of lysergide; the recurrence or 'flashback' may be spontaneous or induced by alcohol, other drugs, stress, or fatigue.

The subjective effects of lysergide may be preceded or accompanied by somatic effects that are mainly sympathomimetic in nature and include mydriasis, tremor, hyperreflexia, hyperthermia, piloerection, muscle weakness, and ataxia. There may be nausea and vomiting and increased heart rate and blood pressure. Derangement of blood clotting mechanisms has been described. In addition, respiratory arrest, convulsions, and coma may result from overdoses. There is no evidence of fatal reactions to lysergide in man, although accidental deaths, suicides, and homicides have occurred during lysergide intoxication.

Tolerance develops to the behavioural effects of lysergide after several days and may be lost over a similar period. There is cross-tolerance between lysergide, mescaline, and psilocybine and psilocin, but not to amfetamine or to cannabis.

Physical dependence on lysergide does not seem to occur.

Mace Oil

Macis, aceite de.

NOTE. Mace has also been used as a name for solutions of chloroacetophenone (p.2280), a tear gas.

Profile

Mace oil is a volatile oil obtained by distillation from mace, the arillus of the seed of *Myristica fragrans* (Myristicaceae).

Nutmeg (p.2355) is the dried kernel of the seed of *M. fragrans*.

Mace is used as a flavour and carminative similarly to nutmeg. It has also been used with herbal substances and other volatile agents in preparations for musculoskeletal and respiratory-tract disorders. As with nutmeg, large doses of mace may cause epileptiform convulsions and hallucinations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** China-Eisenwein; ***Cz.:*** Dr Theiss Schwedenbitter; Original Schwedenbitter; ***Rus.:*** Himcolin (Химколин).

Macrogols

Macrogola; Macrogoles; Macrogoller; Makrogoler; Makrogoliai; Makrogolit; Makrogolok; Makrogoly; PEGs; Polietilen Glikoller; Polyethylene Glycols; Polyoxyethylene Glycols.

$CH_2(OH)(CH_2OCH_2)_mCH_2OH$. Alternatively some authorities use the general formula $H(OCH_2CH_2)_nOH$ when the number assigned to *n* for a specified macrogol is 1 more than that of *m* in the first formula.

CAS — 25322-68-3 (macrogols); 37361-15-2 (macrogol 300).

ATC — A06AD15.

ATC Vet — QA06AD15.

Nomenclature. Macrogol is *BAN* and *rINN*. The name is followed by a figure which corresponds approximately to its average molecular weight.

Pharmacopoeias. Macrogols of various molecular weights are included in many pharmacopoeias.

Eur. (see p.vii) has a general monograph describing macrogol 300, 400, 600, 1000, 1500, 3000, 3350, 4000, 6000, 8000, 20 000, and 35 000. *USNF* has a general monograph describing Polyethylene Glycol which requires that it be labelled with the average nominal molecular weight as part of the official title.

Ph. Eur. 6.2 (Macrogols). Mixtures of polymers with the general formula $H(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

Macrogol 300, 400, and 600 are clear, viscous, colourless or almost colourless, hygroscopic liquids. Miscible with water; very soluble in alcohol, in acetone, and in dichloromethane.

Macrogol 1000 is a white or almost white, hygroscopic solid with a waxy or paraffin-like appearance. Very soluble in water; freely soluble in alcohol and in dichloromethane.

Macrogol 1500 is a white or almost white solid with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; freely soluble in alcohol.

Macrogol 3000 and 3350 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; very slightly soluble in alcohol.

Macrogol 4000, 6000, and 8000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; practically insoluble in alcohol.

Macrogol 20 000 and 35 000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water; practically insoluble in alcohol; soluble in dichloromethane.

All macrogols are practically insoluble in fatty oils and in mineral oils. All macrogols should be stored in airtight containers.

USNF 26 (Polyethylene Glycol). Addition polymers of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups. They may contain a suitable antoxidant. Each macrogol is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight increases, the water solubility, hygroscopicity, and solubility in organic solvents decrease, while the viscosity increases.

Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids, having a slight, characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material having a consistency similar to beeswax, or as creamy-white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethoxyethanol, in ethyl acetate, and in toluene; all grades are insoluble in ether and in hexane. The pH of a 5% solution of a macrogol in water is between 4.5 and 7.5.

Store in airtight containers.

Incompatibility. Macrogols can demonstrate oxidising activity leading to incompatibilities. The activity of bacitracin or benzylpenicillin may be reduced in a macrogol base. Some plastics are softened by macrogols.

Adverse Effects and Precautions

Macrogols appear to have relatively low toxicity, although any toxicity appears to be greatest with the macrogols of low molecular weight. They may cause stinging when used topically, especially on mucous membranes, and have been associated with hypersensitivity reactions such as urticaria. Hyperosmolality, metabolic acidosis, and renal failure have been reported after topical application of macrogols to burn patients. Topical preparations with a macrogol base should therefore be used with caution in patients with renal impairment and/or large areas of raw surfaces, burns, or open wounds.

Patients undergoing bowel cleansing with mixtures of macrogols (3350 or 4000) and electrolytes commonly experience local gastrointestinal discomfort, bloating, and nausea. Abdominal cramps, vomiting, and anal irritation may also occur and there have been rare reports of possible hypersensitivity reactions. These colonic lavage solutions are contra-indicated in gastrointestinal obstruction or perforation, ileus, gastric retention, peptic ulcer disease, and toxic megacolon; caution is advisable in patients with ulcerative colitis. Since aspiration may be a problem, they should be used with caution in patients with an impaired gag reflex, reflux oesophagitis, or diminished levels of consciousness. They should be given with caution to diabetic patients. Drugs taken within one hour of starting colonic lavage with an oral macrogol and electrolyte mixture may be flushed from the gastrointestinal tract unabsorbed.

Effects on fluid and electrolyte homoeostasis. A syndrome of elevated total serum calcium (with a concomitant decrease in ionised calcium), hyperosmolality, metabolic acidosis, and renal failure has been observed in *animals*[1] and in burn patients[2] after the topical application of preparations with a macrogol base. The FDA has recommended that topical preparations containing macrogols should be used with caution in burn patients with known or suspected renal impairment, as macrogols absorbed through denuded skin and not excreted normally by a compromised kidney could lead to symptoms of progressive renal impairment.[3]

The use of macrogol and electrolyte solutions for bowel preparation has also been associated with sodium and water retention, resulting in exacerbation of heart failure in a patient with diabetic gastroparesis,[4] and with the development of pulmonary oedema possibly due to aspiration in a child without cardiac or renal disease.[5]

1. Herold DA, *et al.* Toxicity of topical polyethylene glycol. *Toxicol Appl Pharmacol* 1982; **65:** 329–35.
2. Bruns DE, *et al.* Polyethylene glycol intoxication in burn patients. *Burns* 1982; **9:** 49–52.
3. Anonymous. Topical PEG in burn ointments. *FDA Drug Bull* 1982; **12:** 25–6.
4. Granberry MC, *et al.* Exacerbation of congestive heart failure after administration of polyethylene glycol-electrolyte lavage solution. *Ann Pharmacother* 1995; **29:** 1232–5.
5. Paap CM, Ehrlich R. Acute pulmonary edema after polyethylene glycol intestinal lavage in a child. *Ann Pharmacother* 1993; **27:** 1044–7.

Effects on the kidneys. Macrogol 400, which was present in a lorazepam injection, could have contributed to renal damage suggestive of acute tubular necrosis in a patient who received large doses (averaging lorazepam 95 mg daily) for 43 days.[1] The cumulative dose of macrogol 400 during this period was about 220 mL.

1. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; **29:** 1110–14.

Hypersensitivity. Hypersensitivity to macrogols is uncommon but both immediate urticarial reactions and delayed allergic contact dermatitis have been reported following the topical application of preparations with a macrogol vehicle or base.[1] An anaphylactic reaction has been associated with the ingestion of macrogols in a multivitamin tablet.[2] The manufacturers of preparations containing macrogols and electrolytes for bowel cleansing have reported isolated instances of skin reactions and rhinorrhoea.

1. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978; **4:** 135–8.
2. Kwee YN, Dolovich J. Anaphylaxis to polyethylene glycol (PEG) in a multivitamin tablet. *J Allergy Clin Immunol* 1982; **69:** 138.

Overdosage. Ingestion of 2 litres of a colonic lavage solution containing macrogol 400 instead of macrogol 4000 resulted in a patient developing severe metabolic acidosis due to systemic absorption of the macrogol and rapidly becoming comatose.[1] The patient was successfully treated with intravenous bicarbonate and dialysis.

1. Bélaïche J, *et al.* Coma acidosique après préparation colique par du polyèthylène glycol. *Gastroenterol Clin Biol* 1983; **7:** 426–7.

Pharmacokinetics

Liquid macrogols may be absorbed when taken by mouth but macrogols of high molecular weight, such as macrogol 3350, are not significantly absorbed from the gastrointestinal tract. There is evidence of absorption of macrogols when applied to damaged skin. Macrogols entering the systemic circulation are predominantly excreted unchanged in the urine; low-molecular-weight macrogols may be partly metabolised.

◊ References.

1. DiPiro JT, *et al.* Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. *Clin Pharm* 1986; **5:** 153–5.

Uses and Administration

Macrogols are relatively stable, non-toxic compounds which have a range of properties depending on their molecular weight. They are widely used in pharmaceutical manufacturing as water-soluble bases for topical preparations and suppositories, as solvents and vehicles, and as solubilising agents, tablet binders, plasticisers in film coating, and tablet lubricants. They have also been reported to have antibacterial properties. Macrogols of high molecular weight such as macrogol 4000 have been used as inert markers in studies on intestinal absorption and excretion.

A mixture of macrogol 3350 or 4000 with electrolytes is used for **bowel preparation** before colonoscopy, radiological procedures, or surgery. These preparations have been formulated so that the osmotic activity of the macrogol and concentrations of the electrolytes result in a minimum net effect on the fluid and electrolyte balance. Reconstituted aqueous solutions of different preparations contain about 59 g or 100 g or 105 g of the macrogol per litre. The method of administration depends on the preparation. Adults are given 200 to 300 mL of the reconstituted aqueous solution, which they have to swallow rapidly, and this is repeated every 10 to 15 minutes until the rectal effluent is clear, or until a total of 3 to 4 litres of the solution has been consumed. Alternatively, 2 litres of reconstituted solution is taken in the evening preceding the clinical procedure, or divided as 1 litre in the evening and 1 litre in the early morning of the day of the procedure. A dose for children is 25 mL/kg per hour. Bowel evacuation usually begins about 1 hour after starting dosage and is complete in about 4 hours. Patients should fast for at least 2 or 3 hours before drinking the solution. Additional flavouring ingredients, sugar, or other sweeteners should not be added to the solution. If distension or pain occur, dosage should be temporarily stopped or the interval between drinks extended. For use by nasogastric tube, a rate of 20 to 30 mL per minute has been used.

Similar preparations are used in patients 12 years of age and over for the treatment of **chronic constipation** in a usual dose of 125 mL of a solution containing 105 g of the macrogol per litre, up to three times daily. The maximum course is 2 weeks, which may be repeated if necessary. For children with chronic constipation, the usual initial daily dose for those aged 2 to 6 years is 62.5 mL, and for those aged 7 to 11 years, 125 mL. Thereafter, the dose should be increased or decreased as necessary to produce regular soft stools; the usual maximum dose is 250 mL daily.

In the management of **faecal impaction**, 8 doses of 125 mL of solution should be consumed within 6 hours for a maximum of 3 days. Patients with impaired cardiovascular function should take no more than 2 doses in any one hour. Children aged 5 to 11 years may be treated for faecal impaction in an escalating dose until disimpaction occurs up to a maximum of 7 days; the total daily dose should be divided and consumed within a 12-hour period. Four doses of 62.5 mL of solution are given initially on the first day, increasing steadily to a maximum of 12 doses daily on days 5 to 7. Doses for prevention of recurrence of faecal impaction in children are as for children's doses for chronic constipation (see above). The *BNFC* recommends that children aged 1 to 5 years with faecal impaction may be given two doses of 62.5 mL of solution on the first day, then four doses daily for 2 days, then 6 doses daily for 2 days, and finally 8 doses daily on days 6 and 7.

Conjugation of drugs and therapeutic proteins with macrogols (**pegylation**) has been tried in an attempt to improve their pharmacokinetic profiles and to reduce their adverse effects. Pegylation may also reduce the immunogenicity of therapeutic proteins. Examples of pegylated proteins include pegademase (p.2364), pegaspargase (p.682), and peginterferon alfa (p.888).

Drug delivery systems. References to the use of macrogols in delivery systems for drugs and proteins.

1. Reddy KR. Controlled-release, pegylation, liposomal formulations: new mechanisms in the delivery of injectable drugs. *Ann Pharmacother* 2000; **34:** 915–23.
2. Harris JM, *et al.* Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* 2001; **40:** 539–51.

Phenol poisoning. Washing with liquid macrogols has been recommended in the emergency treatment of skin contamination with phenol, see p.1656.