The incidence and prevalence of renal calculi is increasing.[1,2] The lifetime risk of stone development varies between populations but is about 15% for white men and 6% for white women, with a lifetime recurrence rate of up to 50%.[3] Risk factors include obesity, low fluid intake, and a diet high in protein, refined carbohydrates, and salt.[1] Some conditions can promote calculi formation, including renal tubular acidosis, primary hyperparathyroidism, sarcoidosis, primary hyperoxaluria, inflammatory bowel disease, hyperuricaemic conditions, and cystic fibrosis.[4] Drug-induced calculi can be formed by crystallisation of poorly soluble drugs with a high urinary excretion, or by an effect on calcium oxalate or purine metabolism.[5]

Treatment. Most renal calculi are small, and stones that are less than 5 mm in diameter will usually pass spontaneously.[6-9] Patients may be asymptomatic or may pass small stones with relatively little discomfort, but passage of a larger stone down the ureter can be accompanied by excruciating pain (renal or ureteral colic) requiring analgesia (see Biliary and Renal Colic, p.5). If there is no obstruction, infection, or other complication, conservative treatment is favoured, with the patient being monitored radiographically over several weeks to see if the stone will pass of its own accord.[10] There is some interest in the possible use of drug treatment to ease the spontaneous passage of the stone. Small studies using a calcium-channel blocker (usually nifedipine) or an alpha$_1$-adrenoceptor blocker such as tamsulosin, sometimes with a corticosteroid such as deflazacort, have reported improvements in the rate of stone expulsion and expulsion time, and reductions in analgesic requirements, in patients with uncomplicated lower ureteral stones. A meta-analysis[11] of 9 such studies confirmed the apparent benefit of such treatment; patients had a 65% greater likelihood of spontaneous stone passage than those not given these drugs. Although a suitable randomised controlled study is required to confirm efficacy, such treatment may offer a viable alternative to lithotripsy or uteroscopy.[11] A literature review[12] suggested that daily doses of nifedipine 30 mg, doxazosin 4 mg, tamsulosin 400 micrograms, or terazosin 5 mg given for 28 to 45 days are effective in enhancing expulsion of ureteral stones that are less than 15 mm in diameter.

Where intervention is considered necessary for stone removal the choice of technique depends on the size, composition, and location of the stone. Extracorporeal shock wave lithotripsy is generally favoured, but other procedures such as ureteroscopy or percutaneous nephrolithotomy are used for more complex cases.[7,8,13] Antibacterials may be needed for infection (see Urinary-tract Infections, p.199).

Prevention. In the prevention of recurrence it is important to identify, and where possible correct, any underlying disease process or biochemical or anatomical abnormality. Certain general measures are also appropriate. Patients should drink at least 2 to 3 litres of fluid daily in order to maintain an adequate volume of urine.[1,3,7,14] In hot climates or working environments a higher volume of fluid should be taken.

In preventing the recurrence of *calcium stones*, a balanced diet that is low in protein and salt[1,3,10,15] and high in fibre[1,7] is generally advocated. In the past patients were advised to decrease their calcium intake, but studies have found an inverse relationship between dietary calcium intake and stone formation.[3,7,14,15] Also, because oxalate is bound by calcium in the gut, preventing its absorption, a low calcium intake can increase oxalate absorption and the risk of stone formation. Therefore, a normal level of dietary intake of calcium is now advised[1,3,7,15,16] (an exception to this is in patients with absorptive hypercalciuria type I, a rare condition of intestinal calcium hyperabsorption).[1] However, calcium supplements appear to increase the risk of stone formation and are generally avoided.[3,7,15] If they are used, they should be taken with meals to avoid hypercalciuria.[1,16] Excessive dietary oxalate intake should also be avoided;[3,7,10,15] foods containing large quantities of bioavailable oxalate include spinach, rhubarb, nuts, and cocoa.[15]

Where pharmacological therapy is indicated, choice of treatment depends on the underlying metabolic abnormality and stone composition. Alkaline citrate, usually given as potassium citrate, is commonly used to prevent the recurrence of calcium stones. It acts as a urinary alkaliniser and increases citrate excretion; citrate forms complexes with calcium to reduce urinary saturation of calcium salts and inhibits crystallisation.[2,7,14,16] Potassium citrate is the main treatment option in patients with hypocitraturia and renal tubular acidosis.[1,3,7] In hypercalciuria, a thiazide diuretic or indapamide can also be used to increase distal tubular calcium reabsorption;[1-3,6,7,10,14,17] potassium citrate can also prevent diuretic-induced hypokalaemia in these patients. In the prevention of calcium stones with hyperoxaluria, a restriction of oxalate-rich food and an adequate dietary calcium intake (or calcium supplements taken with meals) are advocated.[6,10,15,16] The use of magnesium has also been suggested[1] although it may be no better than placebo.[3,7] Some patients with primary hyperoxaluria may respond to high doses of pyridoxine.[1,3,7,10,16] In hyperuricosuria, reduced purine intake and allopurinol may be effective.[1,3,7,10]

Prevention of *uric acid stones* is based on adequate fluid intake, a low purine diet, and urinary alkalinisation with potassium citrate. Allopurinol may be used if there are high levels of urate.[1-3,6,7] Acetazolamide has been used short term.[6]

Struvite stones are caused by urease-producing bacteria. Antibacterials are used, and may be required long term, with urinary acidification using ammonium chloride[7] or methionine.[1,7] Dietary phosphate restriction may also be appropriate for patients with phosphate excretion of more than 35 mmol/day.[1] Acetohydroxamic acid, an inhibitor of bacterial urease, may be used as an adjunct in selected cases of severe infection,[7] but its use has been limited by adverse effects.[3,10]

Cystine stones are associated with cystinuria (p.1459) and are prevented by alkalinisation of the urine and a high fluid intake (3 to 4 litres daily).[2,3,6,7] Penicillamine may be used as a chelating agent.[3,6,10] Ascorbic acid, tiopronin,[1,7] and captopril[7] have also been suggested.

1. Straub M, Hautmann RE. Developments in stone prevention. *Curr Opin Urol* 2005; **15:** 119–26.
2. Moe OW. Kidney stones: pathophysiology and medical management. *Lancet* 2006; **367:** 333–44.
3. Reynolds TM. Chemical pathology clinical investigation and management of nephrolithiasis. *J Clin Pathol* 2005; **58:** 134–40.
4. Matlaga BR, Assimos DG. Urologic manifestations of nonurologic disease: urolithiasis. *Urol Clin North Am* 2003; **30:** 91–9.
5. Daudon M, Jungers P. Drug-induced renal calculi: epidemiology, prevention and management. *Drugs* 2004; **64:** 245–75.
6. Bihl G, Meyers A. Recurrent renal stone disease—advances in pathogenesis and clinical management. *Lancet* 2001; **358:** 651–6.
7. Tiselius H-G, *et al.* European Association of Urology guidelines on urolithiasis (update March 2008). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/Urolithiasis.pdf (accessed 02/09/08)
8. Anagnostou T, Tolley D. Management of ureteric stones. *Eur Urol* 2004; **45:** 714–21.
9. Miller NL, Lingeman JE. Management of kidney stones. *BMJ* 2007; **334:** 468–72.
10. Parmar MS. Kidney stones. *BMJ* 2004; **328:** 1420–4.
11. Hollingsworth JM, *et al.* Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet* 2006; **368:** 1171–9.
12. Beach MA, Mauro LS. Pharmacologic expulsive treatment of ureteral calculi. *Ann Pharmacother* 2006; **40:** 1361–8.
13. Preminger GM, *et al.* American Urological Association. AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol (Baltimore)* 2005; **173:** 1991–2000. Also available at: http://www.auanet.org/guidelines/staghorncalculi05.cfm (accessed 29/11/05)
14. Pearle MS. Prevention of nephrolithiasis. *Curr Opin Nephrol Hypertens* 2001; **10:** 203–9.
15. Baker MJ, Longyhore DS. Dietary calcium, calcium supplements, and the risk of calcium oxalate kidney stones. *Am J Health-Syst Pharm* 2006; **63:** 772–5.
16. Tiselius H-G. Epidemiology and medical management of stone disease. *BJU Int* 2003; **91:** 758–67.
17. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13:** 679–85.

Renal colic

For the treatment of urological pain see Biliary and Renal Colic, p.5.

Renal failure

For discussions of acute and chronic renal failure and their management, see p.1672.

Sexually transmitted diseases

For discussion of sexually transmitted diseases and their treatment see p.191.

Syndrome of inappropriate ADH secretion

In some patients secretion of antidiuretic hormone (ADH; vasopressin) occurs despite hypotonicity of the extracellular fluid and normal or raised fluid volume, and such patients are said to have the syndrome of inappropriate ADH secretion (SIADH). With severe water excess, the resultant hyponatraemia may result in symptoms ranging from lassitude or headache to profound neurological symptoms such as confusion, convulsions, or coma. Some patients may experience inappropriate thirst as well as ADH secretion, thus exacerbating their condition. For a discussion of sodium homoeostasis and dilutional hyponatraemia, see p.1670.

Conditions that can precipitate SIADH include CNS disorders, infections such as encephalitis and meningitis, head trauma, porphyria, or pulmonary diseases such as tuberculosis and pneumonia. ADH may also be secreted ectopically from malignancies, most commonly from small-cell bronchial carcinoma. SIADH may also be drug-induced; drugs associated with the condition include carbamazepine, chlorpropamide, cytotoxic drugs such as cyclophosphamide and the vinca alkaloids, oxytocin, some antipsychotics, tricyclic antidepressants, and SSRIs.

Diagnosis of SIADH is initially prompted by the presence of hyponatraemia and corresponding plasma hypo-osmolality with or without neurological symptoms. Hypervolaemia, persistent excess sodium excretion, lack of oedema, and normality of both renal and adrenal function are confirmatory.

Mild water excess is frequently asymptomatic and may not require specific therapy, but patients with SIADH often have a more severe disorder and treatment is best aimed at the underlying cause. If such treatment is not possible or if symptoms persist, water restriction may be considered. However, fluid restriction is unpleasant, particularly for patients who retain inappropriate thirst, and may not be tolerable. In these patients demeclocycline may be given to antagonise the effect of ADH on the renal tubules. Lithium has been given as an alternative but has a high frequency of adverse effects, and phenytoin has been used occasionally to inhibit pituitary ADH secretion. Diuretics such as furosemide (used with oral sodium chloride) have also been tried in an attempt to optimise diuresis while retaining sodium. In patients with life-threatening severe acute water intoxication (see Hyponatraemia, p.1670), treatment initially involves cautious improvement of the profound hyponatraemia by intravenous infusion of hypertonic (usually 3%) or isotonic sodium chloride, often with furosemide or another loop diuretic to avoid volume expansion. Drugs that act directly in the renal tubules as vasopressin V_2 receptor antagonists are under investigation.

References.

1. Kinzie BJ. Management of the syndrome of inappropriate secretion of antidiuretic hormone. *Clin Pharm* 1987; **6:** 625–33.
2. Kovacs L, Robertson GL. Syndrome of inappropriate antidiuresis. *Endocrinol Metab Clin North Am* 1992; **21:** 859–75.
3. Miller M. Syndromes of excess antidiuretic hormone release. *Crit Care Clin* 2001; **17:** 11–23.
4. Verbalis JG. Vasopressin V receptor antagonists. *J Mol Endocrinol* 2002; **29:** 1–9.
5. Rabinstein AA. Vasopressin antagonism: potential impact on neurologic disease. *Clin Neuropharmacol* 2006; **29:** 87–93.
6. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356:** 2064–72.

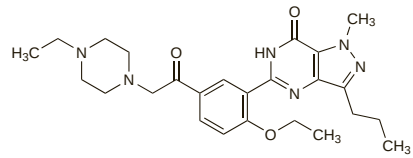
Urinary-tract infections

The treatment of urinary-tract infections is discussed on p.199.

Acetildenafil

Hongdenafil. 5-{2-Ethoxy-5-[2-(4-ethylpiperazine-1-yl)-acetyl]-phenyl}-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one.

$C_{25}H_{34}N_6O_3$ = 466.6.



Profile

Acetildenafil is an analogue of sildenafil (p.2193) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction. Other analogues of sildenafil detected in similar products include homosildenafil and hydroxyhomosildenafil.

Alfuzosin Hydrochloride

(BANM, USAN, rINNM)

Alfutsosiinihydrokloridi; Alfuzosin Hidroklorür; Alfuzosine, chlorhydrate d'; Alfuzosin-hydrochlorid; Alfuzosinhydroklorid; Alfuzosini hydrochloridum; Alfuzozin-hidroklorid; Alfuzozino hidrochloridas; Hidrocloruro de alfuzosina; SL-77499-10; SL-77499 (alfuzosin). *N*-{3-[4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino]propyl}tetrahydro-2-furamide hydrochloride.

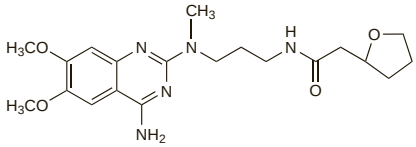
Альфузозина Гидрохлорид

$C_{19}H_{27}N_5O_4,HCl$ = 425.9.

CAS — 81403-80-7 (alfuzosin); 81403-68-1 (alfuzosin hydrochloride).

ATC — G04CA01.

ATC Vet — QG04CA01.



(alfuzosin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Alfuzosin Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375. Alfuzosin may be more selective for the urinary tract and vasodilator effects may be less frequent. It should be avoided in severe hepatic impairment, and doses may need to be reduced in mild to moderate hepatic impairment and in renal impairment (see below).

Incidence of adverse effects. In postmarketing surveillance involving 13 389 patients given alfuzosin 2.5 mg three times daily by mouth for benign prostatic hyperplasia, about 3.7% of patients failed to complete treatment because of adverse effects. These were mostly vasodilatory in nature (vertigo or dizziness, syncope or malaise, hypotension, and headache), and were more common in patients over 75 years of age and during the first week of treatment.[1]

1. Lukacs B, *et al.* Safety profile of 3 months' therapy with alfuzosin in 13,389 patients suffering from benign prostatic hypertrophy. *Eur Urol* 1996; **29:** 29–35.

Surgical procedures. Alpha blockers, including alfuzosin, have been associated with intraoperative floppy iris syndrome in cataract surgery patients. For further details, see under Tamsulosin, p.2197.

Interactions

As for Prazosin Hydrochloride, p.1376. Potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, itraconazole, and ritonavir, may increase blood concentrations of alfuzosin.

Pharmacokinetics

Alfuzosin is readily absorbed after oral doses and peak plasma concentrations generally occur 0.5 to 3 hours after a dose; bioavailability is about 64%. Absorption from modified-release preparations is improved if given with food. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to inactive metabolites that are excreted primarily in faeces via the bile. Only about 11% of a dose is excreted unchanged in the urine. Alfuzosin has a plasma elimination half-life of 3 to 5 hours. It is 90% bound to plasma proteins.

Uses and Administration

Alfuzosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376). It acts preferentially on receptors in the lower urinary tract and is therefore used in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction, including acute urinary retention.

Alfuzosin is given orally as the hydrochloride. Like other alpha$_1$-adrenoceptor blockers, it may cause collapse in some patients after the first dose, which should therefore be given just before bedtime to reduce the risk. Doses may need to be reduced in patients with hepatic or renal impairment (see below); the initial dose should also be reduced in the elderly.

In **benign prostatic hyperplasia,** the usual dose of alfuzosin hydrochloride is 2.5 mg three times daily, increased to 10 mg daily if necessary. In elderly patients, and those receiving treatment for hypertension, a lower initial dose of 2.5 mg twice daily should be considered. A modified-release preparation may also be used in a dose of 10 mg once daily after a meal.

In patients aged over 65 years catheterised for **acute urinary retention** associated with benign prostatic hyperplasia, a modified-release preparation may be given in a dose of 10 mg once daily after a meal for 3 to 4 days.

◊ Reviews.

1. Wilde MI, *et al.* Alfuzosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993; **45:** 410–29.
2. McKeage K, Plosker GL. Alfuzosin: a review of the therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. *Drugs* 2002; **62:** 633–53.
3. Lee M. Alfuzosin hydrochloride for the treatment of benign prostatic hyperplasia. *Am J Health-Syst Pharm* 2003; **60:** 1426–39. Correction. *ibid.* 2004; **61:** 437.
4. Weiner DM, Lowe FC. Alfuzosin for the management of benign prostate hyperplasia. *Expert Opin Pharmacother* 2003; **4:** 2057–63.
5. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother* 2004; **2:** 14–23.
6. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 2005; **66:** 780–8.
7. McVary KT. Alfuzosin for symptomatic benign prostatic hyperplasia: long-term experience. *J Urol (Baltimore)* 2006; **175:** 35–42.

Administration in hepatic or renal impairment. In patients with mild to moderate hepatic impairment the initial dose of alfuzosin hydrochloride should be 2.5 mg daily, increased to 2.5 mg twice daily according to response; modified-release preparations are not recommended.

In patients with renal impairment, 2.5 mg twice daily should be given initially, adjusted according to response. Although UK and US licensed product information advises caution with the use of modified-release preparations in severe renal impairment (creatinine clearance below 30 mL/minute), a study[1] in patients with varying degrees of renal impairment (including severe) suggested that no dose reduction was necessary.

1. Marbury TC, *et al.* Pharmacokinetics and safety of a single oral dose of once-daily alfuzosin, 10 mg, in male subjects with mild to severe renal impairment. *J Clin Pharmacol* 2002; **42:** 1311–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dalfaz; UroXatral; ***Austria:*** Urion†; Xatral; ***Belg.:*** Xatral; ***Braz.:*** Xatral; ***Canad.:*** Xatral; ***Chile:*** UroXatral; ***Cz.:*** Alfuzostad; Xatral; ***Denm.:*** Xatral; ***Fin.:*** Xatral; ***Fr.:*** Urion; Xatral; ***Ger.:*** Urion; UroXatral; ***Gr.:*** Alfuprost; Alfural; Alfuzin; Innosensitive; Spedamyl; Xatral; ***Hong Kong:*** Xatral; ***Hung.:*** Alfetim; Alfuzostad; ***India:*** Flotral; ***Indon.:*** Xatral; ***Irl.:*** Xatral; ***Israel:*** Xatral; ***Ital.:*** Mittoval; Xatral; ***Malaysia:*** Xatral; ***Mex.:*** Xatral; ***Neth.:*** Mittoval; Urion; UroXatral; Xatral; ***Norw.:*** Xatral; ***Philipp.:*** Xatral; ***Pol.:*** Alfuzostad; Dalfaz; ***Port.:*** Benestan; ***Rus.:*** Dalfaz (Дальфаз); ***S.Afr.:*** Xatral; ***Singapore:*** Xatral; ***Spain:*** Alfetim†; Benestan; Unibenestan; ***Swed.:*** Xatral; ***Switz.:*** Xatral; ***Thai.:*** Xatral; ***Turk.:*** Xatral; ***UK:*** Besavar; Xatral; ***USA:*** UroXatral; ***Venez.:*** Xatral.

Alprostadil *(BAN, USAN, rINN)*

Alprostadiili; Alprostadilis; Alprostadilum; Alprosztadil; PGE$_1$; Prostaglandin E$_1$; U-10136. (*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprost-13-enoic acid; 7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}heptanoic acid.

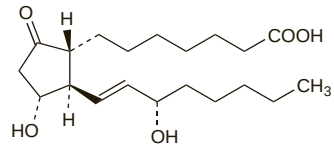
Алпростадил

$C_{20}H_{34}O_5$ = 354.5.

CAS — 745-65-3.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.



NOTE. In *Martindale* the term alprostadil is used for the exogenous substance and prostaglandin E$_1$ for the endogenous substance.

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

Ph. Eur. 6.2 (Alprostadil). A white or slightly yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in ethyl acetate.

USP 31 (Alprostadil). A white to off-white crystalline powder. M.p. about 110°. Soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in chloroform and in ether; slightly soluble in ethyl acetate. Store between 2° and 8° in airtight containers.

Alprostadil Alfadex *(BAN, rINNM)*

Alprostadilum Alfadexum; α-Cyclodextrin Alprostadil; PGE$_1$ α-CD; Prostaglandin E$_1$ α-Cyclodextrin Clathrate Compound.

Алпростадил Альфадекс

$C_{20}H_{34}O_5,x[C_{36}H_{60}O_{30}]$.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

The adverse effects reported most commonly in **infants** with congenital heart disease treated with alprostadil are apnoea, fever, flushing, hypotension, bradycardia, tachycardia, diarrhoea, and convulsions. Other adverse effects reported include oedema, cardiac arrest, hypokalaemia, disseminated intravascular coagulation, and cortical proliferation of the long bones. Weakening of the wall of the ductus arteriosus and pulmonary artery may occur on prolonged infusion. Alprostadil should be avoided in neonates with respiratory distress syndrome and should be used with caution in those with bleeding tendencies; blood pressure and respiratory status should be monitored during infusion.

Adverse effects reported in **adults** given alprostadil have included headache, flushing, hypotension, diarrhoea, and pain and inflammation at the infusion site.

After intracavernosal or intra-urethral alprostadil for the treatment of erectile dysfunction, the most frequently reported adverse effect is pain during erection. Local reactions including penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported. Priapism may occur (see below). Systemic effects are less common but hypotension and other adverse effects have been reported. Intracavernosal or intra-urethral use should be avoided in patients with complicating penile deformities or with sickle-cell disease, myeloma, leukaemias, or other conditions predisposing to prolonged erection.

In children. Reviews[1,2] of adverse effects associated with alprostadil in infants with congenital heart disease.

1. Lewis AB, *et al.* Side effects of therapy with prostaglandin E in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.
2. Lucron H, *et al.* Complications du traitement par prostaglandines E1 des cardiopathies congénitales en réanimation médicale pédiatrique. *Arch Mal Coeur Vaiss* 2005; **98:** 524–30.

Effects on the bones. Periosteal or cortical hyperostosis has been reported in infants given alprostadil for cyanotic congenital heart disease.[1-4] A retrospective review of 30 infants[2] treated with alprostadil revealed radiographic signs of periosteal reactions in 5. Changes could be detected after even short courses of therapy; 3 developed relatively mild periosteal changes in the ribs after infusions ranging from 9 to 205 hours and one had involvement of the left femur after infusion for 71 hours. Resolution of lesions had occurred in most bones 6 to 12 months later. In a further study,[5] radiological evidence of cortical hyperostosis was found in 53 of 86 infant heart transplant recipients who had received alprostadil infusion pre-operatively. Of 53 of the infants who had received alprostadil for less than 30 days, 21 were affected (2 severely). Correspondingly, of those treated for 30 to 60 days, 18 of 22 were affected (13 severely). All 14 infants treated