NOVARTIS

Methergin®

Specific uterotonic agent

COMPOSITION

Active substance: Methylergometrine maleate

Coated tablets containing 0.125 mg methylergometrine maleate

Excipients: Tableting excipients

Oral solution (1 mL = 25 drops) containing 0.25 mg methylergometrine maleate per mL

Excipients: Preservatives E 216 and E 218; excipients to vol., equivalent to 6% ethanol V/V.

Solution for injection, in 1 mL ampoules, containing 0.2 mg methylergometrine maleate per mL

Excipients: Sodium chloride, water.

PROPERTIES AND ACTIONS

Methylergometrine, a semi-synthetic derivative of the naturally occurring alkaloid ergometrine, is a potent and specific uterotonic agent. It acts directly on uterine smooth muscle and increases the basal tone, frequency and amplitude of rhythmic contractions.

Compared with other ergot alkaloids its effect on the cardiovascular and central nervous systems is less pronounced. The strong and selective oxytocic effect of methylergometrine results from its specific pattern of actions as partial agonist and antagonist at serotoninergic, dopaminergic and alpha-adrenergic receptors. This does not entirely preclude vasoconstrictive complications, however (see **ADVERSE EFFECTS**).

PHARMACOKINETICS

Methylergometrine takes effect 30–60 seconds after intravenous administration, 2–5 minutes after intramuscular administration and 5–10 minutes after oral administration, and continues to act for 4–6 hours.

Absorption

Studies in fasting female volunteers showed oral absorption from a 0.2 mg methylergometrine tablet to be rapid, with a mean peak plasma concentration (C_{max}) of 3243 ± 1308 pg/mL observed at 1.12 ± 0.82 hours (t_{max}). Following i.m. injection of 0.2 mg methylergometrine, C_{max} was 5918 ± 1952 pg/mL and t_{max} 0.41 ± 0.21 hours. The bioavailability was dose-proportional following oral administration of 0.1 mg, 0.2 mg and 0.4 mg of the i.m. solution, and was equivalent to the bioavailability of the 0.2 mg tablet. Following i.m. injection the extent of absorption was approx. 25% greater than after oral administration. Delayed gastrointestinal absorption (t_{max} approx. 3 hours) was observed in postpartum women during continuous treatment with Methergin tablets.

Distribution

Following i.v. injection, methylergometrine is rapidly distributed from plasma to peripheral tissues (within 2–3 minutes or less). In female volunteers the distribution volume is 56.1 ± 17.0 litres (~ 0.5 litres/kg). It is not known whether the active substance passes the blood-brain barrier.

Metabolism

Methylergometrine is metabolized mainly in the liver. The metabolic pathway has not been investigated in humans. *In vitro* studies showed N-demethylation and hydroxylation of the phenyl ring.

Elimination

In female volunteers plasma clearance is 14.4 ± 4.5 litres/hour and the mean elimination half-life is 3.29 ± 1.31 hours. A study in male volunteers showed that only 3% of an oral dose is excreted unchanged in the urine. The active substance is excreted mainly via the bile in the faeces. In patients given continuous treatment it is also excreted in the breast milk. A milk-plasma ratio of approx. 0.3 was found.

INDICATIONS / POTENTIAL USES

Active management of the third stage of labour (to promote separation of the placenta and reduce blood loss).

Treatment of uterine atony/haemorrhage during and after the third stage of labour; in association with Caesarean section; following abortion.

Treatment of subinvolution of the uterus, lochiometra and puerperal bleeding.

Use of Methergin during lactation is not recommended (see **Pregnancy and Lactation**).

DOSAGE AND ADMINISTRATION

Active management of the third stage of labour

0.5–1 mL (= 0.1–0.2 mg) slowly i.v. following delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant (see Precautions). Expulsion of the placenta – usually separated by the first strong uterine contraction following administration of Methergin – should be manually assisted by applying fundal pressure.

The recommended dose for delivery under general anaesthesia is 1 mL (0.2 mg).

Uterine atony/haemorrhage

1 mL i.m. or 0.5–1 mL i.v. This may be repeated as required at intervals of no less than 2 hours, although no more than 5 injections should be given during a 24 hour period.

Subinvolution of the uterus, lochiometra, puerperal bleeding

0.125–0.25 mg orally (1–2 tablets or 0.5–1 mL [13–25 drops] oral solution) or 0.5–1 mL s.c. or i.m. up to 3 times daily (see Pregnancy and Lactation).

RESTRICTIONS ON USE

Contraindications

Pregnancy; first stage of labour, second stage of labour before crowning of the head (Methergin must not be used for induction or augmentation of labour); severe hypertension, pre-eclampsia, eclampsia, occlusive vascular disease (including ischaemic heart disease); sepsis; known hypersensitivity to ergot alkaloids or any of the other ingredients; hepatic and renal insufficiency.

Precautions

In breech and other abnormal presentations, Methergin should not be given before delivery of the infant is complete, and it should not be given in multiple birth before the last infant has been delivered.

Active management of the third stage of labour requires obstetric supervision.

Intravenous injections should be given slowly over a period of no less than 60 seconds and with careful monitoring of blood pressure. Intra- or periarterial injection must be avoided.

Caution is required in the presence of mild to moderate hypertension (severe hypertension is a contraindication), anaemia or severe hyperthyroidism because of possible aggravation of cardiovascular symptoms.

Caution is required when coadministering sulprostone and/or oxytocin in the treatment of postpartum atonic uterine haemorrhage (see **INTERACTIONS**).

Pregnancy and Lactation

There is clear evidence of risk to the human fetus. Methergin is contraindicated during pregnancy on account of its potent uterotonic effect, which increases the risk of abortion or premature contractions.

Methergin passes into the breast milk. There have been isolated reports of intoxication in breastfed infants whose mothers had been given Methergin over a period of several days.

One or more of the following symptoms were observed in breastfed infants (and disappeared on withdrawal of the medication): raised blood pressure, bradycardia or tachycardia, vomiting, diarrhoea, restlessness, clonic seizures.

Methergin may impair milk secretion.

On account of the risks of adverse effects in the infant and reduced milk secretion, use of Methergin during lactation is not recommended.

ADVERSE EFFECTS

Central nervous system

Common: Headache.
Uncommon: Light-headedness, dizziness, seizures.
Rare: Hallucinations.

Cardiovascular system

Common: Hypertension.
Uncommon: Chest pain, hypotension.
Rare: Bradycardia, tachycardia, palpitations, peripheral vasospastic reactions, myocardial infarction.

Gastrointestinal tract

Uncommon: Nausea, vomiting.

Skin and appendages

Common: Skin rash.
Uncommon: Increased sweating.

Urogenital system

Common: Abdominal pain (due to uterine contractions).

Other

Rare: Anaphylactic reactions (dyspnoea, hypotension, collapse, shock).

INTERACTIONS

Methergin may increase the vasoconstrictor/vasopressor effects of other drugs, such as sympathomimetics (including those in local anaesthetics) or other ergot alkaloids. The concomitant use of bromocriptine and Methergin during the puerperium is therefore not recommended.

For the prevention and treatment of uterine haemorrhage by i.m. injection, it may be advantageous to combine the two uterotonic agents, Methergin and oxytocin, since oxytocin has a very short latency period, while methylergometrine has a prolonged duration of action.

However, caution is required: There have been reports of sometimes fatal ventricular tachycardia/fibrillation and myocardial infarction/cardiac arrest in connection with coadministration of sulprostone and/or oxytocin and/or methylergometrine in the treatment of postpartum atonic uterine haemorrhage.

Anaesthetics such as halothane or methoxyflurane may reduce the uterotonic efficacy of Methergin.

OVERDOSE

Signs and symptoms

Nausea, vomiting; hypertension or hypotension; numbness, tingling and pain in the extremities; respiratory depression; seizures, coma.

Management

Elimination of orally ingested drug by repeated administration of high doses of activated charcoal.

Symptomatic treatment with strict cardiovascular and respiratory monitoring.

Benzodiazepines may be given if sedation is necessary.

In the event of severe arteriospasm, vasodilators should be administered (e.g. sodium nitroprusside, phentolamine or dihydralazine). In the event of coronary constriction, appropriate anti-anginal therapy (e.g. nitrates) should be given.

OTHER INFORMATION

Shelf-life

Keep medicines out of the reach of children.

Coated tablets: Do not store above 30°C.

Oral solution: Store in a refrigerator (2–8°C) and protect from light.

Instructions for use of the oral solution

To open the tamper-evident seal, raise the plastic cap and pull in the direction of the arrow. Do not shake. Use within three months of opening.

Ampoules: Store in a refrigerator (2–8°C) and protect from frost and light.

Do not use after the expiry date (= EXP) printed on the pack.

PACK SIZES

Country specific pack sizes.

MANUFACTURER

See folding box.

Information last revised : August 2005

Approval date (text) : 10 August 2005

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

2029359 **R02** WEH