obtained about 2 to 4 hours after a dose. The plasma elimination half-life is about 10 to 20 hours. Sotalol has low lipid solubility. Very little is metabolised and it is excreted unchanged in the urine. Binding to plasma proteins is reported to be low. It crosses the placenta and is distributed into breast milk; concentrations in milk may be higher than those in maternal serum (see Breast Feeding, above). Only small amounts are reported to cross the blood-brain barrier and enter the CSF. Sotalol is removed by dialysis.

◊ General references.

1. Singh BN, *et al.* Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs* 1987; **34:** 311–49.
2. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; **46:** 678–719.

Pregnancy. The systemic clearance of sotalol in 6 healthy women after an intravenous dose was significantly higher during pregnancy than in the postnatal period, and the mean elimination half-life was shorter (6.6 versus 9.3 hours), although the latter difference was not significant.[1] Clearance after an oral dose was also higher during pregnancy than afterwards, but half-lives (10.9 versus 10.3 hours) and mean bioavailability were similar. The changes were probably due to alterations in renal function in the antenatal period.

In a study[2] of transplacental therapy, sotalol was found to cross the placenta easily and completely, with steady-state plasma concentrations similar in mother and fetus. Sotalol accumulated in the amniotic fluid but not in the fetus; it was not associated with fetal growth restriction.

1. O'Hare MF, *et al.* Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 521–4.
2. Oudijk MA, *et al.* Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; **42:** 765–70.

Uses and Administration

Sotalol is a non-cardioselective beta blocker (p.1225). It is reported to lack both intrinsic sympathomimetic and membrane-stabilising properties. In addition to the class II antiarrhythmic activity of beta blockers, sotalol lengthens the duration of the action potential resulting in class III antiarrhythmic activity. For a classification and explanation of antiarrhythmic activity, see p.1153.

Sotalol is used in the management of ventricular and supraventricular arrhythmias (p.1160). Because of its proarrhythmic effects, it is usually reserved for severe or life-threatening arrhythmias, and it should not be used in patients with asymptomatic ventricular arrhythmias. Although it was formerly used for its beta-blocking effects in the management of angina pectoris, hypertension, and myocardial infarction, it is no longer recommended for these indications because of the risk of precipitating arrhythmias.

Sotalol is given as the hydrochloride. Treatment should be started in hospital with suitable monitoring facilities. The QT interval should be assessed before the start of treatment and whenever the dosage is adjusted (see Precautions above); plasma-electrolyte concentrations and renal function should also be monitored. The dose should be reduced in patients with renal impairment (see below).

The usual initial oral dose of sotalol hydrochloride is 80 mg daily, as a single dose or in two divided doses. The dosage is then individualised according to response, and doses are increased gradually allowing 2 or 3 days between increments. US licensed product information recommends a higher initial dose of 80 mg twice daily and this should not be increased for at least 3 days. Most patients respond to doses of 160 to 320 mg daily (usually given in two divided doses). Some patients with ventricular arrhythmias may require doses as high as 640 mg daily.

Sotalol may be given intravenously to control acute arrhythmias, to substitute for oral therapy, and for programmed electrical stimulation. To control acute arrhythmias, sotalol hydrochloride is given in a dose of 20 to 120 mg (500 to 1500 micrograms/kg) intravenously over 10 minutes. This dose may be repeated every 6 hours if necessary. To substitute for oral therapy an intravenous infusion of 200 to 500 micrograms/kg per hour may be used. The total daily dose should not exceed 640 mg. For programmed electrical stimulation (to test antiarrhythmic efficacy) an initial dose of 1.5 mg/kg is given over 10 to 20 minutes, followed by an intravenous infusion of 200 to 500 micrograms/kg per hour.

Sotalol is used as a racemic mixture; *d*-sotalol (dexsotalol; (+)-sotalol) has also been investigated as an antiarrhythmic but development was stopped when it was found to increase mortality (see Action, below).

◊ General references.

1. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; **46:** 678–719.
2. Nappi JM, McCollam PL. Sotalol: a breakthrough antiarrhythmic? *Ann Pharmacother* 1993; **27:** 1359–68.
3. Zanetti LAF. Sotalol: a new class III antiarrhythmic agent. *Clin Pharm* 1993; **12:** 883–91.
4. Hohnloser SH, Woosley RL. Sotalol. *N Engl J Med* 1994; **331:** 31–8.
5. Anderson JL, Prystowsky EN. Sotalol: an important new antiarrhythmic. *Am Heart J* 1999; **137:** 388–409.

Action. Sotalol is used as the racemic mixture of the two stereoisomers, *d*-sotalol (dexsotalol; (+)-sotalol) and *l*-sotalol ((−)-sotalol). A comparison of the effects of *d*-sotalol and racemic sotalol in 6 healthy subjects[1] showed that the beta-blocking activity resided almost entirely in the *l*-isomer, while the effects on the QT interval, which are consistent with type III antiarrhythmic activity, appear to be due to both isomers. A study in 8 healthy subjects also showed a lack of beta blockade by *d*-sotalol.[2] This would suggest that the electrophysiological effects of sotalol are unrelated to its beta-blocking properties. *d*-Sotalol has been investigated as an antiarrhythmic.[3] However, a preliminary placebo-controlled study in patients with myocardial infarction at high risk of arrhythmia due to impaired left ventricular function was terminated early when increased mortality was seen in the treatment group.[4,5]

1. Johnston GD, *et al.* A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol* 1985; **20:** 507–10.
2. Yasuda SU, *et al.* d-Sotalol reduces heart rate in vivo through a β-adrenergic receptor-independent mechanism. *Clin Pharmacol Ther* 1993; **53:** 436–42.
3. Advani SV, Singh BN. Pharmacodynamic, pharmacokinetic and antiarrhythmic properties of d-sotalol, the dextro-isomer of sotalol. *Drugs* 1995; **49:** 664–79.
4. Choo V. SWORD slashed. *Lancet* 1994; **344:** 1358.
5. Waldo AL, *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348:** 7–12. Correction. *ibid.*; 416.

Administration in children. Sotalol has been used to treat both ventricular and supraventricular arrhythmias in children aged from newborn to adolescent;[1-3] it appears to be effective and well-tolerated, although proarrhythmic effects may occur. Neonates may be more sensitive to the QT-prolonging effects of sotalol[3] and lower doses may be appropriate. In the UK, the *BNFC* recommends the following oral doses of sotalol hydrochloride:

- Neonates: initial dose 1 mg/kg twice daily, increased as necessary every 3 to 4 days to a maximum of 4 mg/kg twice daily
- Children aged 1 month to 12 years: initial dose 1 mg/kg twice daily, increased as necessary every 2 to 3 days to a maximum of 4 mg/kg twice daily (maximum total dose 80 mg twice daily)

Licensed product information in the USA recommends doses of sotalol hydrochloride based on body surface area. Children aged 2 years and over may be given an initial dose of 30 mg/m^2 three times daily, increased as necessary at intervals of at least 36 hours to a maximum of 60 mg/m^2 three times daily. For children under 2 years of age the dose should be further reduced, and nomograms are available providing age-specific recommendations.

In children with refractory supraventricular tachycardia, sotalol has been given with flecainide; in a study[4] in children aged under 1 year, doses used ranged from 100 to 250 mg/m^2 daily of sotalol and from 40 to 150 mg/m^2 daily of flecainide.

Sotalol has also been used transplacentally to treat fetal tachycardias, including atrial flutter and supraventricular tachycardia. It may be effective as second-line therapy in addition to digoxin,[5] and has also been used first-line.[6,7] However, one retrospective study[6] of 21 fetuses given sotalol transplacentally found that it was more effective in atrial flutter than in supraventricular tachycardia; mortality was also higher in fetuses with supraventricular tachycardia, and the authors therefore suggested that sotalol should only be used in resistant cases.

1. Çeliker A, *et al.* Sotalol in treatment of pediatric cardiac arrhythmias. *Pediatr Int* 2001; **43:** 624–30.
2. Beaufort-Krol GCM, Bink-Boelkens MTE. Effectiveness of sotalol for atrial flutter in children after surgery for congenital heart disease. *Am J Cardiol* 1997; **79:** 92–4.
3. Läer S, *et al.* Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol* 2005; **46:** 1322–30.
4. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.
5. Sonesson S-E, *et al.* Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatr* 1998; **87:** 584–7.
6. Oudijk MA, *et al.* Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000; **101:** 2721–6.
7. Rebelo M, *et al.* Sotalol in the treatment of fetal tachyarrhythmia. *Rev Port Cardiol* 2006; **25:** 477–81.

Administration in renal impairment. Sotalol is excreted mainly unchanged by the kidneys and may accumulate in renal impairment. The usual daily dosage (see above) should therefore be reduced, either by decreasing the size of each dose, or by increasing the interval between doses. UK licensed product information for oral or intravenous sotalol recommends the following doses based on creatinine clearance (CC):

- CC 30 to 60 mL/minute: half usual dose
- CC 10 to 30 mL/minute: quarter usual dose
- CC less than 10 mL/minute: not recommended

Dosage recommendations in the USA depend on both the indication and CC, and incremental increases should not be made until 5 or 6 doses have been given. In the treatment of ventricular arrhythmias, licensed product information for oral sotalol recommends that in renal impairment doses should be given at the following intervals:

- CC 30 to 59 mL/minute: every 24 hours
- CC 10 to 29 mL/minute: every 36 to 48 hours
- CC less than 10 mL/minute: dosage should be individualised

For the treatment of atrial fibrillation, the same dosage intervals are recommended but sotalol is contra-indicated if CC is less than 40 mL/minute.

In a study of 10 hypertensive patients with varying degrees of renal impairment,[1] the apparent first-order elimination rate constant and plasma clearance of sotalol correlated with glomerular filtration rate. Another study[2] compared kinetics in patients with normal renal function, renal impairment, and renal failure. Elimination half-lives of 8.1 and 24.2 hours were reported in patients with CC above 39 mL/minute and between 8 and 38 mL/minute, respectively. It was suggested that an increase in the dosage interval to 48 or 72 hours may be necessary to compensate for longer half-lives. Caution is required when sotalol is used in patients on dialysis; a half-life of 33.9 hours was reported in patients with renal failure but this fell to 5.8 hours during dialysis which removed about 43% of sotalol.

1. Berglund G, *et al.* Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur J Clin Pharmacol* 1980; **18:** 321–6.
2. Blair AD, *et al.* Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther* 1981; **29:** 457–63.

Preparations

BP 2008: Sotalol Injection; Sotalol Tablets;
USP 31: Sotalol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Darob†; Sotacor; ***Austral.:*** Cardol; Solavert; Sotab†; Sotacor; Sotahexal; ***Austria:*** Darob; Sotacor; Sotahexal; Sotamed; Sotanorm; Sotastad; Ventricor†; ***Belg.:*** Sotalex; ***Braz.:*** Sotacor; ***Canad.:*** Sotacor†; ***Chile:*** Hipecor; ***Cz.:*** Darob†; Rentibloc†; Sotahexal; Sotalex; ***Denm.:*** Dutacor; Sotabet†; Sotacor; ***Fin.:*** Sotacor; Sotalin; ***Fr.:*** Sotalex; ***Ger.:*** CorSotalol†; Darob; Favorex; Gilucor; Jutalex; Rentibloc; Sota; Sota Lich; Sota-Puren; Sota-saar; Sotabeta; Sotagamma; Sotahexal; Sotalex; Sotalodoc; Sotaryt†; Sotastad; ***Hong Kong:*** Sotacor; ***Hung.:*** Sotahexal; Sotalex; ***Irl.:*** Sotacor; Sotoger; ***Israel:*** Sotacor†; ***Ital.:*** Rytmobeta; Sotalex; ***Jpn:*** Sotacor†; ***Malaysia:*** Sotacor; ***Mex.:*** Sotaper; ***Neth.:*** Sotacor; ***Norw.:*** Sotacor; ***NZ:*** Sotacor; Sotahexal; ***Philipp.:*** Sotalex; ***Pol.:*** Biosotal; Darob; Sotahexal; ***Port.:*** Darob; ***Rus.:*** Sotahexal (Сотагексал); Sotalex (Сталекс); ***S.Afr.:*** Sotacor; Sotahexal; ***Singapore:*** Sotacor; ***Spain:*** Sotapor; ***Swed.:*** Sotabet†; Sotacor; ***Switz.:*** Sotalex; ***Turk.:*** Darob; Sotarit; Talozin; ***UK:*** Beta-Cardone; Sotacor; ***USA:*** Betapace.

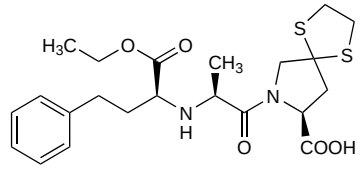
Multi-ingredient: ***S.Afr.:*** Sotazide.

Spirapril Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de espirapril; Sch-33844; Spirapriilihydrokloridi; Spirapril, chlorhydrate de; Spirapril-hydrochlorid; Spiraprilhydroklorid; Spiraprili hydrochloridum; Spiraprilio hidrochloridas; TI-211-950. (*S*)-7-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride.

Спираприла Гидрохлорид

$C_{22}H_{30}N_2O_5S_2,HCl$ = 503.1.
CAS — 83647-97-6 (spirapril); 94841-17-5 (spirapril hydrochloride).
ATC — C09AA11.
ATC Vet — QC09AA11.



(spirapril)

Pharmacopoeias. *Eur.* includes the monohydrate.
Ph. Eur. 6.2 (Spirapril Hydrochloride Monohydrate). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in acetonitrile; practically insoluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile
Spirapril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171). It owes its activity to the diacid spirapriat, to which it is converted after oral doses. It is given orally as the hydrochloride in a usual maintenance dose of 6 mg once daily.

◊ References.

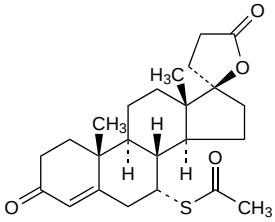
1. Noble S, Sorkin EM. Spirapril: a preliminary review of its pharmacology and therapeutic efficacy in the treatment of hypertension. *Drugs* 1995; **49:** 750–66.
2. Widimský J, *et al.* Czech and Slovak spirapril intervention study (CASSIS): a randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur J Clin Pharmacol* 1995; **49:** 95–102.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Quadropril; ***Cz.:*** Renpress; ***Ger.:*** Quadropril; ***Hung.:*** Quadropril; ***Ital.:*** Renormax; Setrilan; ***Neth.:*** Quadropril; ***Rus.:*** Quadropril (Квадроприл); ***Spain:*** Renormax; Renpress; ***Switz.:*** Cardiopril†.

Spironolactone *(BAN, rINN)* ⊗

Espironolactona; SC-9420; Spirolactone; Spironolactonum; Spironolakton; Spironolaktonas; Spironolaktoni. 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone; (7α,17α)-7-(Acetylthio)-17-hydroxy-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone.

Спиронолактон
$C_{24}H_{32}O_4S$ = 416.6.
CAS — 52-01-7.
ATC — C03DA01.
ATC Vet — QC03DA01.



NOTE. Compounded preparations of spironolactone may be represented by the following names:
- Co-flumactone (*BAN*)—spironolactone and hydroflumethiazide in equal parts (w/w)
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Spironolactone). A white or yellowish-white powder. Practically insoluble in water; soluble in alcohol. It exhibits polymorphism. Protect from light.
USP 31 (Spironolactone). A light cream-coloured to light tan, crystalline powder with a faint to mild mercaptan-like odour. Practically insoluble in water; soluble in alcohol and in ethyl acetate; freely soluble in chloroform and in benzene; slightly soluble in methyl alcohol and in fixed oils.

Stability. There was no appreciable loss of spironolactone from extemporaneously prepared suspensions of spironolactone, 2.5, 5 and 10 mg/mL, in a cherry syrup after storage for 2 weeks at 5° or 30° or at ambient room temperature under intense fluorescent light.[1] Degradation was less than 5% for samples stored for 4 weeks, but was more noticeable in suspensions with a higher initial concentration. There were no changes in colour or odour. Bacterial and fungal counts were well within acceptable limits after 4 weeks at 30°.

1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989; **46:** 2040–2.

Adverse Effects
Spironolactone may give rise to headache and drowsiness, and gastrointestinal disturbances, including cramp and diarrhoea. Ataxia, mental confusion, and skin rashes have been reported as adverse effects. Gynaecomastia is not uncommon and in rare cases breast enlargement may persist. Other endocrine disorders include hirsutism, deepening of the voice, menstrual irregularities, and impotence. Transient increases in blood-urea-nitrogen concentrations may occur and mild acidosis has been reported. Spironolactone has been shown to cause tumours in *rats*.

Spironolactone may cause hyponatraemia and hyperkalaemia.

Incidence of adverse effects. A survey found that of 788 patients given spironolactone 164 developed adverse effects.[1] These included hyperkalaemia in 8.6%, dehydration in 3.4%, hyponatraemia in 2.4%, gastrointestinal disorders in 2.3%, neurological disorders in 2%, rash, and gynaecomastia. Hyperkalaemia was associated with renal impairment and the use of potassium supplements: only 2.8% of nonuraemic patients not receiving potassium chloride developed hyperkalaemia, while 42.1% of those with marked uraemia and treated with potassium chloride became hyperkalaemic.

In a study[2] of 54 patients (53 female, 1 male) taking spironolactone 200 mg daily for hirsutism or acne adverse effects were reported in 91%.[2] Menstrual disturbances occurred in 72% of patients, breast tenderness in 39%, dry skin in 39%, and breast enlargement in 24%. Other adverse effects included nausea and vomiting, dizziness, headache, drowsiness, and skin rashes. Two patients developed a chloasma-like pigmentation of the face. The gynaecological effects were reduced in patients taking oral contraceptives.

1. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.
2. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Carcinogenicity. Breast cancer was reported in 5 patients taking spironolactone and hydrochlorothiazide for prolonged periods[1] although it was suggested[2] that the association with spironolactone therapy was unlikely to be causal.

Although the *rat* may not be an appropriate model for determining long-term safety in man,[3,4] evidence of carcinogenicity in this species prompted the UK CSM to limit the product licences of spironolactone-containing products to exclude use in essential hypertension or idiopathic oedema.[5]

1. Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; **i:** 1428–9.
2. Jick H, Armstrong B. Breast cancer and spironolactone. *Lancet* 1975; **ii:** 368–9.
3. Lumb G, *et al.* Effects in animals of chronic administration of spironolactone—a review. *J Environ Pathol Toxicol* 1978; **i:** 641–60.
4. Wagner BM. Long-term toxicology studies of spironolactone in animals and comparison with potassium canrenoate. *J Drug Dev* 1987; **1** (suppl 2): 7–11.
5. Committee on Safety of Medicines. Spironolactone. *Current Problems* 1988; 21. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)

Effects on the blood. Agranulocytosis has been reported[1,2] in association with the use of spironolactone.

1. Stricker BHC, Oei TT. Agranulocytosis caused by spironolactone. *BMJ* 1984; **289:** 731.
2. Whitling AM, *et al.* Spironolactone-induced agranulocytosis. *Ann Pharmacother* 1997; **31:** 582–5.

Effects on electrolyte balance. ***CALCIUM.*** A report[1] suggested that spironolactone may have a calcium-sparing effect, in addition to its well known potassium-sparing properties.

1. Puig JG, *et al.* Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J Clin Pharmacol* 1991; **31:** 455–61.

POTASSIUM. There have been reports[1-3] of severe hyperkalaemia in patients taking spironolactone, including patients with renal impairment and those with a high potassium intake from either dietary sources or potassium supplements. In the Boston Collaborative Drug Surveillance Program[4] hyperkalaemia was reported in 42.1% of patients with uraemia taking spironolactone and receiving potassium supplements compared with 2.8% of those without uraemia and not receiving potassium supplements. Two deaths were attributed to hyperkalaemia in patients taking spironolactone and potassium chloride. Potassium supplements should be avoided in patients receiving spironolactone, and plasma-potassium concentrations should be carefully monitored in those with renal impairment.

1. Pongpaew C, *et al.* Hyperkalemic cardiac arrhythmia secondary to spironolactone. *Chest* 1973; **63:** 1023–5.
2. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgrad Med J* 1980; **56:** 254–5.
3. O'Reilly PH, *et al.* Life-threatening hyperkalaemia after bladder decompression for high pressure chronic retention. *Lancet* 1987; **ii:** 859.
4. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.

Effects on endocrine function. Spironolactone has been associated with disturbances of endocrine function. The most prominent in men is gynaecomastia which appears to be related to both dose and duration of treatment. Incidences of 62%[1] and 100%[2] have been reported. Gynaecomastia has also been accompanied by impotence.[3,4] The effects are generally reversible on stopping treatment. Reversal of male-pattern baldness has also been reported.[5]

In women symptoms include breast enlargement and tenderness.[6] The incidence of menstrual abnormalities may be high: unspecified disturbances have been reported in 33 of 53 women,[6] secondary amenorrhoea in 6 of 9,[7] and secondary and primary amenorrhoea in 1 and 2 patients, respectively.[8] The incidence of gynaecological disturbances has been found to be lower in women taking oral contraceptives.[6]

The mechanism of the effects of spironolactone on the endocrine system is unclear. Some workers[9] suggested that although spironolactone affects testosterone synthesis, the more likely explanation was its anti-androgenic action, and reduction in 17-hydroxylase activity. Others[10] found an alteration in the testosterone/oestrogen ratio due to an increase in testosterone clearance and increased peripheral conversion to estradiol. In addition, spironolactone is reported to inhibit binding of dihydrotestosterone to receptors.

1. Huffman DH, *et al.* Gynecomastia induced in normal males by spironolactone. *Clin Pharmacol Ther* 1978; **24:** 465–73.
2. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
3. Greenblatt DJ, Koch-Weser J. Gynecomastia and impotence complications of spironolactone therapy. *JAMA* 1973; **223:** 82.
4. Greenlaw C. Spironolactone induced gynecomastia: a case report. *Drug Intell Clin Pharm* 1977; **11:** 70–3.
5. Thomas PS. Hair: wanted and unwanted. *BMJ* 1986; **293:** 698.
6. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.
7. Levitt JI. Spironolactone therapy and amenorrhea. *JAMA* 1970; **211:** 2014–15.
8. Potter C, *et al.* Primary and secondary amenorrhea associated with spironolactone therapy in chronic liver disease. *J Pediatr* 1992; **121:** 141–3.
9. Loriaux DL, *et al.* Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85:** 630–6.
10. Rose LI, *et al.* Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87:** 398–403.

Effects on lipid metabolism. Unlike thiazide diuretics, spironolactone appeared not to increase serum-cholesterol concentrations in a study of 23 patients.[1]

1. Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. *Arch Intern Med* 1984; **144:** 710–14.

Effects on the liver. Hepatotoxicity characterised by cholestatic lesions has been reported in a patient receiving spironolactone.[1] Only one other published case of spironolactone-associated hepatotoxicity was known to the authors.

1. Renkes P, *et al.* Spironolactone and hepatic toxicity. *JAMA* 1995; **273:** 376–7.

Effects on the skin. Lichen-planus-like skin eruptions developed in a 62-year-old woman who was taking digoxin, propranolol, diazepam, spironolactone, and iron tablets.[1] Flares of the lichen-planus-like eruption seemed to be associated with use of spironolactone and there was evidence of resolution when spironolactone was withdrawn. Cutaneous vasculitis was associated with spironolactone on 3 occasions in an 80-year-old man.[2] A chloasma-like pigmentation of the face was reported in 2 patients receiving spironolactone for hirsutism or acne.[3]

1. Downham TF. Spironolactone-induced lichen planus. *JAMA* 1978; **240:** 1138.
2. Phillips GWL, Williams AJ. Spironolactone induced vasculitis. *BMJ* 1984; **288:** 368.
3. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Hypersensitivity. Eosinophilia and a rash developed in 2 patients with alcoholic cirrhosis while taking spironolactone.[1]

1. Wathen CG, *et al.* Eosinophilia associated with spironolactone. *Lancet* 1986; **i:** 919–20.

Precautions
Spironolactone should not be used in patients with hyperkalaemia or severe renal impairment. It should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include the elderly, those with diabetes mellitus, and those with some degree of renal or hepatic impairment. It should also be given with care to patients likely to develop acidosis. Serum electrolytes and blood-urea-nitrogen should be measured periodically.

Breast feeding. The concentration of canrenone was measured[1] in the serum and milk of a breast-feeding woman taking 25 mg of spironolactone four times daily. The milk to serum concentration ratios of canrenone at 2 and 14.5 hours after a dose of spironolactone were 0.72 and 0.51 respectively, and it was estimated that the amount of canrenone ingested by the infant would be 0.2% of the mother's daily dose of spironolactone. The serum potassium and sodium levels of the infant were in the normal range. The American Academy of Pediatrics[2] considers that spironolactone is therefore usually compatible with breast feeding.

1. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977; **66:** 1203.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)