Pregnancy. Although there has been a report of limb and ear deformities in the infant of a woman given cytarabine at the estimated time of conception and 4 to 8 weeks later,[1] no congenital abnormalities were noted in 17 infants, 5 therapeutic abortions, and one still-birth (after pre-eclamptic toxaemia) resulting from over 20 known cases in which cytarabine was given during pregnancy.[2]

1. Wagner VM, *et al.* Congenital abnormalities in baby born to cytarabine treated mother. *Lancet* 1980; **ii:** 98–9.
2. Morgenstern G. Cytarabine in pregnancy. *Lancet* 1980; **ii:** 259.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antifungals. Cytarabine has been reported to inhibit the action of *flucytosine*—see p.534.

Antineoplastics. Acute pancreatitis has been reported in patients given cytarabine who had previously received *asparaginase* therapy.[1] Subclinical damage to the pancreas by asparaginase may have rendered it susceptible to cytarabine.

For a report of hepatic dysfunction in patients who had received cytarabine and *daunorubicin* see under Daunorubicin Hydrochloride, p.709.

Giving cytarabine after *fludarabine* is reported to result in a five-fold increase in intracellular cytarabine concentrations in leukaemic cells,[2] producing improved clinical response rates.

1. Altman AJ, *et al.* Acute pancreatitis in association with cytosine arabinoside therapy. *Cancer* 1982; **49:** 1384–6.
2. Avramis VI, *et al.* Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. *Clin Cancer Res* 1998; **4:** 45–52.

Pharmacokinetics

Cytarabine is not effective orally due to rapid deamination in the gastrointestinal tract; less than 20% of an oral dose is absorbed. After intravenous injection it disappears rapidly from the plasma with an initial half-life of about 10 minutes; the terminal elimination half-life ranges from 1 to 3 hours. It is converted by phosphorylation to an active form, which is rapidly deaminated, mainly in the liver and the kidneys, to inactive 1-β-D-arabinofuranosyluracil (uracil arabinoside, ara-U). The majority of an intravenous dose is excreted in the urine within 24 hours, mostly as the inactive metabolite with about 10% as unchanged cytarabine.

There is only moderate diffusion of cytarabine across the blood-brain barrier after intravenous injection, but, because of low deaminase activity in the CSF, concentrations achieved after continuous intravenous infusion or intrathecal injection are maintained for longer in the CSF than are those in plasma, with a terminal elimination half-life of 3.5 hours. After intrathecal doses of the liposomal formulation, a terminal elimination half-life of 100 to 263 hours was seen. Cytarabine also crosses the placenta.

◊ References.

1. Slevin ML, *et al.* The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. *Br J Clin Pharmacol* 1981; **12:** 507–10.
2. DeAngelis LM, *et al.* Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992; **29:** 173–7.
3. Hamada A, *et al.* Clinical pharmacokinetics of cytarabine formulations. *Clin Pharmacokinet* 2002; **41:** 705–18.

Uses and Administration

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits the synthesis of deoxyribonucleic acid. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Cytarabine is one of the mainstays of the treatment of acute myeloid leukaemias, together with an anthracycline, (see p.652), and is used for the prophylaxis of meningeal leukaemia, as well as in regimens for consolidation, in patients with acute lymphoblastic leukaemia (p.651). It has also been investigated in the blast crisis of chronic myeloid leukaemia (p.653) and the myelodysplasias (p.654) (see also Low-dose Therapy, under Administration, below). It may be used in salvage regimens for Hodgkin's disease (p.655), as part of the complex regimens sometimes employed in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p.656), and for meningeal lymphoma.

Cytarabine is usually given intravenously. Higher doses can be tolerated when given by rapid injection rather than slow infusion, because of the rapid clearance of cytarabine, but there is little evidence of clinical advantage either way. Cytarabine may be given intrathecally for leukaemic or lymphomatous meningitis.

For the induction of remission in adults and children with acute leukaemias many dosage regimens have been used: 100 mg/m^2 twice daily by rapid intravenous injection, or 100 mg/m^2 daily by continuous intravenous infusion, have often been employed. These doses are generally given for 5 to 10 days, depending on therapeutic response and toxicity. Children reportedly tolerate high doses better than adults.

For maintenance 1 to 1.5 mg/kg once or twice weekly has been given intravenously or subcutaneously; other regimens have been used.

In the treatment of refractory disease high-dose regimens have been used, with cytarabine given in doses of up to 3 g/m^2 every 12 hours for up to 6 days. These doses should be given by intravenous infusion over at least 1 hour.

In leukaemic meningitis cytarabine has been given intrathecally, often in a dose of 10 to 30 mg/m^2 every 2 to 4 days; it has also been used prophylactically. A liposomal formulation is available in some countries for intrathecal use, and permits less frequent dosing because of its longer duration of action: the recommended dose for lymphomatous meningitis is 50 mg intrathecally every 2 weeks for 5 doses then every 4 weeks for 5 doses.

White cell and platelet counts should be determined regularly during treatment with cytarabine and therapy should be stopped immediately if the count falls rapidly or to low values (see also Bone-marrow Depression, p.639).

Cytarabine ocfosfate is an orally active prodrug of cytarabine under investigation in chronic myeloid leukaemia.

Administration. ***Intrathecal.*** Intrathecal doses of the liposomal formulation of cytarabine result in prolonged drug exposure when compared with intrathecal doses of the conventional formulation (see Pharmacokinetics, above). In a randomised study,[1] the liposomal formulation given once every 2 weeks produced a higher response rate and improved Karnofsky score compared with the conventional formulation given twice a week in patients with lymphomatous meningitis secondary to lymphoma. The use of liposomal formulations intrathecally to treat leukaemic or lymphomatous meningitis has been reviewed.[2,3]

1. Glantz MJ, *et al.* Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol* 1999; **17:** 3110–16.
2. Rueda Domínguez A, *et al.* Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 2005; **7:** 232–8.
3. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother* 2008; **9:** 301–9.

Low-dose therapy. Because of initial suggestions that low doses of cytarabine might induce differentiation and maturation of leukaemic cells, low-dose therapy has been tried in patients with myelodysplastic syndrome and acute myeloid leukaemia. Although complete remission may occur in about 20% of patients with myelodysplastic syndromes a similar proportion succumb to treatment-related mortality, and remissions do not appear to be particularly long-lasting. Bone-marrow suppression may be marked even at these doses.[1] Low-dose subcutaneous cytarabine (20 mg twice daily for 10 days, at intervals of 4 to 6 weeks) was found to be superior to hydroxycarbamide (with or without all-trans retinoic acid) in elderly patients with acute myeloid leukaemia. Although the authors considered the prognosis for these patients to still be unsatisfactory, they suggested that therapy with low-dose cytarabine could represent a baseline against which other promising treatments might be compared.[2]

1. Aul C, Gattermann N. The role of low-dose chemotherapy in myelodysplastic syndrome. *Leuk Res* 1992; **16:** 207–15.
2. Burnett AK, *et al.* The National Cancer Research Institute Haematological Oncology Study Group Adult Leukemia Working Party. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; **109:** 1114–24.

Leukoencephalopathy. There are anecdotal reports[1-3] of marked improvement in patients with progressive multifocal leukoencephalopathy secondary to AIDS or chemotherapy-induced immunosuppression who were given intravenous or intrathecal cytarabine. However, a randomised multicentre study[4] indicated that cytarabine was ineffective and had no role in this condition (see also Infections in Immunocompromised Patients, p.859). Others[5] have suggested that even intrathecal dosage may not provide adequate delivery of cytarabine to target cells, and that delivering the drug directly into the brain under pressure might be an alternative. Cytarabine has also been used with cidofovir.[6]

1. O'Riordan T, *et al.* Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* 1990; **20:** 51–4.
2. Portegies P, *et al.* Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1991; **337:** 680–1.
3. Nicoli F, *et al.* Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1992; **339:** 306.
4. Hall CD, *et al.* Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 1345–51.
5. Levy RM, *et al.* Convection-enhanced intraparenchymal delivery (CEID) of cytosine arabinoside (AraC) for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). *J Neurovirol* 2001; **7:** 382–5.
6. Terrier B, *et al.* Leucoencéphalite multifocale progressive en dehors du sida: efficacité de l'association cytarabine-cidofovir. *Rev Med Interne* 2007; **28:** 488–91.

Preparations

BP 2008: Cytarabine Injection;
USP 31: Cytarabine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aracytin†; Citagenin; ***Austria:*** Alexan; ARA-cell; ***Belg.:*** Cyta-Cell; Cytosar; DepoCyte; ***Braz.:*** Aracytin; Citab†; Citarax; Darbin; Serotabir†; Tabine†; ***Canad.:*** Cytosar; DepoCyt†; ***Chile:*** Alexan; Aracytin; Laracit; ***Cz.:*** Alcysten†; Alexan; Cytosar; DepoCyte; ***Denm.:*** Arabine; Cytosar†; DepoCyte; ***Fin.:*** Arabine; DepoCyte; ***Fr.:*** Aracytine; DepoCyte; ***Ger.:*** Alexan; ARA-cell; DepoCyte; Udicil; ***Gr.:*** Aracytin; Citabion; ***Hong Kong:*** Alexan; Cytosar; ***Hung.:*** Alexan; Cytosar; ***India:*** Biobin; Cytarine; ***Indon.:*** Cytosar-U; ***Irl.:*** Cytosar†; ***Israel:*** Alexan; Cytosar; ***Ital.:*** Aracytin; DepoCyte; Erpalfa; ***Jpn:*** Cylocide; Starasid; ***Malaysia:*** Cytosar-U; ***Mex.:*** Alexan†; Cytosar; Ifarab; Laracit; Medsara; Novumtrax; ***Neth.:*** Alexan; Cytosar; DepoCyte; ***Norw.:*** Cytosar†; DepoCyte; ***Philipp.:*** Cytosar-U; Leucyt; Tabine; ***Pol.:*** Alexan; Cytosar; DepoCyte; ***Port.:*** Alexan†; ARA-cell; Citaloxan; Cytosar; Depocyte; ***Rus.:*** Alexan (Алексан); Cytosar (Цитозар); ***S.Afr.:*** Alexan; Cytosar; ***Singapore:*** Alexan†; Cytosar†; ***Spain:*** DepoCyte; ***Swed.:*** Arabine; Cytosar†; DepoCyte; ***Switz.:*** Cytosar; ***Thai.:*** Alexan†; Cytarine; Cytosar; ***Turk.:*** Alexan; ARA-cell; Cytonal; ***UK:*** DepoCyte; ***USA:*** Cytosar-U†; DepoCyt; ***Venez.:*** Cytosar.

Dacarbazine *(BAN, USAN, rINN)*

Dacarbazina; Dacarbazinum; Dakarbatsiini; Dakarbazin; DIC; DTIC; Imidazole Carboxamide; NSC-45388; WR-139007. 5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide.

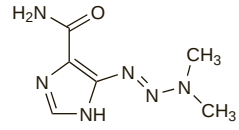
Дакарбазин

$C_6H_{10}N_6O$ = 182.2.

CAS — 4342-03-4 (dacarbazine); 64038-56-8 (dacarbazine citrate).

ATC — L01AX04.

ATC Vet — QL01AX04.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Dacarbazine). A white or slightly yellowish, crystalline powder. Slightly soluble in water and in anhydrous alcohol; practically insoluble in dichloromethane. Store at 2° to 8°. Protect from light.

USP 31 (Dacarbazine). Store in airtight containers at 2° to 8°. Protect from light.

Incompatibility. Dacarbazine has been reported to be incompatible with hydrocortisone sodium succinate but not with the sodium phosphate.[1] It has been reported to be incompatible with heparin,[2] although only with concentrated dacarbazine solutions (25 mg/mL).

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Nelson RW, *et al.* Visual incompatibility of dacarbazine and heparin. *Am J Hosp Pharm* 1987; **44:** 2028.

Stability. References to the photodegradation of dacarbazine solution.[1-4] Dacarbazine is more sensitive to direct sunlight than to artificial lighting or diffuse daylight.

1. Stevens MFG, Peatey L. Photodegradation of solutions of the antitumour drug DTIC. *J Pharm Pharmacol* 1978; **30** (suppl): 47P.
2. Horton JK, Stevens MFG. Search for drug interactions between the antitumour agent DTIC and other cytotoxic agents. *J Pharm Pharmacol* 1979; **31** (suppl): 64P.
3. Kirk B. The evaluation of a light-protecting giving set. *Intensive Therapy Clin Monit* 1987; **8:** 78–86.
4. El Aatmani M, *et al.* Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2002; **59:** 1351–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Leucopenia and thrombocytopenia with dacarbazine, although usually moderate, may be severe. The nadir of the white cell count usually occurs 21 to 25 days after a dose. Anorexia, nausea, and vomiting occur in more than 90% of patients initially but tolerance may develop after repeated doses. Less frequent adverse effects include diarrhoea, skin reactions, alopecia, a flu-like syndrome, facial flushing and paraesthesia, headache, blurred vision, seizures, and rare but potentially fatal hepatotoxicity. There may be local pain at the injection site; extravasation produces pain and tissue damage. Anaphylaxis has occurred occasionally.

Dacarbazine should be used with caution in hepatic and renal impairment, and consideration given to reducing the dose. Haematological monitoring is required during therapy. Dacarbazine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. A report[1] of haemorrhagic cystitis associated with dacarbazine treatment for melanoma. The patient developed gross haematuria with inflammation and oedema of the bladder wall 2 weeks after completing 3 cycles of monotherapy with dacarbazine; the condition responded to symptomatic management with saline lavage and oral and intravenous hydration. Two subsequent transient episodes of haematuria resolved spontaneously.

1. Mohammadianpanah M, *et al.* Hemorrhagic cystitis in a patient receiving conventional doses of dacarbazine for metastatic malignant melanoma: case report and review of the literature. *Clin Ther* 2007; **29:** 1161–5.

Effects on the liver. Dacarbazine has been associated with fatal hepatic vascular toxicity, caused by thrombosis of the hepatic veins, necrosis, and extensive haemorrhage.[1] As the reaction usually occurs during the second course of dacarbazine it is thought to be immune mediated, and early corticosteroid treatment has been tried with a few reported cases of patient survival.[2] Other adverse hepatic effects have included[3] necrosis without inflammation, granulomatous hepatitis, and acute toxic hepatitis during the first course of dacarbazine. Morphological studies have suggested that dacarbazine may exert a toxic effect on the microfilamentous cytoskeleton of the hepatocytes.[3]

1. Ceci G, *et al.* Fatal hepatic vascular toxicity of DTIC: is it really a rare event? *Cancer* 1988; **61:** 1988–91.
2. Herishanu Y, *et al.* The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine. *Anticancer Drugs* 2002; **13:** 177–9.
3. Dancygier H, *et al.* Dacarbazine (DTIC)-induced human liver injury. *Gut* 1982; **23:** A447.

Handling. Dacarbazine is irritant; avoid contact with skin and mucous membranes.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Levodopa. For a report of dacarbazine reducing the effects of levodopa, see Antineoplastics, p.807.

Pharmacokinetics

Dacarbazine is poorly absorbed from the gastrointestinal tract. On intravenous injection it is rapidly distributed with an initial plasma half-life of about 20 minutes; the terminal half-life is reported to be about 5 hours. The volume of distribution is larger than body water content, suggesting localisation in some body tissues, probably mainly the liver. Only about 5% is bound to plasma protein. It crosses the blood-brain barrier to a limited extent; concentrations in CSF are about 14% of those in plasma. Dacarbazine is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP2E1 (and possibly in the tissues by CYP1A1) to its active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), which spontaneously decomposes to the major metabolite 5-aminoimidazole-4-carboxamide (AIC). About half of a dose is excreted unchanged in the urine by tubular secretion.

Uses and Administration

Dacarbazine is a cell-cycle non-specific antineoplastic that is thought to function as an alkylating agent after it has been activated in the liver. Dacarbazine is used mainly in the treatment of metastatic malignant melanoma (p.673). It is also given to patients with Hodgkin's disease (p.655), notably with doxorubicin, bleomycin, and vinblastine (ABVD). Dacarbazine is used with other drugs in the treatment of soft-tissue sarcoma (p.676), and may be given in neuroblastoma (p.674), Kaposi's sarcoma (p.675), and other tumours.

Dacarbazine is given by the intravenous route. Injections may be given over 1 to 2 minutes. The reconstituted solution can be further diluted with up to 300 mL of glucose 5% or sodium chloride 0.9% and given by infusion over 15 to 30 minutes.

Dacarbazine is licensed for use as a single agent for **metastatic melanoma** in doses of 2 to 4.5 mg/kg daily for 10 days, repeated at intervals of 4 weeks, or 200 to 250 mg/m^2 daily for 5 days, repeated at intervals of 3 weeks. It can also be given in a dose of 850 mg/m^2 by intravenous infusion at 3-week intervals. In the treatment of **Hodgkin's disease** doses of 150 mg/m^2 daily for 5 days repeated every 4 weeks, or 375 mg/m^2 every 15 days have been given with other agents. In the treatment of **soft-tissue sarcoma**, dacarbazine 250 mg/m^2 is given daily for 5 days repeated every 3 weeks; it is usually given with doxorubicin.

◊ References.

1. D'Incan M, Souteyrand P. Dacarbazine (Déticène). *Ann Dermatol Venereol* 2001; **128:** 517–25.
2. Eggermont AMM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? *Eur J Cancer* 2004; **40:** 1825–36.

Preparations

BP 2008: Dacarbazine Injection;
USP 31: Dacarbazine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Deticene†; Oncocarbil; ***Austral.:*** DTIC; ***Austria:*** DTIC-Dome; ***Braz.:*** Asercit†; Dacarb; ***Canad.:*** DTIC†; ***Chile:*** Deticene; ***Fin.:*** Dacatic; ***Fr.:*** Deticene; ***Ger.:*** Detimedac; ***Gr.:*** Dacarbion; Deticene; ***India:*** Dacarin; Decarb; DTIC†; ***Israel:*** Deticene; ***Ital.:*** Deticene; ***Malaysia:*** DTI†; ***Mex.:*** Deticene†; Detilem; Ifadac; ***Neth.:*** Deticene; ***NZ:*** DTIC-Dome†; ***Philipp.:*** Duticin; ***Port.:*** Deticene; Fauldetic; ***S.Afr.:*** DTIC-Dome; ***Swed.:*** DTIC; ***Switz.:*** Dacin; DTIC; ***Turk.:*** Deticene; ***UK:*** DTIC-Dome†; ***USA:*** DTIC-Dome.

Dactinomycin *(BAN, USAN, rINN)*

Actinomycin C_1; Actinomycin D; Dactinomicina; Dactinomycine; Dactinomycinum; Daktinomisin; Daktinomycin; Daktinomysiini; Daktynomycyna; Meractinomycin; NSC-3053. $N^{2.1}$,$N^{2'.1'}$-(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyldicarbonyl)-bis[threonyl-D-valylprolyl(*N*-methylglycyl)(*N*-methylvaline) 1.5–3.1-lactone].

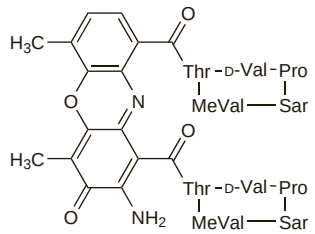
Дактиномицин

$C_{62}H_{86}N_{12}O_{16}$ = 1255.4.

CAS — 50-76-0.

ATC — L01DA01.

ATC Vet — QL01DA01.



Description. Dactinomycin is an antineoplastic antibiotic produced by *Streptomyces parvulus* and other species of *Streptomyces.*

Cactinomycin (actinomycin C; HBF-386; NSC-18268) is a mixture of dactinomycin (actinomycin D) (10%), actinomycin C_2 (45%), and actinomycin C_3 (45%) produced by *Streptomyces chrysomallus.*

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

USP 31 (Dactinomycin). A bright red, somewhat hygroscopic, crystalline powder, affected by light and heat. It has a potency of not less than 950 and not more than 1030 micrograms/mg, calculated on the dried basis. Soluble in water at 10° and slightly soluble in water at 37°; freely soluble in alcohol; very slightly soluble in ether. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adsorption. Dactinomycin binds to cellulose ester filters,[1] and such filtration should be avoided.[2] Although it has been suggested that significant amounts of drug may be adsorbed to glass or plastic,[3] dactinomycin is reportedly compatible with glass and PVC infusion containers,[4] and giving into the tubing of a fast-running intravenous infusion is recommended—see Uses and Administration, below.

1. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Rapp RP, *et al.* Guidelines for the administration of commonly-used intravenous drugs—1984 update. *Drug Intell Clin Pharm* 1984; **18:** 218–32.
4. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Apart from nausea and vomiting adverse effects are often delayed, beginning 2 to 4 days after the completion of a course of treatment and reaching a maximum after 1 to 2 weeks. Fatalities have occurred. Bone-marrow depression and gastrointestinal effects (particularly stomatitis and diarrhoea) may prove dose-limiting. Bone-marrow depression is apparent 1 to 7 days after therapy and may be manifest first as thrombocytopenia; the nadir of the platelet and white cell counts usually occurs within 14 to 21 days, with recovery in 21 to 25 days. Other adverse effects include oral and gastrointestinal effects such as cheilitis, oesophagitis, gastrointestinal ulceration, and proctitis; fever, malaise, hypocalcaemia, erythema, myalgia, alopecia, pneumonitis, and kidney and liver abnormalities. Anaphylactoid reactions have occurred. Dactinomycin is very irritant and extravasation results in severe tissue damage.

The effects of radiotherapy are enhanced by dactinomycin and severe reactions may follow the use of high doses. Erythema and pigmentation of the skin may occur in areas previously irradiated. An increase in incidence of second primary tumours has been seen in patients treated with radiation and dactinomycin.

Dactinomycin should not be given to patients with varicella or herpes zoster, as severe and even fatal systemic disease may occur. Its use is best avoided in infants under 1 year as they are reported to be highly susceptible to the toxicity of dactinomycin. Blood counts and renal and hepatic function should be monitored frequently.

Effects on the liver. Although doses less than about 50 micrograms/kg or 1.5 mg/m^2 do not seem to be associated with an unacceptable degree of hepatotoxicity,[1] giving dactinomycin as a single dose of 60 micrograms/kg (about 1.8 mg/m^2) every 3 weeks to children with Wilms' tumour was associated with a high incidence of severe hepatotoxicity;[2] reduction of the dose to 45 micrograms/kg every 3 weeks reduced this incidence to levels comparable with a standard regimen of 15 micrograms/kg daily for 5 successive days.[3] Others have not seen such a high incidence of hepatotoxicity with doses of 60 micrograms/kg (despite some raised liver enzyme values), but in this case the high dose was given only every 6 weeks.[4] In general, dactinomycin should be given with caution to children with a history of antecedent liver damage, including abdominal irradiation or recent halothane anaesthesia.[1]

Reversible veno-occlusive disease has been seen particularly in children with Wilms' tumour who have received dactinomycin and vincristine. One study[5] found age of less than 1 year to be a risk factor and a study in children with rhabdomyosarcoma given dactinomycin, vincristine, and cyclophosphamide also found that young age (under 3 years) was associated with a greater risk of severe hepatic toxicity.[6] A literature review[7] noted a significant predominance of veno-occlusive disease in right-sided Wilms' tumour, possibly because the tumour mass could interfere with blood flow in the hepatic veins, which might make the liver more susceptible to the effects of dactinomycin.

1. Pritchard J, *et al.* Hepatotoxicity of actinomycin-D. *Lancet* 1989; **i:** 168.
2. D'Angio GJ. Hepatotoxicity with actinomycin D. *Lancet* 1987; **ii:** 104.
3. D'Angio GJ. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.
4. de Camargo B. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.