Desflurane - Revisited

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Abstract

The search for an ideal inhalational general anesthetic agent continues. Desflurane, which was recently introduced in the Indian market, possesses favorable pharmacokinetic and pharmacodynamic properties and is closer to the definition of an ideal agent. It offers the advantage of precise control over depth of anesthesia along with a rapid, predictable, and clear-headed recovery with minimal postoperative sequelae, making it a valuable anesthetic agent for maintenance in adults and pediatric patients in surgeries of all durations. The agent has advantages when used in extremes of age and in the obese. Its use may increase the direct costs of providing anesthetic care. Methods or techniques, such as low-flow anesthesia, to reduce the overall cost and along with minimal environmental implications must be followed.

Key words: Anesthetics, desflurane, inhalational, low-flow anesthesia

Introduction

Medical, social, and economic advances over disease is increasing longevity and tilting the age spectrum toward the geriatric end. The elderly population has expanded dramatically in most countries in the world, but in some of the developing countries it has doubled in just 20 years.[1] This change in the age-spectrum presents tremendous challenge as an increasing number of elderly need surgery and present with multiple comorbidities. Obesity trends are causing serious public health concern and threatening the viability of basic health care delivery. The prevalence of obesity in India has shown a significant increase from 9.8% in 2006 to 11.7% in 2009.[2]

Pharmacoeconomics dictates the importance of cost-effective analyses of both direct and indirect costs of new drugs and therapeutic modalities. It is an ever-increasing challenge to provide high-quality anesthesia care at a reduced cost. It has been recommended that low-flow anesthesia be practiced for economic reasons and to reduce pollution.[3] However, clinical practice techniques such as low-flow anesthesia require scientific skill and modern monitors. Fast-tracking, ambulatory anesthesia and day-care surgery are in trend and are also the need of the day. The use of the relatively new inhalational anesthetic, desflurane, addresses some of the above issues. However, its use may increase the direct costs of providing anesthetic care, and thus, we should consider methods or techniques to reduce the overall cost and along with minimal environmental implications.[4]

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Physicochemical Properties

Desflurane is an ether inhalational general anesthetic agent, which is clear, nonflammable liquid with a "strong" odor at room temperature.[5] It is a structurally identical to isoflurane except for the substitution of a fluorine atom for the chlorine atom on the α-ethyl carbon. Desflurane's relatively low boiling point (23.5°C) makes it extremely volatile; however, since this temperature is close to ambient operating theater temperature, full vapor saturation cannot be guaranteed if a conventional vaporizer is employed. A vaporizer, which heats the agent to 39°C at a pressure of 2 atm, is needed to ensure full vapor saturation and addition of a carefully regulated amount of vapor to the fresh gas flow (FGF).[6]

Pharmacokinetics

Pharmacokinetic differences between inhalational agents account for the differences in anesthesia outcomes and thereby the quality of care provided.

Biotransformation and degradation

Currently available data suggest that desflurane resists both *in vitro*[7] and *in vivo*[8] degradation to an extent greater than any other potent halogenated agent. Its biodegradation is approximately one-tenth that of isoflurane, the least degraded of the currently available halogenated anesthetics. In rats, compared with isoflurane, desflurane does not appear to be toxic to either the renal or hepatic systems.[9] In the presence of dry or desiccated carbon-dioxide (CO_2) absorbent (particularly barium hydroxide absorbents) and at high temperature (45°C), desflurane (like other inhalational anesthetic agents) produces carbon monoxide (CO) [Figure 1]. However, this generation of CO can be avoided with use of soda lime with ≥ 4.8% water content or "Baralyme" which has ≥ 9.7% water content.[10]

Solubility

Desflurane has the lowest blood/gas solubility of 0.42 as compared to the solubilities of other common anesthetic agents (diethyl-ether 12.0; halothane 2.3; enflurane 1.9; isoflurane 1.3; sevoflurane 0.67; nitrous oxide 0.47). The lower blood/gas solubility allows anesthetic alveolar concentration to remain near inspired concentration permitting a rapid and large change, with precise control, in the anesthetic depth, and early awakening.[11,12] Differences in the inhalational anesthetic agent decrement times such as "context-sensitive half times" (the time needed for a 50% decrease in anesthetic concentration) and other decrement times (such as the times needed for 80% or 90% decreases in anesthetic concentration) roughly parallel their blood/gas solubility coefficients and these differences become greater with increasing duration of anesthesia.[13] The 90% decrement time of desflurane, sevoflurane, isoflurane, and enflurane as a function of the duration of anesthetic administration is shown in Figure 2.[14]

Potency and MAC

Desflurane has lower anesthetic potency leading to higher MAC values. As with other potent agents, the MAC of desflurane decreases with age[15] [Table 1], concurrent administration of nitrous oxide[16] and CNS depressants (fentanyl[17] or midazolam[18]) [Table 2]; however the duration of anesthesia or concomitant use of cocaine does not alter MAC.[19]

Clinical effects

Cardiovascular system The cardiovascular system (CVS) effects of desflurane can be divided into 2 types: The direct effects of the anesthetic and a transient response involving sympathetic nervous system (SNS) activation.[20] The direct effects of desflurane on the CVS are remarkably similar to those of isoflurane.[21] In pigs and dogs, desflurane decreases myocardial contractility, cardiac output, and blood pressure (BP) in a dose-dependent fashion.[22,23] As with isoflurane, desflurane produces vasodilation, which results in dose-dependent reductions in systemic vascular resistance and arterial BP in healthy volunteers and patients with coronary artery disease.[24-27] Desflurane does not appear to have a specific, direct effect on the SNS.[28] The sympathetic activation may arise from stimulation to rapidly adapting

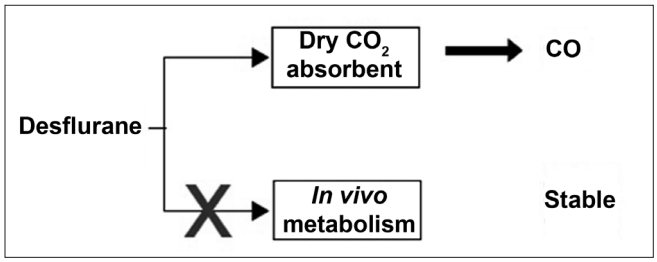

Figure 1: Desflurane degradation in dessicated sodalime

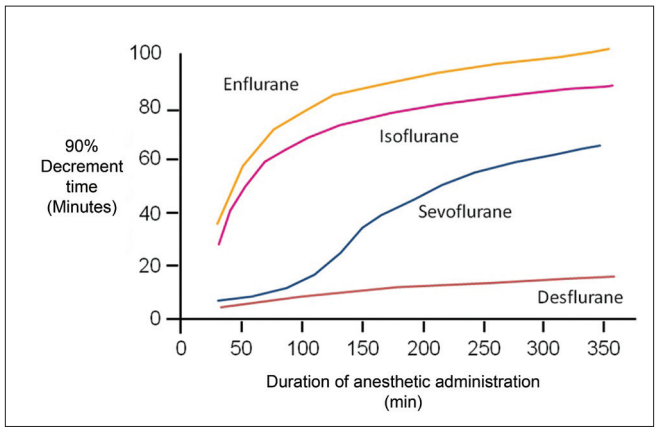

Figure 2: Faster 90% terminal decrement times with desflurane (adapted from Bailey JM. Anesth Analg 1997;85:681-6.)

Table 1: Desflurane MAC is age-specific and decreases with 60% nitrous oxide

Age	MAC in 100% oxygen (%)	MAC in 60% nitrous oxide (%)
0–1 year	8.95–10.65	5.75–7.75*
1–12 years	7.2–9.4	5.75–7.0**
18–30 years	6.35–7.25	3.75–4.25
30–65 years	5.75–6.25	1.75–3.25
Over 65 years	5.17+0.6	1.67+0.4

**3–12 months; **1– 5 years.*

Table 2: Desflurane MAC with Fentanyl or Midazolam (percent reduction)

Dose	18–30 years Mean ± SD	31–65 years Mean ± SD
No fentanyl	6.4 ± 0.0	6.3 ± 0.0
3 mcg/kg fentanyl	3.15 ± 1.9 (46%)	3.1 ± 0.6 (51%)
6 mcg/kg fentanyl	3.0 ± 1.2 (53%)	2.3 ± 1.0 (64%)
No midazolam	6.9 ± 0.1	5.9 ± 0.6
25 mcg/kg midazolam	–	4.9 ± 0.9 (16%)
50 mcg/kg midazolam	–	4.9 ± 0.5 (17%)

upper airway receptors[29] and from an unrecognized systemic arterial site,[30] causing central activation of the SNS, rather than mediation through a carotid sinus reflex.[31] β-adrenergic activation leads to significant elevations of BP and heart rate (HR)[32] mediated by release of plasma adrenaline and noradrenaline. The degree of sympathetic stimulation is related in part to the absolute concentration of desflurane (>1.25 MAC) and the rapid rise in desflurane concentration, as rapid increase leads to more sympathetic stimulation.[33] There is evidence that these sympathetic responses normalize after a few minutes and that subsequent repetition does not cause the same response (i.e., they were attenuated) again.[34] Sympathetic response by desflurane can be prevented by increasing the desflurane concentration slowly, in 0.5–1.0% increments every 2–3 breaths, avoiding the overpressurizing technique. Prior administration of alfentanil, fentanyl, sufentanil, clonidine, or β-adrenergic blocking drugs can minimize the sympathetic and/or CVS response.[35,36] Desflurane provided more rapid control of hemodynamic response to surgical stimulation than isoflurane at high (3 l/min)[37] as well as low (1 l/min)[38] FGF rates.

Desflurane caused fewer episodes of intraoperative hypotension, without the occurrence of more hypertensive episodes, than sevoflurane when studied using an experimental inhalation bolus technique in morbidly obese patients.[39] When used for hypotensive anesthesia, with desflurane HR was statistically unchanged from baseline throughout surgery, with a significantly faster return to baseline arterial BP at the end of anesthesia, as compared to sevoflurane and propofol.[40] In patients undergoing spinal surgery requiring moderate arterial hypotension, desflurane was found to maintain tighter arterial BP control than isoflurane. Systolic BP was 21.2% (9.5–41.7) of time outside the range 80–100 mmHg with isoflurane as compared to 5.1% (0.6–10.3) with desflurane ($P < 0.01$).[41]

In a manner similar to ischemic preconditioning, volatile anesthetics can trigger an acute cardioprotective memory effect, called "anesthetic or pharmacologic preconditioning," which lasts beyond their elimination.[42] Volatile anesthetics also have postconditioning effects that may contribute to protection when administered after the onset of ischemia, such as mitigation of Ca^{2+} overload, free-radical production, and neutrophil adhesion.[43-45] Cardioprotective effects of volatile anesthetic agents are measured by cardiac biomarkers. The most popular biomarker for myocardial damage is cardiac troponin (cTn), with nearly total myocardial tissue specificity and extreme sensitivity, reflecting even very small amounts of myocardial necrosis.[46] Under desflurane anesthesia, patients undergoing off-pump coronary artery bypass surgery had less myocardial damage as evidenced by a significant ($P < 0.001$) reduction in postoperative median (25^{th}–75^{th} percentiles) peak of cTn, reduced ($P = 0.04$) number of patients requiring postoperative inotropes, and a reduced number of patients needing prolonged hospitalization (>7 days).[47]

Pulmonary system

The respiratory system may be adversely affected by inhalational anesthetic agents by causing respiratory depression, airway irritation, and bronchospasm. In healthy volunteers, at concentrations up to 1.66 MAC, desflurane (with or without nitrous oxide) produced a dose-dependent decrease in tidal volume with an increase in respiratory frequency.[48] *In vitro* data have shown that desflurane produces dose-dependent relaxation of preconstricted proximal and distal canine tracheal smooth muscle, with the latter being relaxed approximately 30% more than the former.[49]

Data indicate that for each anesthetic, there is a threshold concentration above which irritation develops. Desflurane can irritate the airway when given in high concentration above threshold for respiratory irritation (1–1.5 MAC) to patients.[50] Irritation of the airway, coughing, breath-holding, and laryngospasm do not occur at end-tidal concentration of 5.4% (1 MAC) or less.[51] Concentrations that may have been irritating during the induction of anesthesia do not necessarily increase the incidence of airway irritation during maintenance.[52] In a study in which 27% of patients received desflurane concentrations above 6% administered with approximately 50% nitrous oxide, the incidence of coughing or breath holding in these patients did not differ from the incidence in patients not given concentrations exceeding 6%.[52] The threshold for irritation seems to be influenced by age, opioid administration, and smoking. Increasing age decreases airway responsiveness to irritants.[53] Administration of a small dose of fentanyl, 1 mcg/kg, can significantly decrease the incidence of airway irritation with a decrease in coughing by 80%.[54] Similar incidence of respiratory events is there with laryngeal mask airway (LMA) in adult patients receiving up to 100 μg of fentanyl, prior to induction and concomitant N_2O during the procedure, with use of desflurane and sevoflurane.[52,55,56] With use of LMA, on awakening, desflurane provides more rapid recovery of pharyngeal reflexes as compared with sevoflurane.[57]

In vitro, increasing concentrations of all volatile anesthetics directly depress hypoxic pulmonary vasoconstriction (HPV) in a dose-dependent manner. *In vivo*, however, volatile anesthetics may affect HPV, directly as well as indirectly, by their influence on cardiac output, venous oxygen saturation, and shunt fraction. It is difficult to predict to the extent to which increasing concentrations of volatile anesthetics will affect oxygenation *in vivo*. A study on pigs, evaluating the effects of

increasing concentrations of desflurane on systemic oxygenation during one-lung ventilation (OLV) *in vivo*, has shown that increasing concentrations of desflurane do not necessarily worsen oxygenation during OLV.[58] The influence of propofol and desflurane anesthesia on postoperative lung function and pulse oximetry value in overweight patients was evaluated and it was found that, for superficial surgical procedures of up to 120 min, propofol impairs early postoperative lung function and pulse oximetry values more than with desflurane. Increasing obesity decreases pulmonary function at 2 h after propofol but not after desflurane anesthesia.[59,60]

Neurological system

The effects of desflurane on cerebral physiology and function are similar to those of isoflurane. Both agents appear to reduce cerebral vascular resistance and increase intracranial pressure. In rats, desflurane is a cerebral vasodilator that balances the induced hypotension to yield no change in cerebral blood flow (CBF) or intracranial pressure up to 2 MAC.[61] In humans, both agents are dose-related cerebral vasodilators but at >1.5 MAC the vasodilation seen with desflurane exceeds that with halothane.[62,63] Cerebrospinal fluid (CSF) production is increased slightly more with desflurane than isoflurane.[64] Cerebral vascular autoregulation appears to be delayed but maintained at least up to 0.5 MAC; at 1.5 MAC autoregulation is abolished, as is the case with isoflurane.[65] In dogs, both desflurane and isoflurane seem to decrease intracranial compliance if the CSF pressure is normal, and both agents can produce raised intracranial pressure.[66]

In humans, anesthetizing concentrations of desflurane and isoflurane provide a dose-related depression of EEG activity[67,68] and evoked potentials,[69] though neither agent predisposes to convulsive activity. Normal concentrations of desflurane (up to 1 MAC) do not abolish somato-sensory evoked potentials.[70] In humans, desflurane produced central respiratory depression (ventilatory response to CO_2) comparable with that seen with enflurane and greater than that seen with isoflurane.[48] Desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSF pressure. Increasing attention is being focused on the importance of subanesthetic concentration of inhaled anesthetics, which can depress the response to hypoxia. At low dose, the halogenated anesthetic agents halothane, isoflurane, and enflurane depress the ventilatory response to isocapnic hypoxia in humans. Subanesthetic concentrations of desflurane do not blunt normocapnic hypoxic ventilator response but do reduce the response to CO_2, suggesting that it does affect the chemoreceptors of the carotid bodies.[71] CBF alterations on variation of $PaCO_2$ indicate that cerebrovascular CO_2 reactivity is not impaired by application of 1 MAC desflurane.[72]

In overweight and obese patients undergoing craniotomy desflurane-based anesthesia allows early postoperative cognitive recovery and reversal to normocapnia and normal pH. In patients receiving sevoflurane-based anesthesia, early postoperative cognitive recovery was found to be more delayed with lower short orientation memory concentration test scores at 15 and 30 min postanesthesia, $PaCO_2$ at 15 and 30 min higher and pH up to 45 min postextubation lower, than in those receiving desflurane-based anesthesia ($P < 0.005$).[73]

Hepatic and renal effects

Studies in humans have not shown evidence of hepatic injury secondary to anesthesia with desflurane. Absence of hepatotoxicity[74] is consistent with the minimal biodegradation of desflurane, the sustained hepatic arterial blood flow,[75] and the rapid elimination of desflurane after termination of anesthesia. A recent study in rats demonstrated that unlike halothane, biodegradation of desflurane produces no covalently-bound fluorine (the agent which may be responsible for hepatic damage) and thus the potential for hepatotoxicity seems to be low.[76] This low potential has also been shown in human volunteers and patients with postanesthetic renal function tests in human volunteers[77] and patients[78] showing no change after desflurane anesthesia.

Neuromuscular effects

Desflurane produces dose-related muscle relaxation comparable with that seen with isoflurane.[79,80] In addition, it potentiates the action of nondepolarizing neuromuscular blocking agents to a slightly greater degree than that seen with isoflurane. For example, 90% response time was more prolonged after vecuronium and desflurane as compared with isoflurane.[81,82] After mivacurium too, 90% response time is also prolonged in the presence of desflurane.[83]

Obstetrics

Desflurane has been used for cesarean section with no significant maternal complications and only slightly longer neonatal time to sustained respirations, compared with enflurane and nitrous oxide.[84] Desflurane has been well tolerated when used for control of labor pain.[85]

Malignant hyperthermia

Desflurane has been shown to be a trigger of malignant hyperthermia, though the onset may be delayed compared with that after halothane.[86]

Elderly population

More rapid recovery from prolonged anesthesia may be an

advantage in the elderly in whom hepatic and renal function are decreasing and cognitive impairment (e.g., delirium, confusion) is a problem during recovery.[87] Desflurane does not increase pre-existing hepatic or renal injury, does not rely upon metabolism for its elimination, and minimally influences metabolism of other drugs.[88] Several (Chen[89] and Heavner[90]) studies have demonstrated a faster, clear-headed, and more predictable recovery in elderly patients after desflurane as compared with sevoflurane.

Obese population

Compared to nonobese patients, obese patients are at higher risk of aspiration, hypoventilation, airway obstruction, and desaturation during early recovery from anesthesia. Rapid recovery and early return of airway reflexes may be desirable in these patients. There is a link between overweight and elderly patients as body weight may stay stable with increase in fat percentage with age.[91] Several studies have demonstrated a more rapid and predictable recovery, with faster washout, in obese/overweight[73] and morbidly obese[92] patients after desflurane as compared with sevoflurane. Desflurane has thus gained popularity for bariatric surgery due to favorable profiles of emergence and recovery.

Small concentrations (5–10% of MAC) can impair pharyngeal function and the ability to manage foreign material in the pharynx. McKay *et al.* demonstrated that the more rapid and predictable recovery of desflurane compared with sevoflurane also applies to the return of protective airway reflexes in overweight/obese patients[93] [Figure 3].

Pediatric population

Desflurane is not approved for induction and maintenance of anesthesia in nonintubated children due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm, and secretions. Desflurane is primarily used as maintenance agent for intubated children during pediatric anesthesia. Caution should be exercised when desflurane is used for maintenance anesthesia with laryngeal mask airway (LMA) in children 6 years old or younger because of the increased potential for adverse respiratory events, e.g., coughing and laryngospasm, especially with removal of the LMA under deep anesthesia. In a study comparing desflurane with sevoflurane, there were no significant differences in hemodynamic parameters, renal and hepatic functions, postoperative recovery, and postoperative nausea and vomiting between the two groups. The recovery time was shorter in the desflurane group compared to the sevoflurane group.[94]

Chronic obstructive airway disease

Inhalational anesthetics have bronchodilatory effects and

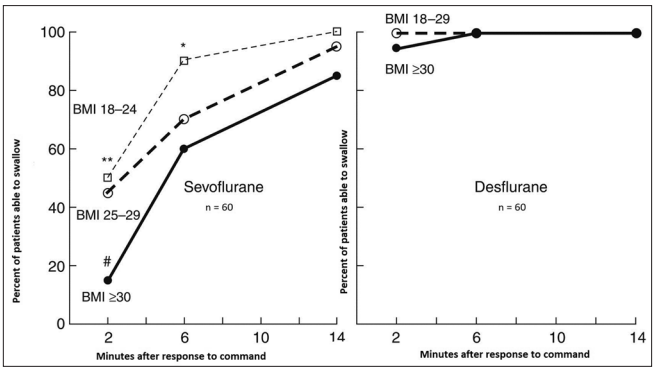

Figure 3: Return of protective airway reflexes after sevoflurane and desflurane-based anesthesia (measured as ability to swallow 20 ml of water without coughing or drooling) (adapted from McKay et al. Br J Anaesth 2010;104:175-82.)

their use is recommended in Chronic obstructive airway disease patients with hyperreactive airways.[95] Inhalational anesthetics are equipotent (isoflurane, desflurane, and sevoflurane) in treating intraoperative bronchospasm, but desflurane may provoke coughing, bronchospasm, laryngospasm, and bronchial hypersecretion. Desflurane exhibits a bronchodilator effect at 1 MAC concentration but at higher MAC values increases airway resistance.[96]

Dosage and Administration[97]

The high vapor pressure of desflurane (664 mmHg at 20°C), compared with other inhalational anesthetic agents, necessitates delivery from an electrically heated vaporizer specially designed and designated for use with this drug.[98] Desflurane is indicated as an inhalation agent for maintenance of anesthesia for inpatient and outpatient surgery in adults. After induction of anesthesia with agents other than desflurane and tracheal intubation, desflurane is indicated for maintenance of anesthesia in infants and children.

After induction in adults with an intravenous drug such as thiopental or propofol, desflurane can be started at approximately 0.5–1 MAC, whether the carrier gas is O_2 or N_2O/O_2. It is suggested that in adults, after preinduction administration of opioid, 3% desflurane be started, which may then be increased in 0.5–1.0% increments every 2 to 3 breaths. Overpressurizing technique (moving the dial setting in large shifts) should be avoided as desflurane, having a low partition coefficient, will achieve desired end tidal concentrations faster and concentrations of desflurane exceeding 1 MAC rapidly may increase HR (an increased HR may not serve reliably as a sign of inadequate anesthesia).

Surgical levels of anesthesia in adults may be maintained with concentrations of 2.5–8.5% desflurane with or without the concomitant use of nitrous oxide. In children, surgical levels of anesthesia may be maintained with concentrations of 5.2–10%

desflurane with or without the concomitant use of nitrous oxide. During the maintenance phase of anesthesia, desflurane provides precise control[92] and rapid titrations in the anesthetic depth and increasing concentrations of desflurane produce dose-dependent decreases in BP.

Toward the end of anesthesia, there is little need to apply any tapering technique, and desflurane can be switched off after the last skin suture or wound dressing. Timely reversal, administration of analgesics and antiemetics, is required at the time of recovery from anesthesia. Concentrations of 1–4% desflurane in nitrous oxide/oxygen have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery. Because of minimal metabolism, a need for dose adjustment in patients with renal and hepatic impairment is not to be expected. The use of desflurane is contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia, in those whom general anesthesia is contraindicated, and those with known sensitivity to desflurane or to other halogenated agents.

Desflurane has been clinically shown to provide faster emergence and extubation, which is more predictable, thus reducing the variability of extubation times and hence chances of prolonged extubation times compared to isoflurane,[99] sevoflurane,[100] and propofol.[101] These properties of desflurane can have a significant effect on indirect costs through reduction in operative time and postanesthesia care unit discharges.

Postoperative Events

Incidence of postoperative events are similar among inhalational agents in various studies.[88-90] No difference between the desflurane and sevoflurane was found in pain, shivering, nausea, vomiting, and incidence of postoperative hemodynamic events.[102]

Limitations

Desflurane being pungent gas, has limited use as an induction agent and is not approved for induction and maintenance of anesthesia in non-intubated children due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm, and secretions. Its use may increase the direct costs of providing anesthetic care, however, low flow techniques (upto 2L/min) minimize cost and environmental implications.

Place in Clinical Anesthesia

The pharmacodynamic properties of desflurane are similar its predecessors, particularly isoflurane. However, the physical and pharmacokinetic properties of desflurane are markedly different from those of other halogenated inhalational anesthetic agents: Higher vapor pressure; better stability against chemical degradation; lower potency and solubility in blood or body tissues; more rapid uptake and wash out, precise control, and rapid titration of depth of anesthesia; and negligible metabolism. These properties make it a potentially favorable anesthetic agent in the context of changing population where proportion of obese and older people is on constant rise. Rapid and predictable recovery with desflurane helps in fast tracking of the patients as in day care and certain surgeries where early wake up of the patient is warranted.

The focus on cost reduction in medicine has led the anesthesia care team to seek less costly approaches to clinical practice. One of the cost-saving measures we should consider is low-flow and closed circuit anesthesia.[103-105] Chemical inertness, minimal metabolism, and low solubility of desflurane make it use for low-flow anesthesia easy. Low solubility of desflurane reduces the diluting effect of expired gas on fresh gas allowing for low FGF, low vapor use, and low cost for anesthesia along with the advantages of rapid induction, titration of depth of anesthesia, and recovery from anesthesia as compared with other inhalational anesthetic agents.[106]

Conclusion

Although not completely the ideal inhalational general anesthetic agent, desflurane possesses some favorable pharmacokinetic and pharmacodynamic properties. The advantage of a precise control over depth of anesthesia (without using overpressure technique) coupled with a rapid, predictable, and clear-headed recovery, with minimal postoperative sequelae, makes it a valuable anesthetic agent for maintenance in adults and pediatric patients in surgeries of all durations.

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