cal carcinoma, although other drugs are usually preferred, and has also been tried in other malignant neoplasms, notably those of the brain.

In addition to myelosuppression, which is usually dose-limiting, and manifests chiefly as leucopenia and thrombocytopenia, adverse effects include gastrointestinal disturbances, skin rashes, grey pigmentation of the skin, transient disturbances of hepatic function, elevated blood-urea nitrogen (BUN), and hypersensitivity reactions. Blood counts should be taken regularly during treatment and mitolactol withdrawn if bone-marrow depression occurs.

Mitomycin *(BAN, USAN, rINN)*

Mitomicina; Mitomicinas; Mitomicinum; Mitomisin; Mitomycin C; Mitomycine; Mitomycine C; Mitomycinum; Mitomysiini; NSC-26980. 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-hydroxymethyl-8a-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione carbamate; (1*S*,2*S*,9*S*,9a*R*)-7-Amino-2,3,5,8,9,9a-hexahydro-9a-methoxy-6-methyl-5,8-dioxo-1,2-epimino-1-*H*-pyrrolo[1,2-*a*]indol-9-ylmethyl carbamate.

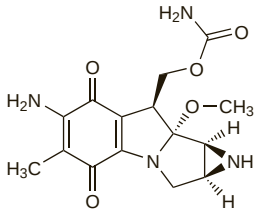
Митомицин

$C_{15}H_{18}N_4O_5$ = 334.3.

CAS — 50-07-7.

ATC — L01DC03.

ATC Vet — QL01DC03.



Description. Mitomycin is an antineoplastic antibiotic produced by the growth of *Streptomyces caespitosus*.

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

Ph. Eur. 6.2 (Mitomycin). A substance produced by a strain of *Streptomyces caespitotus*. Blue-violet crystals or crystalline powder. Slightly soluble in water and in acetone; freely soluble in dimethylacetamide; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 7.5. Protect from light.

USP 31 (Mitomycin). A blue-violet crystalline powder. It has a potency of not less than 970 micrograms/mg. Slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. A 0.5% suspension in water has a pH of 6.0 to 7.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Mitomycin may be incompatible with drugs that are acid in solution—for a report of incompatibility with topotecan, see p.780.

Stability. Mitomycin undergoes degradation in acid solution,[1] and two studies[2,3] suggested that mitomycin was much less stable in glucose 5% injection than in sodium chloride 0.9%. These findings were queried by a manufacturer (*Bristol, USA*) whose own results suggested[4] that mitomycin was stable for 48 hours in glucose injection 5% at 25°, and it is uncertain whether different manufacturers' formulations differ in stability, or, as has been suggested, that an unsuitable assay was used by the manufacturer to measure stability.[5]

1. Beijnen JH, Underberg WJM. Degradation of mitomycin C in acidic solution. *Int J Pharmaceutics* 1985; **24:** 219–29.
2. Benvenuto JA, *et al.* Stability and compatibility of antitumour agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
3. Quebbeman EJ, *et al.* Stability of mitomycin admixtures. *Am J Hosp Pharm* 1985; **42:** 1750–4.
4. Keller JH. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 59,64.
5. Quebbeman EJ, Hoffman NE. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 64.

Adverse Effects, Treatment, and Precautions

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

The main adverse effect of mitomycin is delayed cumulative bone-marrow suppression. Profound leucopenia and thrombocytopenia occurs after about 4 weeks with recovery in about 8 to 10 weeks after a dose. Blood counts may not recover in about one-quarter of patients. Other serious adverse effects include renal damage and pulmonary reactions; a potentially fatal haemolytic-uraemic syndrome has been reported in some patients. US licensed product information states that the degree of renal impairment does not appear to be related to dose or duration of therapy although it has been suggested that the incidence of renal toxicity is greatly increased if the total cumulative dose exceeds 120 mg (see also Effects on the Kidneys, below). Gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and rarely cardiotoxicity may also occur. Local tissue necrosis, ulceration, and cellulitis may follow extravasation.

Mitomycin is contra-indicated in patients with impaired renal function or coagulation disorders. Renal function should be tested before beginning treatment and after each course.

Effects on the bladder. Intravesical instillation of mitomycin after resection of superficial bladder tumours has led to the development of indolent asymptomatic ulcers at the resection site which may persist for months, and must be distinguished from persistent infiltrating bladder cancer.[1,2] Persistent ulceration, inflammation, necrosis, and pain has also occurred, possibly because of mitomycin extravasation at the resection site.[3] There are also a few reports[4] of eosinophilic cystitis, in which eosinophilic infiltration of the mucosa and muscle were accompanied by oedema, inflammation, muscle necrosis and fibrosis. Severe bladder contracture is a rare, and often irreversible, complication of intravesical mitomycin;[5] urinary diversion may be required in cases of intolerable urinary frequency.[6] Formation of papillary-like calcifications at the resection site,[7] and calcification of the bladder wall have also been described after the use of mitomycin for superficial transitional cell carcinoma of the bladder.

See also under Effects on the Skin, below.

1. Richards B, Tolley D. Benign ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 45.
2. Hetherington JW, Whelan P. Persistent ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 324.
3. Cliff AM, *et al.* Perivesical inflammation after early mitomycin C instillation. *BJU Int* 2000; **85:** 556–7.
4. Ülker V, *et al.* Eosinophilic cystitis induced by mitomycin-C. *Int Urol Nephrol* 1996; **28:** 755–9.
5. Punga-Maole ML, *et al.* Rétraction vésicale, complication de la chimioprophylaxie du cancer vésical superficiel par mitomycine C endovésicale: a propos d'un cas et revue de la littérature. *Prog Urol* 1995; **5:** 580–5.
6. Wajsman Z, *et al.* Severely contracted bladder following intravesical mitomycin C therapy. *J Urol (Baltimore)* 1983; **130:** 340–1.
7. Fiore AA, *et al.* Papillary-like bladder calcifications following intravesical mitomycin C: a case report. *Minerva Urol Nefrol* 1993; **45:** 171–3.

Effects on the eyes. Early complications after the topical use of mitomycin with glaucoma filtering surgery (see Glaucoma, below) include hypotony, shallow anterior chamber, cataract formation, choroidal effusions, hypotonous maculopathy, and suprachoroidal haemorrhage.[1] Late complications include bleb leak, blebitis, and endophthalmitis.[2] Complications from the topical use of mitomycin with or after pterygium surgery (see Pterygium, below) commonly include irritation and photophobia. Other effects include delayed epithelial healing, avascularity of the sclera and cornea, scleral calcification and ulceration, necrotising scleritis, corneal or scleral perforation, iridocyclitis, cataract formation, glaucoma, and symblepharon.[1] Some of these effects may be severe and sight-threatening, and require further surgery.[3] Complications most commonly reported after the use of topical mitomycin in ocular surface neoplasia were hypersensitivity reactions and epiphora (an overflow of tears) secondary to stenosis of the lachrymal punctum.[4]

1. Hardten DR, Samuelson TW. Ocular toxicity of mitomycin-C. *Int Ophthalmol Clin* 1999; **39:** 79–90.
2. DeBry PW, *et al.* Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. *Arch Ophthalmol* 2002; **120:** 297–300.
3. Rubinfeld RS, *et al.* Serious complications of topical mitomycin C after pterygium surgery. *Ophthalmology* 1992; **99:** 1647–54.
4. Khong JJ, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006; **90:** 819–22.

Effects on the kidneys. A syndrome of thrombotic microangiopathy resembling the haemolytic-uraemic syndrome has been seen in patients receiving mitomycin, either alone[1] or more often with other drugs, particularly fluorouracil[2] or tamoxifen.[3,4] The syndrome is characterised by haemolytic anaemia, thrombocytopenia, and progressive renal failure, and may be accompanied by hypertension, pulmonary oedema, and neurological effects including confusion, headache, and seizures.[1,2] Onset is usually delayed, sometimes occurring several months after the end of a course of mitomycin.[1,2]

There is some uncertainty as to whether mitomycin dose is significant, but one study[1] found that all of 25 cases they reported had received total doses of 70 mg or more, and another[2] reported that 74 of 83 cases had received 60 mg or more.

Symptoms may be exacerbated by blood transfusions.[2] The use of erythropoietin allowed the cessation of blood transfusion, with subsequent haematological improvement and slower progression of chronic renal failure in one case report.[5] Plasma exchange has been suggested as possibly helpful,[1] although only a minority of patients may benefit from this treatment.[2] Captopril therapy may also be useful.[6]

1. Cordonnier D, *et al.* La néphrotoxicité de la mitomycine C (à propos de 25 observations): résultats d'une enquête multicentrique organisée par la société de néphrologie. *Nephrologie* 1985; **6:** 19–26.
2. Lesesne JB, *et al.* Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; **7:** 781–9.
3. Montes A, *et al.* A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. *Eur J Cancer* 1993; **29**A: 1854–7.
4. Ellis PA, *et al.* Haemolytic uraemic syndrome in a patient with lung cancer: further evidence for a toxic interaction between mitomycin-C and tamoxifen. *Clin Oncol (R Coll Radiol)* 1996; **8:** 402–3.
5. Catalano C, *et al.* Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron* 2002; **91:** 324–6.
6. Schiebe ME, *et al.* Mitomycin C-related hemolytic uremic syndrome in cancer patients. *Anticancer Drugs* 1998; **9:** 433–5.

Effects on the liver. Hepatic veno-occlusive disease developed in 6 of 29 patients given intensive mitomycin therapy and autologous bone marrow transplantation.[1] The effect was manifest as abdominal pain, hepatomegaly, and ascites, and liver failure was progressive and fatal in 3. A further patient, who had no symptoms, was found to have veno-occlusive disease at post mortem.

1. Lazarus HM, *et al.* Veno-occlusive disease of the liver after high-dose mitomycin C therapy and autologous bone marrow transplantation. *Cancer* 1982; **49:** 1789–95.

Effects on respiratory function. Mitomycin-induced pulmonary toxicity has been reviewed.[1,2] There have been reports of toxicity at total dosages as low as 20 mg/m^2 of mitomycin,[2] although others report[1] that the average cumulative dose associated with toxicity is 78 mg. Premedication with corticosteroids may reduce the incidence of lung toxicity.[2]

See also Effects on the Lungs, p.638. For reference to the respiratory effects of mitomycin used with a vinca alkaloid see Interactions, Antineoplastics, under Vinblastine Sulfate, p.786.

1. Linette DC, *et al.* Mitomycin-induced pulmonary toxicity: case report and review of the literature. *Ann Pharmacother* 1992; **26:** 481–4.
2. Okuno SH, Frytak S. Mitomycin lung toxicity: acute and chronic phases. *Am J Clin Oncol* 1997; **20:** 282–4.

Effects on the skin. Severe eczema of the hands and feet and generalised rash have been reported in patients receiving intravesical mitomycin.[1,2] These symptoms appear to be due to a delayed hypersensitivity (type IV) reaction,[1,2] which is probably also responsible for the bladder irritation and cystitis that may follow intravesical mitomycin[1] (see above). Leucocytoclastic vasculitis caused by an immune-complex mediated (type III) reaction and presenting as purpuric papules has also been described.[2]

1. Colver GB, *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; **122:** 217–24.
2. Kunkeler L, *et al.* Type III and type IV hypersensitivity reactions due to mitomycin C. *Contact Dermatitis* 2000; **42:** 74–6.

Interactions

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

Antineoplastics. Cardiotoxicity developed in 14 of 91 patients who received mitomycin therapy as second-line treatment for breast cancer after the failure of *doxorubicin*-containing regimens, compared with 3 of 89 similar patients whose second-line treatment did not include mitomycin.[1]

For reports of acute bronchospasm after injection of a *vinca alkaloid* in patients pretreated with mitomycin see Vinblastine Sulfate, p.786. For the increased risk of haemolytic-uraemic syndrome that may occur if mitomycin is given with *fluorouracil* or *tamoxifen* see under Effects on the Kidneys, above.

1. Buzdar AU, *et al.* Adriamycin and mitomycin C: possible synergistic cardiotoxicity. *Cancer Treat Rep* 1978; **62:** 1005–8.

Pharmacokinetics

Mitomycin disappears rapidly from the blood after intravenous injection with an initial (distribution) half-life of 17 minutes. It is widely distributed but does not appear to cross the blood-brain barrier. Mitomycin is metabolised mainly but not exclusively in the liver. The terminal half-life is about 50 minutes. After normal doses about 10% of a dose is excreted unchanged in the urine; small amounts are also present in bile and faeces. With increasing doses metabolic pathways are saturated, and more drug is excreted unchanged in the urine.

Uses and Administration

Mitomycin is a highly toxic antibiotic with antineoplastic properties. It acts as an alkylating agent after activation *in vivo* and suppresses the synthesis of nucleic acids. It is a cell-cycle non-specific agent, but is most active in the late G_1 and early S phases.

Mitomycin is used, with other antineoplastic agents, in the treatment of many solid tumours including those of the bladder, breast, cervix, eye, liver, lung, stomach, and prostate as indicated by the cross-references given below. Mitomycin has been tried in other neoplasms including those of the gastrointestinal tract, head and neck, pancreas, in melanoma, sarcomas, and in leukaemias.

Dosage regimens include an initial dose of 10 to 20 mg/m^2 intravenously; subsequent doses are repeated at intervals of 6 to 8 weeks if blood counts permit, and should be reduced according to the previous haematological response. Another suggested regimen is 2 mg/m^2 daily for 5 days, repeated after 2 days. Other regimens may be used, particularly in combination.

Doses are adjusted according to the effect on bone marrow and treatment should not be repeated until the leucocyte and platelet counts are above acceptable levels (see also Bone-marrow Depression, p.639).

Mitomycin is also used as a bladder instillation: 10 to 40 mg is instilled once weekly or three times a week for a total of 20 doses in the treatment of superficial bladder tumours. For the prevention of recurrent bladder tumours 20 mg may be instilled every 2 weeks, or 40 mg monthly or 3-monthly. Alternatively 4 to 10 mg may be instilled once weekly or three times a week. These doses are usually given in 10 to 40 mL of water for injection. The solution should be retained in the bladder for at least 1 hour.

Mitomycin has been given by the intra-arterial route in the treatment of liver tumours, sometimes as an infusion of microcapsules designed to produce localised embolisation.

Mitomycin is used for its effect on fibroblasts to improve outcomes and reduce scarring in certain types of surgery, notably in glaucoma (see below).

◊ References.

1. Abraham LM, *et al.* Mitomycin: clinical applications in ophthalmic practice. *Drugs* 2006; **66:** 321–40.
2. Bolenz C, *et al.* Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 1273–82.
3. Tabaee A, *et al.* Mitomycin C and endoscopic sinus surgery: where are we? *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 40–3.
4. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; **138:** 700–9.

Glaucoma. Mitomycin, like fluorouracil, is effective in improving the outcome of glaucoma filtering surgery in selected patients when used as an adjunct to prevent the formation of scar tissue (see p.1873). Fluorouracil is usually given as a regimen of multiple injections but mitomycin given as a single intra-operative topical application in usual concentrations ranging from 0.2 to 0.5 mg/mL appears to be of similar efficacy.[1,2] A systematic review of 11 studies concluded that intra-operative mitomycin reduced the chances of failure in high-risk patients, and in those having their first trabeculectomy.[3] However it was noted that the nature of the data might have led to overestimation of the effect and that there was some evidence of an increased risk of cataract with mitomycin. Late hypotony is also a problem.[4] For other potential complications see Effects on the Eye, above.

1. Skuta GL, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992; **99:** 438–44.
2. Katz GJ, *et al.* Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. *Ophthalmology* 1995; **102:** 1263–9.
3. Wilkins M, *et al.* Intra-operative mitomycin C for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/04/06).
4. Bindlish R, *et al.* Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up. *Ophthalmology* 2002; **109:** 1336–42.

Malignant neoplasms. Mitomycin is used in the prevention of recurrent bladder cancer (p.659), in the palliative therapy of advanced breast cancer (p.661), in malignancies of the cervix (p.663), eye (p.664), stomach and anus (p.664 and p.666), liver (p.667), and non-small cell lung cancer (p.668), and has been tried in advanced prostatic cancer (see p.671).

Pterygium. Pterygium is a degenerative condition of subconjunctival tissues that results in a vascularised overgrowth of the conjunctiva and cornea. It is cosmetically unappealing but does not usually require treatment. However, if it affects the pupillary area it can be treated surgically. Pterygium often recurs after removal and methods used to prevent recurrence include radiotherapy or the topical application of mitomycin or thiotepa.[1]

Thiotepa has been applied postoperatively as 0.05% eye drops for several weeks, but pterygium may still recur[2] and adverse effects include conjunctival injection, granuloma, hypertrophic conjunctiva, and black deposits in the conjunctival fornix.[1] Depigmentation of the eyelids may also be a problem, so patients should avoid direct sunlight during thiotepa use.[1]

Mitomycin has been applied topically to the surgical site, or given as eye drops postoperatively.[1] The optimal intra-operative exposure time and concentration are uncertain: concentrations of 0.02 or 0.04% have been applied for up to 5 minutes,[1,3] and low-dose treatment with mitomycin 0.02% for 30 seconds has been reported to be effective with few complications.[4] Postoperative treatment has generally been given as 0.02, 0.04, or 0.1% eye drops for up to 2 weeks, but the higher concentrations and longer treatment periods have been associated with more adverse effects,[1] some of which may be severe and sight-threatening (see also Effects on the Eyes, above). Comparisons of intra-operative with postoperative use suggest that pterygium recurrence rates are similar.[1,5]

A range of β-irradiation doses and fractionation methods have been used. Long-term complications include posterior subcapsular changes of the lens, atrophy and ulceration of the sclera, and scleral necrosis leading to endophthalmitis.[1] In one retrospective study,[6] intra-operative use of 0.04% mitomycin was more effective than β-irradiation in preventing recurrence after surgery. In another study,[7] postoperative mitomycin 0.02% for one week was less effective than radiation therapy.

1. Hoffman RS, Power WJ. Current options in pterygium management. *Int Ophthalmol Clin* 1999; **39:** 15–26.
2. Chapman-Smith JS. Pterygium treatment with triethylene thiophosphoramide. *Aust N Z J Ophthalmol* 1992; **20:** 129–31.
3. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. *Ophthalmic Surg Lasers* 2001; **32:** 341–5.
4. Cheng H-C, *et al.* Low-dose intraoperative mitomycin C as chemoadjuvant for pterygium surgery. *Cornea* 2001; **20:** 24–9.
5. Oguz H, *et al.* Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. *Acta Ophthalmol Scand* 1999; **77:** 147–50.
6. Amano S, *et al.* Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery. *Br J Ophthalmol* 2000; **84:** 618–21.
7. Şimşek T, *et al.* Comparative efficacy of β-irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol* 2001; **11:** 126–32.

Preparations

USP 31: Mitomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Asomutan; Crisofimina; Datisan†; Maximiton; Mitocyna; Mitokebir; Mitonovag; Mitotie; Oncotaxina†; Sintemicina; Vetio; ***Braz.:*** Mitocin; ***Canad.:*** Mutamycin; ***Chile:*** Metomit†; ***Fin.:*** Mitostat; Mutamycin; ***Fr.:*** Ametycine; ***Ger.:*** Ametycine; Mitem; Mito-extra; Mito-medac; ***India:*** Mitocin; ***Mex.:*** Ifamit†; Mitocin-C; Mitolem; Mitotie; Mixandex; ***Norw.:*** Mutamycin; ***Philipp.:*** Mytoxid; ***Swed.:*** Mutamycin; ***Switz.:*** Mutamycine†; ***USA:*** Mitozytrex; Mutamycin.

Mitotane *(USAN, rINN)*

CB-313; *o,p'*DDD; Mitotaani; Mitotan; Mitotano; Mitotanum; NSC-38721; WR-13045. 1,1-Dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane.

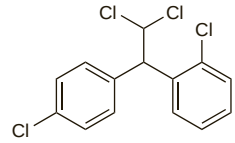
Митотан

$C_{14}H_{10}Cl_4$ = 320.0.

CAS — 53-19-0.

ATC — L01XX23.

ATC Vet — QL01XX23.



Pharmacopoeias. In *US.*

USP 31 (Mitotane). A white crystalline powder with a slight aromatic odour. M.p. is between 75° and 81°. Practically insoluble in water; soluble in alcohol, in ether, in petroleum spirit, and in fixed oils and fats. Store in airtight containers. Protect from light.

Adverse Effects

Almost all patients given mitotane have anorexia, nausea and vomiting, and sometimes diarrhoea, and about 40% suffer some central toxicity with dizziness, vertigo, sedation, lethargy, and depression. Permanent brain damage may develop with prolonged dosage. Bleeding time may be prolonged. Other common adverse effects include leucopenia, thrombocytopenia, anaemia, hypercholesterolaemia, hypertriglyceridaemia, mucositis, gynaecomastia, and headache. Ocular adverse effects may occur including blurred vision, diplopia, lenticular opacities, and retinopathy. Other adverse effects include hypersensitivity reactions, haematuria, albuminuria, skin rashes, fever, myalgia, haemorrhagic cystitis, flushing, hypertension, and orthostatic hypotension.

Precautions

Mitotane inhibits the adrenal cortex and adrenocortical insufficiency may develop during treatment; corticosteroid therapy is often required. In trauma, infection, or shock the drug should be temporarily withdrawn and corticosteroids should be given systemically. Mitotane should be given with care to patients with renal or hepatic impairment. Before mitotane therapy is begun, all possible tumour tissue from large metastases should be surgically removed, in order to minimise possible infarction or haemorrhage in the tumour. Patients should not drive or operate machinery. Behavioural and neurological assessments should be carried out regularly in patients who have been receiving treatment for 2 years or more. Plasma concentrations should be monitored to guide dosage; the therapeutic window lies between 14 and 20 micrograms/mL (see also Therapeutic Drug Monitoring, below).

Interactions

Mitotane may induce hepatic microsomal enzymes and enhance the metabolism of some other drugs, including coumarin anticoagulants.

Spironolactone. Mitotane in a dose of up to 3 g daily in a 65-year-old patient with Cushing's syndrome appeared to be ineffective and did not produce the usual adverse effects associated with mitotane while the patient was also receiving spironolactone.[1]

1. Wortsman J, Soler NG. Mitotane: spironolactone antagonism in Cushing's syndrome. *JAMA* 1977; **238:** 2527.

Pharmacokinetics

Up to 40% of a dose of mitotane is absorbed from the gastrointestinal tract; absorption increases with food. After daily doses of 5 to 15 g, concentrations in the blood of 7 to 90 micrograms/mL of unchanged drug and 29 to 54 micrograms/mL of metabolite have been reported. Mitotane has been detected in the blood for about 6 to 9 weeks after stopping treatment. It is widely distributed and appears to be stored mainly in fatty tissues. It is metabolised in the liver and other tissues and excreted as metabolites in urine and bile. From 10 to 25% of a dose has been recovered in the urine as a water-soluble metabolite.

Therapeutic drug monitoring. Monitoring of mitotane and its major metabolite *o,p'*-DDE in 2 patients receiving mitotane in low doses for Cushing's disease demonstrated that there is a prolonged lag time in the plasma concentration changes in response to alterations in dosage,[1] presumably because of the lipophilicity of both compounds which leads to accumulation in adipose tissue. A study[2] in adrenal carcinoma found that mitotane is preferentially distributed into the very-low-density lipoprotein (VLDL) fraction of the serum of patients with hypertriglyceridaemia, whereas under normolipidaemic conditions, it is bound to high-density lipoproteins and albumin. Because VLDL is not incorporated into the human adrenal cells, mitotane's lipophilicity has implications for treatment and monitoring in patients with hypertriglyceridaemia. In some studies[3,4] tumour responses were seen only in those patients achieving a serum concentration of mitotane above 14 micrograms/mL, and a small prospective study[5] found that therapeutic concentrations (defined as between 14 and 20 micrograms/mL) could be reached by sustained low doses (1 to 3 g daily), thus limiting side-effects.

1. Benecke R, *et al.* Plasma level monitoring of mitotane (o,p'-DDD) and its metabolite (o,p'-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol* 1991; **41:** 259–61.
2. Gebhardt DOE, *et al.* The distribution of *o,p'*-DDD (mitotane) among serum lipoproteins in normo- and hypertriglyceridemia. *Cancer Chemother Pharmacol* 1992; **29:** 331–4.
3. Haak HR, *et al.* Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. *Br J Cancer* 1994; **69:** 947–51.
4. Baudin E, *et al.* Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; **92:** 1385–92.
5. Terzolo M, *et al.* Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; **85:** 2234–8.