Methylmethacrylate monomer acts as a peripheral vasodilator and has caused hypotension and, rarely, cardiac arrest and death when absorbed during the use of polymethylmethacrylate (PMMA) as a bone cement during orthopaedic surgery. Other adverse effects associated with the use of polymethylmethacrylate as a bone cement include thrombophlebitis, pulmonary embolism, haemorrhage, haematoma, short-term irregularities in cardiac conduction, cerebrovascular accident, compression of the spinal cord and/or nerve roots, and new fractures in adjacent non-augmented vertebrae. Recommendations when using PMMA include monitoring with high quality imaging systems to detect leakage, and close monitoring of blood pressure during and immediately after the procedure.

Effects on the nervous system. Sensory polyneuropathy has been reported in a dental technician after occupational exposure to methylmethacrylate monomer.[1]

1. Sadoh DR, *et al.* Occupational exposure to methyl methacrylate monomer induces generalised neuropathy in a dental technician. *Br Dent J* 1999; **186:** 380–1.

Uses and Administration

Methylmethacrylate forms the basis of acrylic bone cements used in orthopaedic surgery. A liquid consisting chiefly of methylmethacrylate monomer with a polymerisation initiator is mixed with a powder consisting of polymethylmethacrylate (PMMA) or a methylmethacrylate ester copolymer. The reaction is exothermic. Barium sulfate or zirconium dioxide may be added as a contrast medium. Polymethylmethacrylate beads containing gentamicin have been implanted for the prophylaxis and treatment of bone infections and some soft-tissue infections. Bone cements containing antibacterials such as gentamicin or erythromycin are also available.

Polymethylmethacrylate has also been used as a material for intra-ocular lenses, for denture bases, as a cement for dental prostheses, and in composite resins for dental restoration.

A number of polymers based on methacrylic acid are used in pharmaceutical technology mainly as film coating agents and binders.

Ph. Eur. 6.2 includes:

- Ammonio Methacrylate Copolymer (Type A) (a copolymer of acrylic and methacrylic acid esters)
- Ammonio Methacrylate Copolymer (Type B) (a copolymer of acrylic and methacrylic acid esters)
- Basic Butylated Methacrylate Copolymer
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:2)
- Polyacrylate Dispersion 30 per cent (a dispersion of an ethyl-acrylate-methyl methacrylate copolymer in water)

USNF 26 includes:

- Methacrylic Acid Copolymer (a copolymer of methacrylic acid and an acrylic or methacrylic ester)
- Amino Methacrylate Copolymer
- Ammonio Methacrylate Copolymer
- Ammonio Methacrylate Copolymer Dispersion
- Ethyl Acrylate and Methyl Methacrylate Copolymer

Bone disorders. Polymethylmethacrylate bone cements may be injected percutaneously into vertebral fractures or lesions to relieve pain and stabilise the damaged vertebra.[1-6] The technique has been used in the treatment of metastatic bone lesions and myeloma (p.660 and p.658) as well as for vertebral compression fractures due to osteoporosis (p.1084). Complications[5,7-9] are uncommon but may include both local and systemic effects (including pulmonary embolism) due to leakage of the cement and sudden drop in blood pressure, probably due to the monomer.

1. Barr JD, *et al.* Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine* 2000; **25:** 923–8.
2. Lingar L. Percutaneous polymethacrylate vertebroplasty. *Radiol Technol* 2004; **76:** 109–13.
3. Burton AW, *et al.* Vertebroplasty and kyphoplasty: a comprehensive review. *Neurosurg Focus* 2005; **18:** e1. Available at: http://www.medscape.com/viewarticle/501670 (accessed 15/02/06)
4. Suresh SP, Whitehouse RW. Vertebroplasty and kyphoplasty. *J Br Menopause Soc* 2005; **11:** 28–32.
5. Guglielmi G, *et al.* Percutaneous vertebroplasty: indications, contraindications, technique, and complications. *Acta Radiol* 2005; **46:** 256–68.
6. Hochmuth K, *et al.* Percutaneous vertebroplasty in the therapy of osteoporotic vertebral compression fractures: a critical review. *Eur Radiol* 2006; **16:** 998–1004.
7. Laredo JD, Hamze B. Complications of percutaneous vertebroplasty and their prevention. *Semin Ultrasound CT MR* 2005; **26:** 65–80.
8. Barragan-Campos HM, *et al.* Percutaneous vertebroplasty for spinal metastases: complications. *Radiology* 2006; **238:** 354–62.
9. Health Canada. Complications associated with the use of bone cements in vertebroplasty and kyphoplasty procedures (issued 30th May, 2007). Available at: http://www.hc-sc.gc.ca/ dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bone_cement-ciment_acrylique_nth-aah_2_e.pdf (accessed 30/5/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Palacos E†; Palacos R; ***Ger.:*** CMW; flint; Palacos R; Palamed; SmartSet HV; ***Port.:*** Septopal; ***Singapore:*** Palacos R†; ***Thai.:*** Palacos R; ***UK:*** Palacos R.

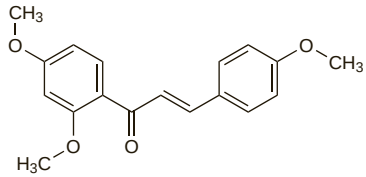
Multi-ingredient: ***Arg.:*** Septopal†; ***Austral.:*** Palacos E with Garamycin; Palacos R with Garamycin; Septopal; ***Austria:*** Septopal; ***Belg.:*** Palacos LV avec Gentamicine†; Palacos R avec Gentamicine†; Septopal; ***Braz.:*** Septopal; ***Chile:*** Palacos E con Gentamicina; Palacos R con Gentamicina; Perlas De PMMA con Gentamicina; ***Cz.:*** Septopal†; ***Denm.:*** Septopal; ***Fin.:*** Palacos R cum Gentamicin†; Septopal; ***Fr.:*** Palacos LV avec Gentamicine; Palacos R avec Gentamicine; ***Ger.:*** CMW mit Gentamicin; Copal; Epiglu; Palamed G; Refobacin-Palacos R; Septopal; SmartSet GHV; ***Gr.:*** Palacos R with Gentamycin†; Septopal†; ***Hong Kong:*** Septopal; ***Hung.:*** Plastubol†; Septopal; ***India:*** Septopal; ***Irl.:*** Epiglu; ***Malaysia:*** Septopal†; ***Neth.:*** Septopal; ***Norw.:*** Septopal; ***NZ:*** Antibiotic Simplex; CMW Gentamicin; Palacos with Garamycin; Vacu-Mix Plus with CMW gentamicin; ***Philipp.:*** Septopal; ***S.Afr.:*** Palacos R with Garamycin; Septopal; ***Singapore:*** Refobacin Bone Cement R; Refobacin-Palacos R†; Septopal†; ***Swed.:*** Septopal†; ***Switz.:*** Septopal; ***Thai.:*** Refobacin-Palacos R; Septopal; ***UK:*** Epiglu; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal.

Metochalcone *(rINN)*

CB-1314; Methochalcone; Metocalcona; Métochalcone; Metochalconum; Trimethoxychalcone. 2′,4,4′-Trimethoxychalcone.

Метохалкон

$C_{18}H_{18}O_4$ = 298.3.
CAS — 18493-30-6.



Profile

Metochalcone has been used as a choleretic.

Preparations

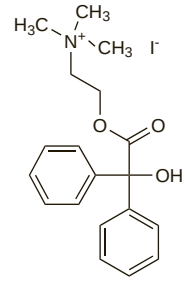
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Neocolan.

Metocinium Iodide *(pINN)*

Ioduro de metocinio; Metocinii Iodidum; Métocinium, Iodure de. (2-Hydroxyethyl)trimethylammonium iodide benzilate.

Метоциния Йодид

$C_{19}H_{24}INO_3$ = 441.3.
CAS — 2424-71-7.



Profile

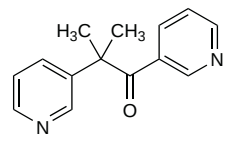
Metocinium iodide is used as an antispasmodic.

Metyrapone *(BAN, USAN, rINN)*

Metirapon; Metirapona; Metyrapon; Métyrapone; Metyraponi; Metyraponum; Su-4885 (metyrapone tartrate). 2-Methyl-1,2-di(3-pyridyl)propan-1-one.

Метирапон

$C_{14}H_{14}N_2O$ = 226.3.
CAS — 54-36-4.
ATC — V04CD01.
ATC Vet — QV04CD01.



Pharmacopoeias. In *Br.*, *Jpn*, and *US*.
BP 2008 (Metyrapone). A white to light amber crystalline powder with a characteristic odour. M.p. 50° to 53°. Sparingly soluble in water; freely soluble in alcohol and in chloroform; it dissolves in dilute mineral acids. Protect from light.
USP 31 (Metyrapone). A white to light amber, fine, crystalline powder, having a characteristic odour. It darkens on exposure to light. Sparingly soluble in water; soluble in chloroform and in methyl alcohol; forms water-soluble salts with acids. Store in air-tight containers. Protect from heat and light.

Adverse Effects

Metyrapone may give rise to nausea and vomiting, abdominal pain, headache, sedation, dizziness, hypotension, and hypersensitivity rashes. Hypoadrenalism, hirsutism, and bone marrow depression may occur rarely. Long-term use of metyrapone can cause hypertension.

Alopecia. Reports of alopecia[1,2] associated with administration of metyrapone for Cushing's syndrome.

1. Harris PL. Alopecia associated with long-term metyrapone use. *Clin Pharm* 1986; **5:** 66–8.
2. Harries-Jones R, Overstall P. Metyrapone-induced alopecia. *Postgrad Med J* 1990; **66:** 584.

Precautions

Metyrapone should be used with extreme caution, if at all, in patients with gross hypopituitarism or with reduced adrenal secretory activity because of the risk of precipitating acute adrenal failure. Thyroid dysfunction or liver cirrhosis may alter the response to metyrapone.

Dizziness and sedation may affect the performance of skilled tasks such as driving.

Porphyria. Metyrapone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Phenytoin is reported to increase the metabolism of metyrapone; doubling the dose of metyrapone may counteract the interaction. However, as many other drugs may interfere with steroid assessment, medication is best avoided where possible during the metyrapone test. Drugs reported to interfere with the metyrapone test include antidepressants such as amitriptyline, antithyroid drugs, antipsychotics such as chlorpromazine, barbiturates, corticosteroids, cyproheptadine, and hormones that affect the hypothalamic-pituitary axis such as oestrogens and progestogens.

Pharmacokinetics

Metyrapone is rapidly absorbed from the gastrointestinal tract. It is metabolised by rapid reduction to metyrapol and excreted in the urine as glucuronide conjugates of metyrapone and metyrapol.

Uses and Administration

Metyrapone inhibits the enzyme 11β-hydroxylase responsible for the synthesis of the glucocorticoids cortisone and hydrocortisone (cortisol) as well as aldosterone from their precursors. The consequent fall in the plasma concentrations of circulating glucocorticoids stimulates the anterior pituitary gland to produce more corticotropin. This, in turn, stimulates the production of more 11-deoxycortisol and other precursors which are metabolised in the liver and excreted in the urine where they can be measured. Metyrapone is therefore used as a test of the feedback hypothalamic-pituitary mechanism in the diagnosis of Cushing's syndrome, although the dexamethasone suppression test (p.1527) may be preferred.

After demonstration of the responsiveness of the adrenal cortex, metyrapone is given orally, usually in a dose of 750 mg every 4 hours for 6 doses. Taking doses with milk or after a meal may minimise the gastrointestinal adverse effects of metyrapone. A suggested oral dose for children is 15 mg/kg, with a minimum dose of 250 mg, every 4 hours for 6 doses. In patients with a normally functioning pituitary gland excretion of 17-hydroxycorticosteroids is increased two- to fourfold and that of 17-ketosteroids about twofold.

Metyrapone is also used in the management of Cushing's syndrome (below) when doses may range from 250 mg to 6 g daily.

Since metyrapone inhibits the synthesis of aldosterone it has been used to treat some cases of resistant oedema; it is given with a glucocorticoid to suppress the normal corticotropin response to low plasma concentrations of glucocorticoids. The suggested usual dosage of metyrapone in resistant oedema is 3 g daily in divided doses.

Metyrapone tartrate has also been used.

Cushing's syndrome. Cushing's syndrome is the result of a chronic excess of glucocorticoids.[1,2] It may be independent of the secretion of adrenocorticotrophic hormone (ACTH; corticotropin), either due to an adrenal tumour secreting cortisol, or to exogenous corticosteroids, or it may be ACTH-dependent, such as Cushing's disease proper, which is caused by excessive ACTH secretion from a pituitary adenoma; other ACTH-dependent forms may be due to pituitary hyperplasia, or an ectopic ACTH-secreting tumour elsewhere—usually bronchus or lung cancer. About two-thirds of all cases are due to Cushing's disease, which is 8 times more common in women than men.

Symptoms may develop insidiously over several years and include obesity, particularly of the trunk, rounding of the face,