

NAME OF MEDICINE

FORTHANE Abbott Laboratories (N.Z.) Ltd

Isoflurane

PRESENTATION

Isoflurane is a nonflammable liquid administered by vaporization. It is a general inhalation anaesthetic medicine with a mildly pungent ethereal odour containing no additives or chemical stabilizers.

USES

ACTIONS

Isoflurane is a general inhalation anaesthetic.

Induction, and particularly recovery are rapid. Although slight pungency may limit the rate of induction, excessive salivation and tracheobronchial secretions are not stimulated. Pharyngeal and laryngeal reflexes are diminished quickly. Levels of anaesthesia may be changed rapidly with Isoflurane. Heart rhythm remains stable. Spontaneous respiration becomes depressed as depth of anaesthesia increases and should be closely monitored and supported when necessary.

During induction there is a decrease in blood pressure, which returns towards normal with surgical stimulation.

Blood pressure tends to fall during maintenance in direct relation to depth of anaesthesia, but cardiac rhythm remains stable. With controlled respiration and normal PaCO₂, cardiac output tends to be maintained despite increasing depth of anaesthesia primarily through a rise in heart rate, which compensates for a reduction in stroke volume. With spontaneous respiration, the resulting hypercapnia may increase heart rate and cardiac output above awake levels.

Cerebral blood flow remains unchanged during light Isoflurane anaesthesia but tends to rise at deeper levels. Increases in cerebrospinal fluid pressure may be prevented or reversed by hyperventilating the patient before or during anaesthesia.

Electroencephalographic changes and convulsions are extremely rare with Isoflurane. In general, Isoflurane produces an EEG pattern similar to that seen with other volatile anaesthetics.

Isoflurane appears to sensitize the myocardium to adrenaline to an even lesser extent than enflurane. Limited data suggest that subcutaneous infiltration of up to 50 ml of 1:200,000 solution adrenaline does not induce ventricular arrhythmias in patients anaesthetized with Isoflurane.

Muscular relaxation may be adequate for some intra-abdominal operations at normal levels of anaesthesia, but should greater relaxation be required small doses of intravenous muscle relaxants may be used.

Isoflurane may be used for the induction and maintenance of general anaesthesia. Adequate data are not available to establish its place in pregnancy.

PHARMACOKINETICS

Relatively little metabolism of Isoflurane occurs in the human body. In the postoperative period only 0.17% of the Isoflurane taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 micromole/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after Isoflurane administration.

Known metabolites of Isoflurane have been found to be either nontoxic or present in too low a concentration to be harmful.

INDICATIONS

Isoflurane may be used for induction and maintenance of general anaesthesia. This anaesthetic agent can also be used for sedation of ventilated patients in the intensive therapy unit for up to 48 hours.

DOSAGE AND ADMINISTRATION

Vaporizers specially calibrated for Isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

General Anaesthesia

MAC values for Isoflurane diminish with age, falling from an average in oxygen of 1.28% in the mid-twenties to 1.15% in the mid-forties, to 1.05% in the mid-sixties age group. For neonates the MAC of Isoflurane in oxygen is 1.6%, in infants aged 1 month to 6 months is 1.87%, and from 6 months to 12 months, 1.80%.

Premedication: Medicines used for premedication should be selected for the individual patient, bearing in mind the respiratory depressant effect of Isoflurane. The use of anticholinergic medicines is a matter of choice.

Induction: A short-acting barbiturate or other intravenous induction agent is usually administered followed by inhalation of the Isoflurane mixture. Alternatively, Isoflurane with oxygen or with an oxygen/nitrous oxide mixture may be used.

It is recommended that induction with Isoflurane be initiated at a concentration of 0.5%. Concentrations of 1.5-3.0% usually produce surgical anaesthesia in 7-10 minutes.

Maintenance: Surgical levels of anaesthesia may be maintained with 1.0-2.5% Isoflurane in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% Isoflurane may be required when given with oxygen alone. If added relaxation is required, supplemental doses of muscle relaxant may be used.

Arterial pressure levels during maintenance tend to be inversely related to alveolar Isoflurane concentrations in the absence of other complicating factors. Excessive falls in blood pressure may be due to depth of anaesthesia and, in these circumstances, should be corrected by reducing the inspired Isoflurane concentration.

Elderly: As with other agents, lesser concentrations of Isoflurane are normally required to maintain surgical anaesthesia in elderly patients. See above for MAC values.

Sedation: Sedation may be maintained with 0.1 - 1.0% Isoflurane in air/oxygen mixtures. This dose will need to be titrated to the requirements of the individual patients.

CONTRAINDICATIONS

Isoflurane is contraindicated in patients with known sensitivity to isoflurane or other halogenated anaesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Isoflurane must not be used in patients who have developed an icterus and/or fever of unknown origin after administration of isoflurane or another halogenated anaesthetic.

WARNINGS AND PRECAUTIONS

General: As with any potent general anaesthetic, Isoflurane should only be administered in an adequately equipped anaesthetizing environment by those who are familiar with the pharmacology of the medicine and qualified by training and experience to manage the anaesthetized patient. Since levels of anaesthesia may be altered quickly and easily with Isoflurane, only vaporizers which deliver a predictable output with reasonable accuracy, or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory depression may provide some indication of anaesthetic depth.

Reports demonstrate that Isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances. Repeat anaesthesia with a halogenated anaesthetic within a short period of time (3 months) is best avoided since the risk of hepatotoxicity is not fully understood.

Regardless of the anaesthetics employed, maintenance of normal haemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease.

As with other halogenated agents, Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary.

The action of non-depolarizing relaxants is markedly potentiated with Isoflurane.

Isoflurane markedly increases cerebral blood flow at deeper levels of anaesthesia. There may be a transient rise in cerebral spinal fluid pressure, which is fully reversible with hyperventilation. Fewer postoperative cerebral effects are likely to be found with Isoflurane than after comparable anaesthesia.

Since levels of anaesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations and flow rates should be used. Hypotension and respiratory depression increase as anaesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing uterine curettage.

Isolated cases of increased carboxyhaemoglobin have been reported with the use of halogenated inhalation agents with a -CF₂H moiety (ie, desflurane, enflurane and isoflurane). No clinically significant concentrations of carbon monoxide are produced in the presence of normally hydrated absorbents. Care should be taken to follow manufacturers' instructions for CO₂ absorbents.

Replacement of Desiccated CO₂ Absorbents: Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during administration of general anaesthesia with

drugs in this class when used in conjunction with desiccated CO₂ absorbents, specifically those containing potassium hydroxide (e.g., Baralyme). When a clinician suspects that the CO₂ absorbent may be desiccated, it should be replaced before the administration of isoflurane. The colour indicator of most CO₂ absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO₂ absorbents should be replaced routinely regardless of the state of the colour indicator.

Use in pregnancy

Category B3.

Reproduction studies have been carried out on animals after repeated exposure to anaesthetic concentrations of Isoflurane. Isoflurane has been shown to have a possible anaesthetic-related foetotoxic effect in mice when given in doses 6 times the human dose. Studies with the rat demonstrated no effect on fertility, pregnancy or delivery or on the viability of the offspring. No evidence of teratogenicity was revealed. Comparable experiments in rabbits produced similar negative results. The relevance of these studies to humans is not known, as there are no adequate and well-controlled studies in pregnant women. Safety in pregnancy has not been established but there is no reason to suspect any specific adverse effect of the agent used for anaesthesia during pregnancy. Blood losses comparable with those found following anaesthesia with other inhalation agents have been observed with Isoflurane in patients undergoing pregnancy termination.

Use in caesarean section

Isoflurane, in concentrations up to 0.75%, has been shown to be safe and efficacious for the maintenance of anaesthesia for caesarean section. No adverse event was experienced by the mother or neonate as a result of administering Isoflurane.

Use in Children under 2 years of age

Isoflurane may be used in neonates and infants under 2 years of age with an acceptable margin of efficiency and safety and is compatible with all medicines commonly used in anaesthetic practice.

Use in Lactation

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when Isoflurane is administered to a nursing woman.

Malignant hyperthermia

In susceptible individuals, Isoflurane anaesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these nonspecific signs may appear with light anaesthesia, acute hypoxia, etc.). An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g. Isoflurane), intravenous administration of dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for intravenous dantrolene sodium for additional information on patient management). Renal failure may appear later, and urine flow should be sustained if possible.

Hyperkalaemic Cardiac Arrest in Paediatric Patients:

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Information to patients

Isoflurane, as well as other general anaesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anaesthesia. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

ADVERSE EFFECTS

Adverse reactions encountered in the administration of Isoflurane are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anaesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anaesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The aetiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the exposure to multiple concomitant drugs, many of which are known to cause such reactions.

Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably non-depolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O in adults.

Isoflurane may cause irritation of the airway.

Reports demonstrate that Isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances.

INTERACTIONS

All commonly used muscle relaxants are markedly potentiated by Isoflurane, the effect being most profound with nondepolarizing agents. Neostigmine reverses the effects of nondepolarizing muscle relaxants but has no effect on the relaxant properties of Isoflurane itself. All commonly used muscle relaxants are compatible with Isoflurane.

Laboratory tests

Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop medicine administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PHARMACEUTICAL PRECAUTIONS

Store at room temperature (below 30°C). Isoflurane contains no additives and has been demonstrated to be stable for the period defined by the expiration dating on the label.

MEDICINE CLASSIFICATION

Prescription Medicine

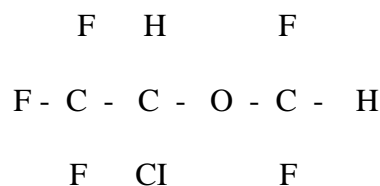
PACKAGE QUANTITIES

Isoflurane is supplied in bottles containing 100 mL and 250 mL.

FURTHER INFORMATION

Isoflurane is identified chemically as 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its molecular weight is 184.5.

Its structural formula is:



Some physical constants are:

Boiling point 760 mmHg	48.5°C
Refractive index n_D^{20}	1.2990 - 1.3005
Specific gravity 25°/25°C	1.496
Vapour pressure in mmHg	18°C 218
	20°C 238
	22°C 261
	24°C 285

25 ⁰ C	295
26 ⁰ C	311
30 ⁰ C	367
35 ⁰ C	450

Equation for vapor pressure calculation:

$$\log_{10}P_{\text{vap}} = A + \frac{B}{T}$$

where A = 8.056
 B = -1664.58
 T = ⁰C + 273.16 (Kelvin)

Partition coefficients @ 37⁰C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.80

Partition coefficients @ 25⁰C -
 rubber and plastic:

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	approx 2.0
Polyurethane/gas	approx 1.4
Polyolefin/gas	approx 1.1
Butyl acetate/gas	approx 2.5
Purity by gas chromatography	>99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23⁰C

None

Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23⁰C

Greater than useful concentration in anesthesia

M.A.C. (minimum alveolar concentration) in man:

Age	100% Oxygen	70% N ₂ O
0 - 1 mo (neonate)	1.60%	
1 - 6 mos	1.87%	
6 - 12 mos	1.80%	
26 ± 4 yrs	1.28%	0.56%
44 ± 7 yrs	1.15%	0.50%
64 ± 5 yrs	1.05%	0.37%

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