ULTANE® (sevoflurane)

CARES

ULTANE®
sevoflurane

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CARES

describes ULTANE's main clinical properties:

Cardiovascular

Airway Tolerability

Recovery

Emergence

Solubility

ULTANE's clinical experience has been established in a variety of patient types.[1-8]

Indication[1]

ULTANE® (sevoflurane) is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery. ULTANE should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of ULTANE should be used.

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Cardiovascular

- ULTANE has dose-related effects on heart rate and blood pressure[1]
  - ULTANE does not increase heart rate at concentration <2 MAC[1]
- Titratable to effect due to its low blood:gas solubility[1]

Safety Considerations[1]

- ULTANE can cause malignant hyperthermia. Postmarketing reports of malignant hyperthermia, some of which have been fatal, have occurred. ULTANE is contraindicated in patients with known sensitivity to any of its product ingredients or to other halogenated agents, or in patients with known or suspected susceptibility to malignant hyperthermia.
- KOH containing CO_2 absorbents are not recommended for use with ULTANE.
- Patients may develop QT prolongation, perioperative hyperkalemia, excessive decreases in blood pressure, respiratory depression, seizures, and postoperative hepatic dysfunction or hepatitis with or without jaundice.
- Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering ULTANE to susceptible patients (e.g. patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval).
- Due to ULTANE's insolubility in blood, hemodynamic changes may occur more rapidly than with other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of ULTANE.

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Airway Tolerability

- Nonpungent – does not cause respiratory irritability during induction[1]
- An option for procedures using the laryngeal mask airway (LMA™)[2]
- ULTANE is the only fast-acting inhalational anesthetic suitable for mask induction in adults and pediatric patients ≥1 year[1]

Safety Considerations[1]

- Findings taken from patient and animal studies suggest that there is a potential for renal injury when ULTANE is used at low flow rates, which is presumed due to Compound A. The level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established. To minimize exposure to Compound A, ULTANE exposure should not exceed 2 MAC-hours at flow rates of 1 to <2 L/min. Fresh gas flow rates <1 L/min are not recommended.
- Seizures have been reported in association with ULTANE use, the majority of which have occurred in children and young adults, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using ULTANE in patients who may be at risk for seizures.
- Adverse events reported by ≥5% of the surgical patients receiving ULTANE during clinical trials during induction included: bradycardia, tachycardia, agitation, laryngospasm, airway obstruction, breathholding, and increased cough; during maintenance and emergence: shivering, hypotension, bradycardia, somnolence, agitation, nausea, vomiting, and increased cough were reported.

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Recovery and Emergence

- Adult patients administered ULTANE showed shorter time to recovery than isoflurane or propofol[1]
  - In two comparative studies, time to emergence (min) (mean ± SEM): ULTANE, 7.7 ± 0.3 (n=395); isoflurane, 9.1 ± 0.3 (n=348)
  - In a three-study meta-analysis, time to emergence (min) (mean ± SEM): ULTANE, 8.6 ± 0.57 (n=255); propofol, 11.0 ± 0.57 (n=260)
- No differences vs desflurane in operating time, anesthesia off to eye opening, and anesthesia off to extubation*[3]
  - Comparable LOS in PACU with ULTANE (144.3 min ± 24.7) vs desflurane (160.2 min ± 41.4) (*P*=0.08)

*In a prospective, randomized, double-blind study of 70 morbidly obese (BMI ≥35) patients undergoing laparoscopic gastroplasty. Patients were randomized to desflurane or ULTANE. Anesthesia was decreased to 0.5 MAC at the initiation of closure and was turned off at the last suture. FGF was increased to 6 L/min on 100% O_2.

Intraoperative Data[3]

	ULTANE (n=35)	Desflurane (n=35)	*P*
Weight (kg)	**131.3 ± 22.8**	**129.5 ± 22.6**	**0.76**
Operative time (min)	**151.7 ± 47.7**	**150.9 ± 22.0**	**0.93**
Off-eye open (min)	**5.6 ± 4.1**	**4.6 ± 3.6**	**0.27**
Off-ext time (min)	**9.4 ± 5.9**	**7.8 ± 5.1**	**0.23**

- In a randomized, prospective blinded study of 40 adult patients with a BMI ≥35 kg/m^2, ASA II-III, undergoing elective surgery >2 hrs duration, no significant difference in emergence or recovery profile was observed when the anesthetic concentration was carefully titrated. During the last 15 minutes of the case, the BIS value was gradually titrated to 60 by decreasing the inhaled anesthetic concentration[4]
  - Response to Verbal Command: 4.6 min ULTANE vs 5.1 min desflurane; *P*=NS
  - Extubation: 6.3 min ULTANE vs 6.7 min desflurane; *P*=NS
- In a randomized study of 102 adult patients during elective knee arthroscopy, times to discharge were similar among the ULTANE, desflurane, and propofol groups[5]
  - Time to Discharge: 56 min ULTANE, 55 min desflurane, 65 min propofol; *P*=NS
- The recovery from general anesthesia should be assessed carefully before a patient is discharged from the post-anesthesia care unit[1]

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Solubility

Does fat solubility affect recovery from anesthesia?[6-8]

- Inhaled anesthetics move rapidly into the highly blood-perfused tissues (VRG*), more slowly into muscle, and much more slowly into fat
- At the end of the typical anesthetic case (2–4 hrs), very little anesthetic has entered into the fat, even with a relatively fat-soluble anesthetic
- The small amount of anesthetic in the fat does not appear to significantly affect recovery
- The low blood:gas solubility of ULTANE facilitates rapid induction and elimination[1]
- Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of ULTANE[1]

*Vessel-rich group: brain, heart, liver, kidney, and endocrine glands.

Note: Vessel-poor group (ligaments, tendons, bones, and cartilage, not pictured) comprises 29% of body mass but receives 0% perfusion as percentage of cardiac output.

Indication[1]

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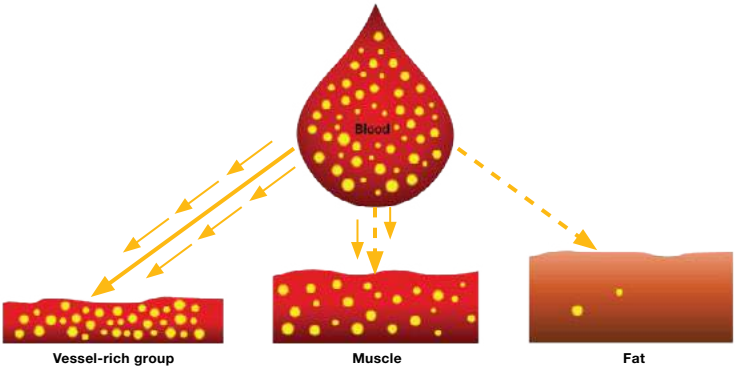
Inhaled anesthetic concentration in tissue[6-8]



Safety Considerations[1]

- ULTANE can cause malignant hyperthermia. Postmarketing reports of malignant hyperthermia, some of which have been fatal, have occurred. ULTANE is contraindicated in patients with known sensitivity to any of its product ingredients or to other halogenated agents, or in patients with known or suspected susceptibility to malignant hyperthermia.
- Use of ULTANE for more than 2 MAC-hours at flow rates of 1 to <2 L/min may be associated with a potential for renal injury, glycosuria, and proteinuria. Fresh gas flow rates <1 L/min are not recommended.
- KOH containing CO_2 absorbents are not recommended for use with ULTANE.
- Patients may develop QT prolongation, perioperative hyperkalemia, excessive decreases in blood pressure, respiratory depression, seizures, and postoperative hepatic dysfunction or hepatitis with or without jaundice.

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IMPORTANT SAFETY INFORMATION[2]

- ULTANE can cause malignant hyperthermia. Postmarketing reports of malignant hyperthermia, some of which have been fatal, have occurred. ULTANE should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents, or in patients with known or suspected susceptibility to malignant hyperthermia.
- Findings taken from patient and animal studies suggest that there is a potential for renal injury when ULTANE is used at low flow rates, which is presumed due to Compound A. The level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established. To minimize exposure to Compound A, ULTANE exposure should not exceed 2 MAC-hours at flow rates of 1 to <2 L/min. Fresh gas flow rates <1 L/min are not recommended.
- Because clinical experience in administering ULTANE to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established.
- ULTANE may be associated with glycosuria and proteinuria when used for long procedures at low flow rates.
- KOH containing CO_2 absorbents are not recommended for use with ULTANE. An exothermic reaction occurs when ULTANE is exposed to CO_2 absorbents. This reaction is increased when the absorbent becomes desiccated. Rare cases of extreme heat, smoke, and/or spontaneous fire have been reported during ULTANE use in conjunction with the use of desiccated CO_2 absorbent, specifically those containing potassium hydroxide (e.g., Baralyme).
- Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering ULTANE to susceptible patients (e.g. patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval).
- Rare increases in serum potassium resulting in cardiac arrhythmias and death have been noted in pediatric patients during the postoperative period following the use of inhaled anesthetic agents. Contributing risk factors appear to be latent or overt neuromuscular disease, particularly Duchenne muscular dystrophy. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. Early, aggressive intervention to treat both hyperkalemia and resistant arrhythmias, and subsequent evaluation for latent neuromuscular disease, is recommended.
- Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in the third trimester of gestation through the first three years of age may result in adverse cognitive or behavioral effects on their developing brains. The studies in children have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors, such as the surgery or underlying illness. Anesthetic and sedation drugs are a necessary part of the care of children when needed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.
- Due to ULTANE's insolubility in blood, hemodynamic changes may occur more rapidly than with other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of ULTANE.
- Seizures have been reported in association with ULTANE use, the majority of which have occurred in children and young adults, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using ULTANE in patients who may be at risk for seizures.
- Drug interactions: Benzodiazepines and opioids would be expected to decrease the MAC of ULTANE. The anesthetic requirement for ULTANE is decreased when administered in combination with nitrous oxide. ULTANE increases both the intensity and duration of neuromuscular blockade induced by nondepolarizing muscle relaxants.
- Very rare cases of mild, moderate, and severe postoperative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences. In addition, rare postmarketing reports of hepatic failure and hepatic necrosis have been associated with the use of ULTANE. Clinical judgment should be used in patients with underlying hepatic conditions or who are under treatment with drugs known to cause hepatic dysfunction. It has been reported that previous exposure to halogenated hydrocarbon anesthetics may increase the potential for hepatic injury.
- Adverse events reported by ≥5% of the surgical patients receiving ULTANE during clinical trials during induction included: bradycardia, tachycardia, agitation, laryngospasm, airway obstruction, breathholding, and increased cough; during maintenance and emergence: shivering, hypotension, bradycardia, somnolence, agitation, nausea, vomiting, and increased cough were reported.

References: 1. ULTANE [package insert]. North Chicago, IL: AbbVie Inc. **2.** Arain SR, Shankar H, Ebert TJ. Desflurane enhances reactivity during the use of laryngeal mask airway. *Anesthesiology.* 2005;103(3):495-499. **3.** Vallejo MC, Sah N, Phelps AL, et al. Desflurane versus sevoflurane for laparoscopic gastroplasty in morbidly obese patients. *J Clin Anesth.* 2007;19:3-8. **4.** Arain SR, Barth CD, Shankar H, Ebert TJ. Choice of volatile anesthetic for the morbidly obese patient: sevoflurane or desflurane. *J Clin Anesth.* 2005;17:413–419. **5.** Dolk A, Cannerfelt R, Anderson RE, Jakobsson J. Inhalation anesthesia is cost-effective for ambulatory surgery: a clinical comparison with propofol during elective knee arthroscopy. *Euro J Anaesth.* 2002;19:88-92. **6.** Torri G, Casati A, Albertin A, et al. Randomized comparison of isoflurane and sevoflurane for laparoscopic gastric banding in morbidly obese patients. *J Clin Anesth.* 2001;13:565-570. **7.** Behne M, Wilke HJ, Harder S. Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet.* 1999;36(1):13-26. **8.** Cork RC, Vaughan RW, Bentley JB. General anesthesia for morbidly obese patients – an examination of postoperative outcomes. *Anesthesiology.* 1981;54:310-313.

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