</sup> topical application can also result in hypersensitivity.<sup>8</sup>

- Chan CS, *et al.* Hydrocortisone-induced anaphylaxis. *Med J Aust* 1984; **141**: 444–6.
- Seale JP. Anaphylactoid reaction to hydrocortisone. *Med J Aust* 1984; **141**: 446.
- Corallo CE, Sosnin M. Bronchospasm, tachycardia following intravenous hydrocortisone. *Aust J Hosp Pharm* 1985; **15**: 103–4.
- Al Mahdy H, Hall M. Anaphylaxis and hydrocortisone. *Ann Intern Med* 1988; **108**: 487–8.
- Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust* 1991; **154**: 210–14.
- Kawane H. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate. *Med J Aust* 1991; **154**: 782.
- Currie GP, *et al.* An unexpected response to intravenous hydrocortisone succinate in an asthmatic patient. *Br J Clin Pharmacol* 2005; **60**: 342.
- Wilkinson SM, *et al.* Hydrocortisone: an important cutaneous allergen. *Lancet* 1991; **337**: 761–2.

**Interactions**

The interactions of corticosteroids in general are described on p.1494.

**Pharmacokinetics**

For a brief account of the pharmacokinetics of corticosteroids, see p.1495.

Hydrocortisone is readily absorbed from the gastrointestinal tract and peak blood concentrations are attained in about an hour. The plasma half-life is about 100 minutes. It is more than 90% bound to plasma proteins. Following intramuscular injection, the absorption of the water-soluble sodium phosphate and sodium succinate esters is rapid, while absorption of hydrocortisone free alcohol and its lipid-soluble esters is slower. Absorption of hydrocortisone acetate after intra-articular or soft-tissue injection is also slow. Hydrocortisone is absorbed through the skin, particularly in denuded areas.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in the urine, mainly conjugated as glucuronides, with a very small proportion of unchanged hydrocortisone. Hydrocortisone readily crosses the placenta.

**Uses and Administration**

Hydrocortisone is a corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity (p.1490). As cortisol it is the most important of the predominantly glucocorticoid steroids secreted by the adrenal cortex. Hydrocortisone is used, usually with a more potent mineralocorticoid, for replacement therapy in adrenocortical insufficiency (p.1498). It may also be used for its glucocorticoid properties in other conditions for which corticosteroid therapy is indicated (p.1495) but drugs with fewer mineralocorticoid effects tend to be preferred for the long-term systemic therapy of auto-immune and inflammatory disease.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of hydrocortisone:

- hydrocortisone acetate 112 mg
- hydrocortisone butepate 135 mg
- hydrocortisone butyrate 119 mg
- hydrocortisone cypionate 134 mg
- hydrocortisone hydrogen succinate 128 mg
- hydrocortisone sodium phosphate 134 mg
- hydrocortisone sodium succinate 134 mg
- hydrocortisone valerate 123 mg

However, esterification generally alters potency and compounds with equivalent hydrocortisone content may not have equivalent clinical effect.

When given orally hydrocortisone free alcohol is usually used; the cypionate ester is used in some formulations. For **replacement therapy** in acute or chronic adrenocortical insufficiency the normal requirement is 20 to 30 mg daily (usually taken in 2 doses, the larger in the morning and the smaller in the early evening, to mimic the circadian rhythm of the body). Children may be given 400 to 800 micrograms/kg daily in 2 or 3 divided doses, adjusted as needed. Additional sodium chloride may be required if there is defective aldosterone secretion, but mineralocorticoid activity is usually supplemented by fludrocortisone acetate orally. Similar regimens have also been used to correct glucocorticoid deficiency in the salt-losing form of congenital adrenal hyperplasia (p.1502).

Hydrocortisone may be given **intravenously**, by slow injection or infusion, in the form of a water-soluble derivative such as hydrocortisone sodium succinate or hydrocortisone sodium phosphate when a rapid effect is required in **emergencies**: such conditions are acute adrenocortical insufficiency caused by Addisonian or post-adrenalectomy crises, by the abrupt accidental withdrawal of therapy in corticosteroid-treated patients, or by the inability of the adrenal glands to cope with increased stress in such patients; certain allergic emergencies such as anaphylaxis; acute severe asthma (status asthmaticus—see also p.1108); and shock. The usual dose is the equivalent of 100 to 500 mg of hydrocortisone, repeated 3 or 4 times in 24 hours, according to the severity of the condition and the patient's response. Children up to 1 year of age may be given 25 mg, those aged 1 to 5 years 50 mg, and those aged 6 to 12 years 100 mg. Fluids and electrolytes should be given as necessary to correct any associated metabolic disorder. Similar doses to those specified above may also be given **intramuscularly** but the response is like-

ly to be less rapid than that observed after intravenous doses. Corticosteroids are considered to be of secondary value in anaphylactic shock because of their relatively slow onset of action, but intravenous hydrocortisone may be a useful adjunct to adrenaline to prevent further deterioration in severely affected patients.

In patients with adrenal deficiency states supplementary corticosteroid therapy may be necessary during some **surgical operations** and hydrocortisone sodium succinate or sodium phosphate may be given intramuscularly or intravenously before surgery. Various regimens have been proposed (see also Surgery, p.1497). In patients taking more than 10 mg of oral prednisolone or its equivalent daily, the *BNF* recommends the following regimen:

- **minor surgery under general anaesthesia**, either the usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25 to 50 mg (usually as the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is resumed after surgery
- **moderate or major surgery**, the usual oral corticosteroid dose on the morning of surgery, *plus* hydrocortisone 25 to 50 mg intravenously at induction, and followed by similar doses of hydrocortisone 3 times daily, for 24 hours after moderate surgery and 48 to 72 hours after major surgery; the usual corticosteroid dose is resumed once hydrocortisone injections are stopped.

For **local injection** into soft tissues hydrocortisone is usually used in the form of the sodium phosphate or sodium succinate esters; doses in terms of hydrocortisone are usually 100 to 200 mg. For intra-articular injection hydrocortisone acetate is usually used in doses of 5 to 50 mg depending upon the size of the joint.

For **topical application** in the treatment of various skin disorders hydrocortisone and the acetate, butepate, butyrate, and valerate esters are normally employed in creams, ointments, or lotions. Concentrations usually used have ranged from 0.1 to 2.5%. Although it is considered that hydrocortisone has fewer adverse effects on the skin and is less liable to cause adrenal suppression than the more potent topical corticosteroids (see p.1497 for a rough guide to the clinical potencies of topical corticosteroids), it should be borne in mind that this property may be considerably modified both by the type of formulation or vehicle used and by the type of esterification present; other factors that may also influence the degree of absorption include the site of application, use of an occlusive dressing, the degree of skin damage, and the size of the area to which the preparation is applied.

Hydrocortisone or its esters are also available in a variety of other dosage forms including those for ophthalmic, aural, dental, and rectal application, for use in allergic and inflammatory disorders.

Other esters of hydrocortisone that have occasionally been used include the aceponate, glycyrrhetinate, and propionate. Esters such as the aceponate may show modified topical activity.

**Preparations**

**BP 2008:** Gentamicin and Hydrocortisone Acetate Ear Drops; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injection; Hydrocortisone Acetate Ointment; Hydrocortisone and Cloquinoxin Cream; Hydrocortisone and Cloquinoxin Ointment; Hydrocortisone and Neomycin Cream; Hydrocortisone Cream; Hydrocortisone Ointment; Hydrocortisone Oromucosal Tablets; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate Injection; Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment;

**USP 31:** Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Cloquinoxin and Hydrocortisone Cream; Cloquinoxin and Hydrocortisone Ointment; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injectable Suspension; Hydrocortisone Acetate Lotions; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Ophthalmic Suspension; Hydrocortisone and Acetic Acid Otic Solution; Hydrocortisone Butyrate Cream; Hydrocortisone Cream; Hydrocortisone Gel; Hydrocortisone Injectable Suspension; Hydrocortisone Lotions; Hydrocortisone Ointment; Hydrocortisone Rectal Suspension; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate for Injection;