ANESTHETICS, INHALATION (Systemic)

Indications

Accepted

Anesthesia, general¾Enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide are indicated for the induction and maintenance of general anesthesia [1], [2], [3], [4], [10].

However, inhalation anesthetic agents are rarely used alone; other medications are frequently administered to induce or supplement anesthesia.

Because of its weak anesthetic potency and muscle relaxant properties, nitrous oxide must be supplemented with another anesthetic or anesthesia adjunct (such as a barbiturate, benzodiazepine, opioid analgesic, or another inhalation anesthetic) and/or a neuromuscular blocking agent. Also, nitrous oxide is often administered concurrently with one of the other inhalation anesthetics to decrease the requirement for the more potent anesthetic.

[Enflurane] *,[isoflurane] * , methoxyflurane, and nitrous oxide are indicated in low doses to provide analgesia for procedures not requiring loss of consciousness.

Enflurane,[isoflurane] * , methoxyflurane, and nitrous oxide are indicated in low doses to provide analgesia for vaginal delivery [2], [12].

For cesarean section: Enflurane,[halothane] * , [isoflurane] * , and [methoxyflurane] * are indicated in low concentrations [2] to supplement other general anesthetics during delivery by cesarean section [2].

Mechanism of action/Effect:

The precise mechanism by which inhalation anesthetics produce loss of perception of sensations and unconsciousness is not known. Inhaled anesthetics act at many areas in the CNS. The Meyer-Overton theory suggests that the site of action of inhalation anesthetics may be the lipid matrix of neuronal membranes or other lipophilic sites. Anesthetics may cause changes in membrane thickness, which in turn affect the gating properties of ion channels in neurons. Interference with the hydrophobic portion of neuronal ion channel membrane proteins may be an important mechanism [22], [23].

Absorption:

Inhalation anesthetics are rapidly absorbed into the circulation via the lungs.

Precautions to Consider

Carcinogenicity

Isoflurane: Although one study indicated that isoflurane may be carcinogenic, it is thought that exposure of the test animals to polybrominated biphenyls may have been responsible. Subsequent studies in which such exposure was avoided have not shown evidence of isoflurane-induced carcinogenicity [4].

Enflurane, halothane, methoxyflurane, and nitrous oxide: These anesthetics have not been shown to be carcinogenic 4.

Tumorigenicity

Enflurane: Studies in mice have not shown evidence of tumorigenicity with enflurane 2.

Mutagenicity

Halothane: In vitro testing (Ames test) has indicated that potential halothane metabolites (but not halothane itself) may be mutagenic.

Enflurane, isoflurane, methoxyflurane, and nitrous oxide: Mutagenic effects have not been observed with these inhalation anesthetics in the Ames test or the sister chromatid exchange test 4.

However, statistically significant increases in sperm abnormalities have been observed in mice following 20 hours of exposure to 1.2% of enflurane 2.

Pregnancy/Reproduction

Pregnancy¾Inhalation anesthetics cross the placenta. Risk-benefit must be considered because studies (by retrospective survey) of operating room personnel chronically exposed to low concentrations of inhalation anesthetics indicate that pregnancies in female personnel and wives of male personnel may be subject to an increased incidence of spontaneous abortions, stillbirths, and possibly birth defects 13, 14.

However, the methods used in obtaining and interpreting the data in these studies have been questioned. Also, several animal studies (in which operating room conditions were simulated) have failed to show fetotoxic or teratogenic effects following chronic exposure of male and/or female animals to low concentrations of inhalation anesthetics prior to and/or during gestation. 13, 14

First trimester: Administration of enflurane, halothane, or isoflurane 4 early in pregnancy (for therapeutic abortion) has been reported to increase uterine bleeding. However, blood loss following enflurane administration was considered to be within acceptable limits.

Enflurane¾Although studies in patients have not been done, some studies in rats and rabbits have not shown that enflurane causes adverse effects on the fetus 2.

However, other studies in animals have shown that enflurane may be teratogenic.

FDA Pregnancy Category B 2.

Halothane¾Although studies in patients have not been done, some animal studies have shown that halothane may be teratogenic 1, 3.

FDA Pregnancy Category C 3.

Isoflurane¾Although isoflurane has not been shown to cause fetal malformations in mice or rats, studies in mice receiving 7 MAC hours (the equivalent of 1 MAC [minimum alveolar concentration that prevents movement in 50% of subjects following a painful stimulus] administered for 7 hours) over a period of 10 days during gestation have indicated possible fetotoxicity as manifested by higher implantation losses and a significantly lower live birth index [4].

Studies have not been done in patients.

FDA Pregnancy Category C [4].

Methoxyflurane¾Although adequate and well-controlled studies in patients have not been done, some studies in animals have shown that methoxyflurane may be teratogenic [12].

Also, studies in rats have indicated that exposure to doses equivalent to 67 hours of 0.2% methoxyflurane caused fetal growth retardation.

FDA Pregnancy Category C.

Nitrous oxide¾Although problems in patients have not been documented, studies in rats have shown that nitrous oxide causes fetal death, growth retardation, and skeletal anomalies.Labor and delivery¾Minimum alveolar concentration (MAC) is decreased in pregnancy. MAC continues to be decreased during the early postpartum period. By 72 hours postpartum, MAC returns to normal [25, 26].

Enflurane, halothane, isoflurane, and methoxyflurane produce dose-dependent uterine relaxation, which may delay delivery and increase postpartum bleeding [4, 12].

Subanesthetic (analgesic) concentrations of enflurane, isoflurane, or methoxyflurane do not significantly decrease uterine contractions [2, 4, 5, 12].

Halothane is the most potent uterine relaxant [3] ; even low concentrations (< 0.5%) may decrease uterine contractions. Also, enflurane and halothane cause a dose-dependent decrease in the uterine response to oxytocics [1, 2].

Use of halothane during vaginal delivery is not recommended unless uterine relaxation is required (as for version or other intrauterine manipulations) [12].

Although its safety in obstetrics has not been established by formal studies, isoflurane is used to provide obstetrical analgesia [4].

Postpartum¾High concentrations of inhalation anesthetics administered during prolonged delivery may increase the risk of neonatal depression.

Methoxyflurane: Inorganic fluoride produced by methoxyflurane metabolism has been detected in cord blood in concentrations that are usually lower than, but sometimes equal to, the maternal blood concentration [5].

The effect of inorganic fluoride on the neonate is not known; however, nephrotoxicity in the infant is thought to be unlikely following recommended doses of methoxyflurane [5].

Breast-feeding

It is not known if enflurane, halothane, isoflurane or methoxyflurane is distributed into breast milk 3.

However, problems in humans have not been documented.

Pediatrics

Studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of inhalation anesthetics in children. However, the MAC of inhalation anesthetics is higher in children than in adults. The MAC is highest in very young children and decreases as the age of the child increases 4.

Geriatrics

The MAC an anesthetic is decreased in geriatric patients 4.

Also, geriatric patients may be more susceptible to anesthetic-induced hypotension and circulatory depression and to methoxyflurane-induced nephrotoxicity; especially careful attention to dosage is recommended 4.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

See Table 3.

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Cerebrospinal fluid (CSF) pressure 4

(anesthetics may increase CSF pressure)

Liver function 4

(abnormalities in liver function as shown by transient, mild increases in serum transaminase and/or lactate dehydrogenase activity may occur in the absence of hepatotoxicity; with enflurane, halothane, or methoxyflurane, significant abnormalities indicating hepatotoxicity may occur rarely)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).