Muscular relaxation may be achieved 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. All commonly used muscle relaxants are markedly potentiated by isoflurane. the effect being most pronounced with non-depolarizing agents. Isoflurane may be used for the induction and maintenance of general anaesthesia. Adequate data are not available to establish its place in pregnancy or obstetric anaesthesia other than for caesarean section.

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

Relative lipid metabolism of isoflurane occurs in the human body. In the post-operative period isoflurane uptake can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 mmol/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours.

Butyl acetate/gas
Polyvinyl chloride/gas

Partition coefficients at 37°C:

<table>
<thead>
<tr>
<th>Component</th>
<th>Butyl acetate</th>
<th>Polyvinyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>75.0</td>
<td>62.0</td>
</tr>
</tbody>
</table>

Specific gravity at 25°C

<table>
<thead>
<tr>
<th>Component</th>
<th>Butyl acetate</th>
<th>Polyvinyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>0.61</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Boiling point at 760 mm Hg

<table>
<thead>
<tr>
<th>Component</th>
<th>Butyl acetate</th>
<th>Polyvinyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>225°C</td>
<td>237°C</td>
</tr>
</tbody>
</table>

Water solubility

<table>
<thead>
<tr>
<th>Component</th>
<th>Butyl acetate</th>
<th>Polyvinyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>1.43</td>
<td>3.85</td>
</tr>
</tbody>
</table>

Purity by gas chromatography: better than 99.9%

Flammability in oxygen or nitrogen oxide

9 at 90°C/sec, and 23°C from 900 joules/sec.

Non flammable at anaesthetic concentrations.

Induction of anaesthesia.

Properties

Induction of anaesthesia is rapid with no added chemical stabiliser.

Isoflurane has a slightly pungent, ethereal odour. No change in the appearance of samples exposed for 10 years in a dry environment by those who are familiar with the pharmacology of these agents. Sensitivity to isoflurane, only vaporisers which deliver a predictable fraction of inhaled gas should be used. Vaporisers specially calibrated for isoflurane should be used.

Produces variously calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

MAC values for isoflurane vary with age.

The table below indicates average MAC values for different age groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>Average MAC Value in 100% Oxygen</th>
<th>70% N2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 x 4 years</td>
<td>0.56%</td>
<td>0.54%</td>
</tr>
<tr>
<td>44 x 7 years</td>
<td>1.15%</td>
<td>1.07%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>0.37%</td>
<td>0.34%</td>
</tr>
<tr>
<td>1-5 years</td>
<td>0.60%</td>
<td>0.56%</td>
</tr>
</tbody>
</table>

Use of inhalation anaesthetics.

Uses

Inhalation anaesthesia.

Other uses

As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients.

Contra-indications

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

Warnings and Precautions

Isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

In such cases hyperventilation may be indicated.

This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery (see Effects on ability to drive and use machines). A potential of neuropeptide fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis.

Isoflurane should be used with caution in these patients. Isoflurane should be administered with caution to patients who may develop respiratory depression because of bronchospasm (see Side-effects).

Beginning the induction of anaesthesia, saliva flow and pharyngeal reflexes can increase and can be the cause of laryngospasm, particularly in children (see Side-effects).


Use of inhaled anaesthetic agents has been associated with reports of postoperative fever and hyperthermia. Some of these reports have been fatal.

Drug interactions

Combinations advised against:

Beta- sympathomimetic agents like isoprenaline and alpha- sympathomimetic agents (see Effects on ability to drive and use machines). A potential of neuropeptide fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis.

Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. Small changes in moods and symptoms are usual for up to 10 days after the administration.

This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery (see Effects on ability to drive and use machines). A potential of neuropeptide fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis.

Isoflurane should be used with caution in these patients. Isoflurane should be administered with caution to patients who may develop respiratory depression because of bronchospasm (see Side-effects).

Beginning the induction of anaesthesia, saliva flow and pharyngeal reflexes can increase and can be the cause of laryngospasm, particularly in children (see Side-effects).

Combinations requiring precautions in using:

Indirect-acting sympathomimetics (amphetamines and their derivatives, pseudepochonamine, phenmetrazine, phenylpropanolamine and their derivatives). Risk of peri-operative hypertensive crisis. In patients undergoing endarterectomy surgery, treatment should ideally be discontinued several days before surgery.
isoflurane in pregnant women. Studies in animals have shown no or limited amount of data from the use of isoflurane in pregnant women. Therefore it is “not known”.

Adverse reactions encountered in the administration of isoflurane in general are dose dependent extensions of other general anaesthetics, transient elevations in white cell count and alkaline phosphatase have been observed. As with other anaesthetics, small changes in moods and symptoms may persist for up to 4 days after anaesthesia. See Warnings and Precautions.

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 post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular (See Warnings and Precautions).

Use of isoflurane and isoniazide can increase the risk of carboxyhaemoglobin levels. Inducers of CYP2E1:

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to significant decreases in plasma fluoride concentrations.

Use of isoflurane and isoniazide can increase the risk of potassium levels.

Caution should be exercised when concomitant administration of isoflurane and isoniazide.

Concomitant use of suxamethonium with 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 post-operative period.

Adverse reactions are in general dose dependent extensions of other general anaesthetics, transient elevations in white cell count and alkaline phosphatase have been observed. As with other anaesthetics, small changes in moods and symptoms may persist for up to 4 days after administration (See Warnings and Precautions).

Side-effects:

a. Summary of the safety profile:

Adverse reactions encountered in the administration of isoflurane in general are dose dependent extensions of pharmaco-physiologic effects and include respiratory depression, hypotension and arrhythmias. Potential serious undesirable effects include malignant hyperthermia, hyperkalaemia, elevated serum creatinine kinase, myoglobinuria, anaesthetic reactions and liver adverse reactions (See Warnings and Precautions). Shivering, nausea, vomiting, and have been observed in the post-operative period.

Cardiac arrhythmias and neuromuscular disease have been observed in general anaesthetic anesthetic drugs including isoflurane. Reports of QT prolongation, associated with fosfate de points (in exceptional cases), have been received.

b. Tabulated summary of adverse reactions:

The following table displays adverse reactions reported in clinical trials and from post-marketing experience. Frequency cannot be estimated from the available data, therefore it is “not known”.

<table>
<thead>
<tr>
<th>SOC</th>
<th>Frequency</th>
<th>ADVERSE REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Not known</td>
<td>Hypotension</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Not known</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Blood glucose increased</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known</td>
<td>Agitation Delirium</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Not known</td>
<td>Convulsion</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Respiratory, thoracic, and</td>
<td>Not known</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>mediastinal disorders</td>
<td></td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Gastrintestinal disorders</td>
<td>Not known</td>
<td>Nausea</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatic necrosis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known</td>
<td>Swelling face</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Not known</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>administration</td>
<td></td>
<td>Malignant condition</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>White blood cell count increased</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Not known</td>
<td>Hypersensitivity</td>
</tr>
</tbody>
</table>

See section c below.

Small changes in blood and blood pressures may be observed 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 skin testing (e.g., methacholine challenge). The etiology 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.

Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anaesthesia due to biodegradation of the agent. It is unlikely that these low levels of inorganic fluoride observed (mean 4.4 μmol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

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 post-operative period (See Warnings and Precautions).

During the induction of anaesthesia, spontaneous flow and tracheobronchial secretions can increase and can be the cause of laryngospasm. (See Warnings and Precautions).

e. Other special populations:

Neuromuscular disease:

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 post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular (See Warnings and Precautions).

Other people:

Laser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. (See Dosages and Administration).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to:

United Kingdom:

Yellow Card Scheme:

Website: www.mhra.gov.uk/yellowcard.

Malta:

ADR Reporting Website: www.medicinesauthority.gov.mt/adportal.

Overdosage:

As with other halogenated anaesthetics, hypotension and respiratory depression have been observed. Close monitoring of blood pressure and respiration is recommended. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of anaesthesia.

Pharmacological precautions:

Do not store above 25°C. Keep container well closed.

Legal category:

Package information:

Isoflurane is supplied in bottles of 100ml and 250ml

Product information:

Nil

Product Licence Number:

PL 41040/0002

MA 530/0201

Marketing Authorisation Holder:

Aesica Queenborough Ltd

Maidenhead

SL6 4UB

UK

Date of Preparation:

November 2015