DEBUNKING VOLATILE ANESTHETIC COST MYTHS BETWEEN SEVOFLURANE AND DESFLURANE

Introducing the Volatile Anesthetic Cost Calculator (CRNA iVAC©) iApp

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Introduction

Inhalational agents have been a mainstay in anesthesia practice. Nitrous oxide, the world's first inhalational agent, was synthesized in 1772 and is still in use today.[1] By the late 1800s diethyl ether, and chloroform, volatile anesthetic agents (VAAs) were introduced and administered by anesthesia professionals to facilitate surgery.[1] Volatile anesthetic agents, while inhalation agents, were liquids as opposed to a gas at room temperature. Therefore, VAAs were inhalation agents that were volatile (evaporated) emitting gases that produced anesthesia. Halogenated (addition of Cl, Fl, Br) hydrocarbon chain VAAs were created in the 1940s and were safer, more stable, and more potent anesthetic agents.[1] The early VAAs had negative side effects and properties that included flammability, high incidence of nausea and vomiting, and high tissue solubilities causing prolonged wake up times (emergence). In order to meet the growing needs for a rapid acting and dissipating anesthetic agent for surgery, lower solubility volatile anesthetic agents (VAAs) were created: isoflurane (1981), desflurane (1992), and sevoflurane (1995).[1] Nurse anesthetists have better control and timing of their anesthetic technique by using these lower solubility agents. The two newest and relatively more expensive agents, sevoflurane and desflurane, have many benefits including faster induction and emergence.[2] Using sevoflurane or desflurane may or may not increase the cost of anesthesia when compared to older VAAs. Is it beneficial to choose one of these newer agent's based on cost differences between the two? Determining the actual cost of specific VAAs is important to many individuals and institutions that attempt to buffer the rising cost of healthcare by cost effective use of drugs and therapies.

Background

Cost containment and cost effective use of resources has become a priority within healthcare. This has created a challenge for anesthesia providers wanting to deliver high quality healthcare that is safe yet economical. In anesthesia, VAAs may account for up to 20% of total anesthesia costs.[3] Sevoflurane and desflurane are the two newest and more expensive VAAs compared to isoflurane. Each VAA has its own characteristic properties offering distinct advantages. Sevoflurane is a potent non-irritating sweet smelling VAA that may be ideal for asthmatic patients and patients with reactive airways. Sevoflurane is a versatile VAA that may be used for mask induction and maintenance of anesthesia. Desflurane has the lowest blood gas and tissue solubility of all VAAs, making it a preferential agent for rapid emergence and earlier cognitive function. Populations that may benefit include the bariatric population and cases requiring neurological assessment immediately post op.

Apart from these distinct characteristics the cost for each VAA varies among institutions, purchasing contracts, and geographic locations. A difficult challenge for institutions is calculating and budgeting VAA cost. Cost assessment for intravenous drugs is much simpler than VAAs since individual and single dose packaging allows a direct correlation between the amount of drug acquired and that delivered per patient. Calculating VAA drug cost, especially per patient, is made obscure by the delivery method. VAAs are purchased in liquid form and administered through a vaporizer, making it difficult to directly measure how much VAA is used per case without the aid of additional measurement technologies. Varying delivery concentrations and delivery techniques may increase or decrease total consumption of VAAs and significantly change cost.

Review of Literature

To perform a cost analysis of sevoflurane versus desflurane, a thorough search of the literature was conducted which yielded ten articles that specifically calculated the cost of administering each VAA. These articles directly compared the cost of administering sevoflurane and desflurane. Two of the articles were from randomized control trials (RCTs). Seven articles favored sevoflurane (Table 1) as more cost effective when comparing similar flow rates, two articles favored desflurane (Table 2), and one article found no significant cost difference between inhalation groups (Table 3). Seven methods were used to determine cost of VAA: A precision weighing system, a computer data log, Minimum alveolar concentration (MAC), a four compartment model, a volume percent formula, Dion's formula, and Loke's formula.

Precision Weighing System

Boldt et al [4] performed a randomized control trial (RCT) in 1998 comparing standard and new anesthetic techniques with cost. Eighty patients undergoing laparoscopic cholecystectomy or a subtotal thyroidectomy were randomly divided into four groups. Group 1 received propofol and sufentanil, Group 2 received desflurane and sufentanil, Group 3 received sevoflurane and sufentanil, and Group 4 received isoflurane and sufentanil for anesthesia. A fresh gas flow (FGF) (aka carrier gases) of 1.5-2 L/min of oxygen and 60% nitrous oxide were used during maintenance. The average end tidal concentration of sevoflurane ranged from 1.1% to 2.5% and end tidal concentration of desflurane ranged from 3.5% to 7.2%. The authors were skeptical about the use of formulas and resorted to weighing vapors using a precision weighing machine. Volatile anesthetic consumption was measured by weighing vaporizers after each case using a precision weighing machine. Each agent was measured to the nearest 0.1 g and subsequently converted to mL (sevoflurane1.52g/mL, desflurane 1.465g/mL). The authors found no significant difference between the cost of using sevoflurane or desflurane. The authors opposed the use of a static formula to determine VAA cost because FGF rates are often adjusted throughout a case. According to the authors, the use of precision weighing machines allow for precise measurement of consumed liquid quantity. The reduction of FGF, regardless of VAA delivered, results in considerable VAA cost savings. Theoretically the authors proposed desflurane would be more economical than sevoflurane at low FGF rates because equilibration (alveolar concentration to inspired concentration ratio, F_A/F_I) occurs more rapidly with desflurane. Their finding was no significant difference in the cost of administering isoflurane, desflurane, or sevoflurane.[4]

Computer Data Log

Cobos et al [5] at the University of Nebraska Medical Center in 2007 used a computer to log FGF and inhaled concentrations of anesthetics every minute during 47 cases. The authors stated that sevoflurane FGF, MAC equivalents, and cost per minute were higher than desflurane at their institution. Average FGF for sevoflurane was 3.4 L/min and desflurane was 2.1 L/min, and cost per minute of sevoflurane was $0.79 and desflurane was $0.56. The authors did not mention how they determined cost of each VAA. The MAC equivalents listed for sevoflurane is lower than desflurane at 0.90 and 1.12 respectively. A MAC equivalent is the blood concentration of a VAA as opposed to MAC which refers to alveolar gas concentration of a VAA. The authors proposed that reducing FGF by half may theoretically decrease the cost of all VAAs by half.[5] Although MAC equivalents are useful and possibly a better representation of true anesthetic need for the patient actual VAA consumption (total amount taken from vaporizer) is what directly affects cost.

Minimum Alveolar Concentration

A simple, but flawed, method to estimate cost is to compare acquisition costs of each VAA and assume it will cost three times as much to deliver desflurane compared to sevoflurane based solely on MAC values. It requires only 2% sevoflurane to induce an equivalent MAC produced by 6% desflurane. Using this rationale some may assume that it will take three times the amount of desflurane to produce the anesthesia of sevoflurane. This assumption has previously been utilized and described in a 2009 pharmacy journal.[6] It was claimed that, although sevoflurane is more expensive per unit than desflurane, it would take three bottles of desflurane to produce the anesthesia of one bottle of sevoflurane.[6] This assumption is supported in part by an editorial in 2010 by Dr. Eger who stated that, although the unit cost of sevoflurane was more expensive than desflurane, it would take roughly three times the amount of desflurane to create a comparable anesthetic depth at a given FGF rate.[7] This is due to their differences in potency, since approximately 2% of sevoflurane and 6% of desflurane is needed to create one MAC. MAC is defined as the minimum alveolar concentration of an inhaled anesthetic agent that produces immobility in 50% of the population exposed to a surgical incision.[8,9] The erroneous assumption of direct MAC to unit cost calculation ignores other variables involved in true cost calculation including the physics of vaporization, anesthetic delivery techniques, and FGF rates. Actual consumption of a VAA determines cost not an assumed potency-to-potency comparison. Despite stated institutional savings of $100,000 over one year no verifiable methods for calculating cost or VAA consumption were disclosed and no cost analysis was made. [6] Additionally, these "savings" were achieved by removing desflurane from the operating suites and limiting anesthesia provider choice of agent to be used. [6]

Four Compartment Model

Lockwood and White [10] in 2001 incorporated the Weiskopf and Eger four compartment model to create a computer model to compare direct cost of isoflurane, desflurane, and sevoflurane in open and closed systems. The four-compartment computer model takes into consideration the solubility, absorption, and elimination of an anesthetic agent in the body. The original study by Weiskopf and Eger [11] compared isoflurane and desflurane which vary significantly in their solubility in blood. Lockwood and White took Weiskopf and Eger's methods and compared isoflurane, desflurane, and sevoflurane. They used actual patient data in a closed and open circuit system and compared it to a computer model. In the first part of their discussion, they predict ratio of liquid anesthetic used at FGF rates of 4, 2, 1, and 0.2 L/min. The authors used their data to create ratio of liquid anesthetic used comparing desflurane to sevoflurane. Unfortunately they did not mention the acquisition cost or formula used to determine cost. Lockwood and White concluded that the ratios of usage shown are invariable and can always be used to determine relative expense. Lockwood and White found in an open circuit system the cost of desflurane and sevoflurane are approximately the same, but in a closed circuit system (greater rebreathing of exhaled gases) desflurane is slightly less expensive than sevoflurane. Clinical correlation of these findings is desflurane becomes less expensive than sevoflurane and more cost effective as FGF rates are decreased. Lower FGF rates essentially make an open circuit system closer to a closed system by decreasing gases added and removed from the system and thus requiring more rebreathing of exhaled gases.

Vaporizer Dial Setting

Puckett and Andrews [12] in 1997 calculated the cost of sevoflurane, desflurane, and isoflurane using the vaporizer dialed percent setting, the volume percent equation, The mL of vapor per mL liquid calculation, and the cost per mL of liquid VAA. The volume percent equation was used to calculate the amount of vapor produced at 1 MAC and a FGF rate of 2 L/min. The vapor produced by one mL of VAA was calculated using the mL of vapor per mL liquid equation

$$\text{Volume \%} = [\text{Vapor Flow Rate}/(\text{FGF} + \text{Vapor Flow Rate})] \times 100$$

The authors were then able to convert the amount of vapor into mL of VAA, and then they used the cost per mL to determine cost per hour. The authors assumed that the vaporizer dial setting accurately denotes the concentration of vapor being delivered. The authors did not establish calibration of the vaporizers pre-measurement nor confirmed accurate delivery output. They compared the cost of sevoflurane and desflurane at the same flow rate and found sevoflurane to be slightly less expensive.[12]

Although these authors premise that actual consumptive use dictates cost, they did not allow for differences in FGF rates for the agents. Fixed 2 L per minute FGF rate negates the real world clinical decision making of lowering FGF rates and the use of low flow anesthesia.

Dion's Formula

In 1992 in a letter to the editor Dion stated a formula for directly measuring the cost of inhaled anesthetic incorporating the ideal gas law.[13] The cost of an anesthetic agent can be calculated from the concentration (%) of gas delivered, FGF (L/min), duration of inhaled anesthetic delivery (min), molecular weight (MW in g), cost per mL (in dollars), a conversion factor, 2412, to account for the molar volume of a gas at 21ºC (24.12 L), and density (D in g/mL). The formula is as follows:

$$\text{Cost (\$)} = \frac{[(\text{Concentration})(\text{FGF})(\text{Duration})(\text{MW})(\text{Cost/mL})]}{[(2412)(\text{D})]}$$

Dion's formula incorporates ideal gas law in order to convert mL VAA vapor into mL of VAA liquid, which is then used to determine cost using the acquisition price per mL. In order to convert volume of vapor into an mL of VAA, the density and molecular weight are used to convert the VAA vapor into moles, and moles are subsequently converted into mL of liquid VAA using a conversion factor of 2412. According to the universal gas law equation, one mole of an ideal gas at one atmosphere pressure and corresponding to 21˚C will liberate 24.12 liters of vapor.

Dion's formula does not take into account patient specific uptake and distribution but rather amount of delivered inhaled agent. The amount of vapor actually consumed determines cost, which makes Dion's formula a reliable method in cost calculation. Additionally, the incorporation of FGF rate better represents real world use of different FGF rates for different VAAs. Seven articles were found in the literature search using Dion's formula, and all five supported sevoflurane as a more economical inhalation agent than desflurane.[6,12,14-18] Unfortunately, comparisons were made using similar FGF rates for each VAA.

Loke's Formula

Loke and Shearer, in a letter to the editor in 1993, questioned the use of Dion's formula in newer volatile agents.[19] They used Dion's original formula and incorporated the ideal gas law directly into the formula rather than using a conversion factor of 2412 for 24.12 Liters, which represents molar volume of gas at one atmosphere at 21°C.

For comparison purposes:

Loke's Formula

$$\text{Cost per MAC hour (\$)} = \frac{[(\text{MAC})(\text{FGF})(60\text{min})(\text{MW})(\text{Cost/mL})]}{[(\text{Pressure}/(\text{RT}))(\text{D})]}$$

Dion's Formula

$$\text{Cost per MAC hour (\$)} = \frac{[(\text{MAC})(\text{FGF})(60\text{min})(\text{MW})(\text{Cost/mL})]}{[(2412)(\text{D})]}$$

These formulas are similar; however with Loke's formula the user would substitute the atmospheric temperature in Pascals, the ideal gas law constant (R) 8.314, and temperature (T) in Kelvin for the constant 2412. Loke and Shearer also included the cost of carrier gases nitrous oxide and oxygen for comparisons of Halothane, Enflurane, and Isoflurane. Unfortunately, desflurane and sevoflurane were unavailable in Australia at the time of this publication and comparison of these agents was not conducted.

Discussion

Determining cost of VAA is a difficult task, made even more challenging by the various methods available to determine cost. Of the seven methods discovered in the literature, six were found to be either impractical or inaccurate. Weighing vapors is impossible to replicate in a busy operating room setting.[4] The computer data log method[5] and four compartment model methods[10,11] do not disclose cost calculation, making it difficult to determine accuracy. A simple comparison of MAC[6] does not factor in important variables such as FGF and differences in VAA properties. Using the volume percent calculation is inaccurate since it is based on a dialed concentration and not an actual concentration determined by a gas analyzer.[12] Loke's formula includes atmospheric pressure and temperature making it a more specific version of Dion's formula but not necessarily a more accurate on because cost comparison would likely occur at the same facility and the atmospheric pressure and temperature would remain relatively constant. Thus, the use of Loke's formula is unnecessarily complicated. Dion's formula, in addition to being the most referenced method for calculating cost in the literature, is easily performed mathematically, accurate, and reproducible. As stated by Weinberg et al "this method is a simple pharmacoeconomic tool that can be used by every anesthetist."[15p853] For these supporting reasons Dion's method was utilized in the creation of a resource iApp tool.

The majority of the literature supports sevoflurane[6,12,14,15-18] as the most cost effective agent using similar FGF rates. (Table 1) Three studies supported cost effectiveness of desflurane.[4,5,10](Table 2) Several articles advocate the use of low FGF rates[4,5,14,16,] however only one[16] makes a case for comparing each agent at each agent's lowest allowable FGF rates. Currently in the United States the FDA recommends FGF rate no less than 1 L/min for cases less than 2 MAC hours and FGF 2 L/min for cases longer than 2 MAC hours for sevoflurane.[20] Desflurane has no restrictions on FGF rate and may be administered with FGF as low as 0.5 L/min. The comparison of sevoflurane and desflurane at lowest allowable FGF rates is the most accurate method in determining true cost in clinical practice. Two of the seven studies that favored sevoflurane as most cost effective with similar FGF rates favored desflurane as the more cost effective agent when the lowest allowable FGF were used compared for cases less than two MAC hours (Table 3), and three studies favored desflurane when comparing cases longer than 2 MAC hours (Table 4). The impact of FGF rates and the cost savings of low flow anesthesia is emphasized by these tables.

Conclusions that one drug is more or less cost effective than another cannot always be translated from one region to another because of the variability in drug acquisition cost and availability of generic formulations (eg, Sevoflurane). Therefore in some institutions sevoflurane may be less expensive than desflurane and in others the opposite may hold true. Using Dion's formula, a cost comparison was made using acquisition prices in California and in Florida 2010. The variability in cost across regions and FGF is evident in the following examples.

In California, the cost of sevoflurane was \$0.38/ml and the cost of desflurane was \$0.61/ml (known to author). Using Dion's formula, a comparison was made at lowest allowable flow rates for cases less than 2 MAC hours. For cases less than two MAC hours, sevoflurane was cheaper to administer than desflurane at lowest allowable FGF rates.

VAA	MAC %	FGF	cost/bottle	ml/bottle	cost/ml	cost/min	Cost/MAC hr
Sevo	2%	1 L/min	\$93.93	250 ml	\$0.38	\$0.04	\$2.46
Des	6%	0.5 L/ min	\$147.00	240 ml	\$0.61	\$0.09	\$5.30

For cases **longer than** 2 MAC hours, FGF for sevoflurane must be increased from 1 L/min to 2 L/min. In this example, sevoflurane is still slightly *less expensive* to administer than desflurane.

VAA	MAC %	FGF	cost/bottle	ml/bottle	cost/ml	cost/min	Cost/MAC hr

Sevo	2%	2 L/min	$ 93.93	250 ml	$0.38	$0.08	$4.92
Des	6%	0.5 L/min	$ 147.00	240 ml	$0.61	$0.09	$5.30

In Florida, the cost of sevoflurane was $0.64/ml and the cost of desflurane was $0.55/ml (known to author). Using Dion's formula, a comparison was made at lowest allowable FGF rates for cases less than 2 MAC hours. For cases less than two MAC hours, sevoflurane was less expensive to administer than desflurane at lowest allowable FGF rates.

VAA	MAC %	FGF	cost/ bottle	ml/bottle	cost/ml	cost/min	Cost/MAC hr
Sevo	2%	1 L/min	$ 159.50	250	$0.64	$0.07	$4.18
Des	6%	0.5 L/min	$ 133.00	240	$0.55	$0.08	$4.79

However, for cases longer than 2 MAC hours, FGF for sevoflurane must be increased from 1 L/min to 2 L/min. In this case, sevoflurane was much *more expensive* to administer than desflurane.

VAA	MAC %	FGF	cost/bottle	ml/bottle	cost/ml	cost/min	Cost/MAC hr
Sevo	2%	2 L/min	$ 159.50	250	$0.64	$0.14	$8.35
Des	6%	0.5 L/min	$ 133.00	240	$0.55	$0.08	$4.79

In accordance with Dion's formula, nurse anesthetists are able to decrease cost of any VAA agent by using low FGF rates.

Advantages of Low Flow Anesthesia

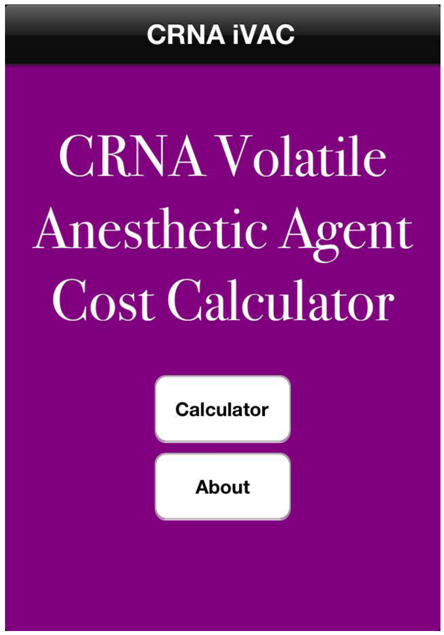
Desflurane and sevoflurane have low blood gas solubility coefficients that make them ideal for use with low flow anesthesia. Through the use of these insoluble agents the anesthetist is able to maintain tight control of the anesthetic depth. The low solubility permits rapid changes in the depth of anesthesia and also provides a greater economy at low FGF rates.[20] Up to 90% of the administered dose of inhaled anesthetic escapes unused nto the atmosphere.[21] Low-flow anesthesia allows rebreathing, which conserves the amount of VAA used. Low-flow anesthesia also conserves patient's body temperature, maintains inspired humidity, and minimizes environmental pollution. The nurse anesthetist primarily controls the immediate cost of the inhaled agent through control of the FGF rate.[21]

Disadvantages of Low Flow Anesthesia

Anesthesia professionals may choose not to incorporate low FGF (low flow anesthesia) because of fears related to anesthetic complications. These fears may include difficulty controlling depth of anesthesia, accidental hypoxic events, hypercapnea, and the potential for toxic trace gases.[21] An important disadvantage with the use of low flow anesthesia is the risk of hypoxia due to the dilution if inspired gases by exhaled oxygen depleted gases. Higher delivered FiO_2 is required to off set the dilution of inspired gases by rebreathing. Fears related to hypoxia and hypercapnea are mitigated with the use of gas analyzers and pulse oximetry. The newer VAAs sevoflurane and desflurane have low blood gas solubilities which make them easier for anesthesia providers to titrate and maintain an adequate depth of anesthesia. With low flow anesthesia the anesthesia provider must remain vigilant and monitor the patient's hemodynamics closely. Low flow anesthesia is not recommended when gas must enter and leave a patient's body quickly, as in induction and emergence. During induction it is common practice to induce with an intravenous agent such as propofol and then deliver a given percent of VAA throughout a case. Consistent FGF and VAA delivery percent make calculation of cost easy. Frequent variable FGF rates and delivered VAA percent make ongoing calculation more labor intensive and time consuming but possible.

There's an App for That!

In order to simplify the cost calculation of a particular VAA use an iApp for cellular smart phones was developed.



This iApp, *The CRNA iVAC,* incorporates Dion's formula which accounts for gas behaviors expressed in the ideal gas law. The ideal gas law (Universal gas law) expresses the relationship of pressure, volume, and temperature of a gas and is necessary when calculating the cost of any VAA. This cost calculation tool addresses the shortcoming of previous literature in which FGF rate were ignored or defaulted to the same FGF rate in calculations. The previous literature confuses the clinician as to the true cost of a particular VAA. The CRNA iVAC incorporates the necessary factors to calculate the cost of a particular VAA anesthetic. Direct comparison of one VAA to another is quickly and easily accomplished with this iApp. The CRNA iVAC dispels misconceptions regarding the perceived cost of VAAs and exemplifies the cost savings advantage of using low flow anesthesia.

Conclusion

The primary clinical determinates of cost is actual delivery concentration of a particular VAA and the FGF rate. VAA percent delivered is dictated to a large extent by patient needs but FGF rate is fully adjustable by the nurse anesthetist. When considering all variables involved in VAA cost of use, FGF rate is the most easily manipulated and efficient cost savings factor available for nurse anesthetists. Using the CRNA iVAC the following generalities regarding VAA cost can be made:

1. Isoflurane cost is inexpensive.
2. At 2L/min FGF rate for both agents, sevoflurane was consistently less expensive than desflurane.
3. Generic offers cost savings compared to brand VAAs.
4. Low flow anesthesia (low FGF rate) for each agent maximizes cost savings for that particular agent.

Although improved outcomes have not been shown from low flow anesthesia, cost effectiveness remains a clinical achievement with this delivery technique. Actual VAA cost is determined by actual consumption and the CRNA iVAC quickly determines actual VAA cost.

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