Methylergonovine Maleate Injection, USP

Rx only

DESCRIPTION
Methylergonovine maleate is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.

Methylergonovine maleate is available in sterile vials of 1 mL, containing 0.2 mg methylergonovine maleate for intramuscular or intravenous injection.

Vials, 1 mL, clear, colorless solution.
Active Ingredient: methylergonovine maleate, USP, 0.2 mg.
inactive Ingredients: maleic acid, 0.10 mg; sodium chloride, 7.0 mg; water for injection, qs to 1 mL.

Chemically, methylergonovine maleate is designated as ergoline-8-carboxamide, 9,10-didehydro-1-(hydroxymethyl)propyl]-6-methyl-,[8(S), (2)-2-butenedioate (1:1) (salt).

Its structural formula is:

\[
\text{C}_{20}\text{H}_{25}\text{N}_{2}\text{O}_{5} \cdot \text{C}_{6}\text{H}_{5}\text{O}_{3} \quad \text{Mol. wt. – 455.51}
\]

CLINICAL PHARMACOLOGY
Methylergonovine maleate acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions. Thus, it induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss. The onset of action after I.V. administration is immediate; after I.M. administration, 2 to 5 minutes, and after oral administration, 5 to 10 minutes.

Pharmacokinetic studies following an I.V. injection have shown that methylergonovine is rapidly distributed from plasma to peripheral tissues within 2 to 3 minutes or less. The bioavailability after oral administration was reported to be about 60% with no accumulation after repeated doses. During delivery, with intramuscular injection, bioavailability increased to 78%. Ergot alkaloids are mostly eliminated by hepatic metabolism and excretion, and the decrease in bioavailability following oral administration is probably a result of first-pass metabolism in the liver.

Bioavailability studies conducted in fasting healthy female volunteers have shown that oral absorption of a 0.2 mg methylergonovine tablet was fairly rapid with a mean peak plasma concentration of 3243 ± 1308 pg/mL observed at 1.12 ± 0.82 hours. For a 0.2 mg intramuscular injection, a mean peak plasma concentration of 5918 ± 1952 pg/mL was observed at 0.41 ± 0.21 hours. The extent of absorption of the tablet, based upon methylergonovine plasma concentrations, was found to be equivalent to that of the I.M. solution given orally, and the extent of oral absorption of the I.M. solution was proportional to the dose following administration of 0.1, 0.2, and 0.4 mg. When given intramuscularly, the extent of absorption of methylergonovine maleate solution was about 25% greater than the tablet. The volume of distribution (Vd,F) of methylergonovine was calculated to be 56.1 ± 17.0 liters, and the plasma clearance (CLp/F) was calculated to be 14.4 ± 4.5 liters per hour. The plasma level decline was biphasic with a mean elimination half-life of 3.39 hours (range 1.5 to 12.7 hours). A delayed gastrointestinal absorption (Tmax about 3 hours) of Methylergonovine Maleate tablet might be observed in postpartum women during continuous treatment with this oxytocic agent.

INDICATIONS AND USAGE
For routine management after delivery of the placenta; postpartum atony and hemorrhage; subinvolution. Under full obstetric supervision, it may be given in the second stage of labor following delivery of the anterior shoulder.

CONTRAINDICATIONS
Hypertension; toxemia; pregnancy; and hypersensitivity.

WARNINGS
This drug should not be administered I.V. routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If I.V. administration is considered essential as a lifesaving measure, methylergonovine maleate should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra-arterial or periarterial injection should be strictly avoided.

PRECAUTIONS
General
Caution should be exercised in the presence of sepsis, obliterative vascular disease, hepatic or renal involvement. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

Drug Interactions
CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)
There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there have been no reports of such interactions with methylergonovine alone, potent CYP 3A4 inhibitors should not be co-administered with methylergonovine. Examples of some of the more potent CYP 3A4 inhibitors include macrolide antibiotics (e.g., erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP 3A4 Inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) orazole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP 3A4 Inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with methylergonovine.

No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Caution should be exercised when methylergonovine maleate is used concurrently with other vasoconstrictors or ergot alkaloids.
Because reports of overdosage with methylergonovine maleate are infrequent, the lethal dose in humans has not been established. The oral LD₅₀ (in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5.² Several cases of accidental methylergonovine maleate injection in newborn infants have been reported, and in such cases 0.2 mg represents an overdose of great magnitude. However, recovery occurred in all but one case following a period of respiratory depression, hypothermia, hypertonicity with jerking movements, and, in one case, a single convulsion.

Also, several children 1-3 years of age have accidentally ingested up to 10 tablets (2 mg) with no apparent ill effects. A postpartum patient took 4 tablets at one time in error and reported paresthesias and clamminess as her only symptoms. Treatment of acute overdosage is symptomatic and includes the usual procedures of:

1. removal of offending drug by inducing emesis, gastric lavage, catharsis, and supportive diuresis.
2. maintenance of adequate pulmonary ventilation, especially if convulsions or coma develop.
3. correction of hypotension with pressor drugs as needed.
4. control of convulsions with standard anticonvulsant agents.
5. control of peripheral vasospasm with warmth to the extremities if needed.³

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Intramuscularly

Doseage same as intramuscular. (See WARNINGS.)

Orally

One tablet, 0.2 mg, 3 or 4 times daily in the puerperium for a maximum of 1 week.

HOW SUPPLIED

Vials

1 mL fill size

Boxes of 20

Store and Dispense

Vials: Store in refrigerator, 2°C to 8°C (36°F to 46°F). Protect from light. Use carton to protect contents until used. Administer only if solution is clear and colorless.

References

1. Information on Adverse Reactions supplied by Medical Services Department, Novartis Pharmaceuticals, E. Hanover, N.J., based on computerized clinical reports.

Manufactured for:           Manufactured by:
PharmaForce, Inc.           PharmaForce, Inc.
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