an association of sulindac with liver disease compared with other NSAIDs, see under NSAIDs, p.98.

See also Effects on the Skin, below.

1. Gallanosa AG, Spyker DA. Sulindac hepatotoxicity: a case report and review. *Clin Toxicol* 1985; **23:** 205–38.
2. Tarazi EM, *et al.* Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104:** 569–74.

Effects on the lungs. For reference to pneumonitis associated with sulindac therapy, see Hypersensitivity, below.

Effects on the skin. Toxic epidermal necrolysis has occurred in patients taking sulindac.[1] In a patient toxic hepatitis and the Stevens-Johnson/toxic epidermal necrolysis syndrome resulted in death.[2]

An unusual pernio-like reaction affecting the toes, which was also confirmed by rechallenge, has been reported.[3]

Sulindac has also been reported to cause photosensitivity reactions.[4]

1. Small RE, Garnett WR. Sulindac-induced toxic epidermal necrolysis. *Clin Pharm* 1988; **7:** 766–71.
2. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol* 1983; **10:** 512–13.
3. Reinertsen JL. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24:** 1215.
4. Anonymous. Drugs that cause photosensitivity. *Med Lett Drugs Ther* 1986; **28:** 51–2.

Hypersensitivity. Hypersensitivity reactions to sulindac include pneumonitis,[1,2] generalised lymphadenopathy,[3] aseptic meningitis,[4] and anaphylactoid reaction.[5]

See also Effects on the Liver and Effects on the Skin, above.

1. Smith FE, Lindberg PJ. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244:** 269–70.
2. Fein M. Sulindac and pneumonitis. *Ann Intern Med* 1981; **95:** 245.
3. Sprung DJ. Sulindac causing a hypersensitivity reaction with peripheral and mediastinal lymphadenopathy. *Ann Intern Med* 1982; **97:** 564.
4. Fordham von Reyn C. Recurrent aseptic meningitis due to sulindac. *Ann Intern Med* 1983; **99:** 343–4.
5. Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151:** 387–8.

Pancreatitis. Reports[1-4] of pancreatitis associated with sulindac therapy.

1. Goldstein J, *et al.* Sulindac associated with pancreatitis. *Ann Intern Med* 1980; **93:** 151.
2. Siefkin AD. Sulindac and pancreatitis. *Ann Intern Med* 1980; **93:** 932–3.
3. Lilly EL. Pancreatitis after administration of sulindac. *JAMA* 1981; **246:** 2680.
4. Memon AN. Pancreatitis and sulindac. *Ann Intern Med* 1982; **97:** 139.

Interactions

For interactions associated with NSAIDs, see p.99.

Dimethyl sulfoxide reduces plasma concentrations of the active metabolite of sulindac and use of the two drugs together has also resulted in peripheral neuropathy. Diflunisal and aspirin are reported to reduce the plasma concentration of the active metabolite of sulindac. Unlike other NSAIDs, sulindac is reported not to reduce the antihypertensive effects of drugs such as thiazide diuretics, but nevertheless licensed product information recommends that blood pressure be closely monitored in patients taking antihypertensives with sulindac.

Pharmacokinetics

Sulindac is absorbed from the gastrointestinal tract. It is metabolised by reversible reduction to the sulfide metabolite, which appears to be the active form, and by irreversible oxidation to the sulfone metabolite. Peak plasma concentrations of the sulfide metabolite are achieved in about 2 hours. The mean elimination half-life of sulindac is about 7.8 hours and of the sulfide metabolite about 16.4 hours. Sulindac and its metabolites are over 90% bound to plasma proteins. About 50% is excreted in the urine mainly as the sulfone metabolite and its glucuronide conjugate, with smaller amounts of sulindac and its glucuronide conjugate; about 25% appears in the faeces, primarily as sulfone and sulfide metabolites. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

◊ References.

1. Davies NM, Watson MS. Clinical pharmacokinetics of sulindac: a dynamic old drug. *Clin Pharmacokinet* 1997; **32:** 437–59.

Uses and Administration

Sulindac is an NSAID (p.99) structurally related to indometacin (p.68); its activity appears to be due to its sulfide metabolite. Sulindac is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and also in the short-term management of acute gout and peri-articular conditions such as bursitis and tendinitis. It has also been used to reduce fever.

A usual initial oral dose of sulindac is 150 or 200 mg twice daily, reduced according to response; the maximum recommended daily dose is 400 mg. Licensed product information recommends that the treatment of peri-articular disorders should be limited to 7 to 14 days; for acute gout, 7 days of therapy is usually adequate.

Sulindac sodium has been given by rectal suppository.

Administration in hepatic or renal impairment. The dose of sulindac may need to be reduced in patients with hepatic or renal impairment but see Adverse Effects and Precautions, above..

Gastrointestinal disorders. In placebo-controlled studies[1,2] sulindac 150 to 200 mg twice daily for 6 to 9 months has reduced the number and size of polyps in patients with familial adenomatous polyposis but the effect may be incomplete and in a study[2] only polyps less than 2 mm in size regressed. In addition, the size and number of polyps has been reported[1] to increase on stopping treatment. The benefit of long-term therapy has therefore been studied. Reduced effectiveness has been seen[3] with long-term use but others[4] have reported management of recurrences by adjustment of maintenance dosage; there seemed to be individual variations in sensitivity to sulindac with respect to prevention of polyp recurrence although an average maintenance dose of 200 mg daily appeared to be needed.[4]

There is evidence[5] that sulindac alters the ratio of apoptosis of surface cells relative to those lying deeper in the crypt of rectal mucosa, thus altering epithelial homoeostasis. Whether sulindac prevents malignant degeneration is unknown but there have been reports[6-8] of patients who developed rectal cancer during or after long-term therapy for adenomatous polyposis. A more recent, placebo-controlled trial[9] has also reported that sulindac did not reduce the development of adenomas in patients with familial adenomatous polyposis. Some[1,9] consider that sulindac is unlikely to replace surgery as primary therapy for familial adenomatous polyposis.

A sulfone metabolite of sulindac, exisulind (p.720) has also been investigated for the treatment of familial adenomatous polyposis.

Sulindac has also been reported to have produced beneficial effects in a patient with duodenal polyps associated with Gardner's syndrome[10] but a placebo-controlled study has suggested that it may not be effective against sporadic type colonic polyps.[11]

For a discussion of evidence suggesting that regular use of NSAIDs may protect against various types of malignant neoplasms of the gastrointestinal tract, see Malignant Neoplasms in NSAIDs, p.100.

1. Giardiello FM, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328:** 1313–16.
2. Debinski HS, *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; **345:** 855–6.
3. Tonelli F, Valanzano R. Sulindac in familial adenomatous polyposis. *Lancet* 1993; **342:** 1120.
4. Labayle D, *et al.* Sulindac in familial adenomatous polyposis. *Lancet* 1994; **343:** 417–18.
5. Keller JJ, *et al.* Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac. *Gut* 1999; **45:** 822–8.
6. Thorson AG, *et al.* Rectal cancer in FAP patient after sulindac. *Lancet* 1994; **343:** 180.
7. Matsuhashi N, *et al.* Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. *Am J Gastroenterol* 1998; **93:** 2261–6.
8. Cruz-Correa M, *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002; **122:** 641–5.
9. Giardiello FM, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002; **346:** 1054–9.
10. Parker AL, *et al.* Disappearance of duodenal polyps in Gardner's syndrome with sulindac therapy. *Am J Gastroenterol* 1993; **88:** 93–4.
11. Ladenheim J, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995; **108:** 1083–7.

Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective $beta_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Sulindac has also been tried[1,2] as an alternative to indometacin as it appears to have little placental transfer and may therefore have fewer fetal adverse effects.[1] However, the authors of a subsequent study suggested that sulindac had many of the same adverse fetal effects as indometacin and its use could only be described as investigational.[3] A study[4] using relatively low doses of sulindac (100 mg twice daily) did not note any significant fetal or maternal adverse effects but also found the drug to be ineffective in extending gestation or improving outcome.

1. Carlan SJ, *et al.* Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. *Obstet Gynecol* 1992; **79:** 223–8.
2. Carlan SJ, *et al.* Outpatient oral sulindac to prevent recurrence of preterm labor. *Obstet Gynecol* 1995; **85:** 769–74.
3. Kramer WB, *et al.* A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999; **180:** 396–401.
4. Humphrey RG, *et al.* Sulindac to prevent recurrent preterm labor: a randomized controlled trial. *Obstet Gynecol* 2001; **98:** 555–62.

Preparations

BP 2008: Sulindac Tablets;
USP 31: Sulindac Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Aclin; Clinoril†; ***Austria:*** Clinoril; ***Belg.:*** Clinoril; ***Canad.:*** Apo-Sulin; Novo-Sundac; ***Cz.:*** Clinoril†; ***Denm.:*** Clinoril†; ***Fr.:*** Arthrocine; ***Hong Kong:*** Aclin; Clinoril; ***Irl.:*** Clinoril; ***Ital.:*** Algocetil; Clinoril; Sulen†; ***Malaysia:*** Aclin†; Apo-Sulin†; Clinoril†; ***Mex.:*** Atriser; Bio-Dac; Clinoril; Clison; Copal; Kenalin; Renidac; Sulifur; Vindacin; ***Norw.:*** Clinoril; ***NZ:*** Clinoril; Daclin; ***Port.:*** Artribid; ***Singapore:*** Apo-Sulin; ***Spain:*** Sulindal; ***Swed.:*** Clinoril; ***Switz.:*** Clinoril†; ***Thai.:*** Cenlidac; Clinoril; ***UK:*** Clinoril; ***USA:*** Clinoril; ***Venez.:*** Clinoril†.

Superoxide Dismutase

SOD; Superóxido dismutasa.

Description. Superoxide dismutase represents a group of water-soluble protein congeners widely distributed in nature which catalyse the conversion of superoxide radicals to peroxide. Several different forms exist, which vary in their metal content; forms containing copper or copper and zinc are common.

Orgotein *(BAN, USAN, rINN)*

Bovine Superoxide Dismutase; Orgoteiini; Orgoteína; Orgotéine; Orgoteinum; Ormetein.

Орготеин

CAS — 9016-01-7.
ATC — M01AX14.
ATC Vet — QM01AX14.

Description. Orgotein is a superoxide dismutase produced from beef liver as Cu-Zn mixed chelate. Mol. wt about 33 000 with a compact conformation maintained by about 4 gram-atoms of chelated divalent metal.

Pegorgotein *(USAN, rINN)*

Pegorgoteína; Pégorgotéine; Pegorgoteinum; PEG-SOD; Win-22118.

Пэгоротеин

CAS — 155773-57-2.

Description. Pegorgotein is a superoxide dismutase conjugated with polyethylene glycol to prolong its duration of action.

Sudismase *(rINN)*

Sudismasa; Sudismasum.

Судизмаза

CAS — 110294-55-8.

Description. Sudismase is a human *N*-acetylsuperoxide dismutase produced by recombinant DNA technology and containing a copper and zinc prosthetic group.

Adverse Effects

Anaphylaxis and other hypersensitivity reactions, sometimes fatal, have been reported with orgotein. Local reactions and pain may occur at the site of injection of orgotein.

Pharmacokinetics

◊ References.

1. Tsao C, *et al.* Pharmacokinetics of recombinant human superoxide dismutase in healthy volunteers. *Clin Pharmacol Ther* 1991; **50:** 713–20.
2. Uematsu T, *et al.* Pharmacokinetics and safety of intravenous recombinant human superoxide dismutase (NK341) in healthy subjects. *Int J Clin Pharmacol Ther* 1994; **32:** 638–41.
3. Jadot G, *et al.* Clinical pharmacokinetics and delivery of bovine superoxide dismutase. *Clin Pharmacokinet* 1995; **28:** 17–25.
4. Rosenfeld WN, *et al.* Safety and pharmacokinetics of recombinant human superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1996; **97:** 811–17.
5. Davis JM, *et al.* Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1997; **100:** 24–30.
6. Schwedhelm E, *et al.* Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. *Clin Pharmacokinet* 2003; **42:** 437–59.

Uses and Administration

Superoxide dismutases have anti-inflammatory properties. Orgotein, a bovine derived superoxide dismutase, has been given by local injection, into the joints for degenerative joint disorders, but hypersensitivity reactions have limited its use. It has also been tried for the amelioration of adverse effects from radiotherapy. Forms of human superoxide dismutase derived by recombinant DNA technology have been developed.