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Comparing the Costs of Inhaled Anesthetics

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Background: **The immediate cost of an inhaled anesthetic results from an interplay between four factors: (1) the cost per milliliter of liquid anesthetic, (2) the volume of vapor that results from each milliliter of liquid, (3) the effective potency of the anesthetic (what concentration must be delivered from a vaporizer to provide a clinically appropriate level of anesthesia), and (4) the background flow of gases that is chosen. A background flow that supplies only the gases/vapors required (taken up) by the patient (a "closed circuit") produces the least cost but also the least control of anesthetic level, whereas a high flow prevents rebreathing (a non-rebreathing system) but produces the greatest cost and control. We define greater "control" as a smaller ratio of delivered to alveolar concentrations. A lower solubility of an anesthetic accords the same level of control at a lower background flow rate than is achieved at a higher background flow rate with a more soluble anesthetic. Thus, a poorly soluble anesthetic may be used with a lower background flow rate than a more soluble anesthetic and may offer greater control and/or decreased cost.**

Methods: **This report presents a method of determining the cost of inhaled anesthetic use. As an example, the cost of delivering a desflurane anesthetic is compared with that of delivering an isoflurane anesthetic, assuming both provide an alveolar concentration of 1 MAC. The comparison is based on the pharmacokinetic differences of the two anesthetics: taking into account that for a given therapeutic anesthetic concentration (MAC), for desflurane a lower flow rate of background gas is needed to produce similar control (relationship between delivered and alveolar gases) than is needed for isoflurane.**

Results: **The analysis demonstrates that the relative cost of administering the newer and less soluble anesthetic, desflurane, can be less than, greater than, or the same as the cost of administering isoflurane, depending on the background gas inflow rate selected.**

Conclusion: **The manner in which inhaled anesthetics are used and their kinetic differences are important determinants of relative cost. (Key words: Anesthetics, inhaled; cost.)**

COST presents an increasingly important consideration in the adoption of new drugs into practice. Not only must a new drug confer a greater therapeutic benefit, but that benefit must not be bought at too high a price. For injected drugs, determination of relative cost is straightforward. This is not true for inhaled anesthetics because cost is related to more than the amount of drug taken up; cost also is determined by waste of anesthetic consequent to delivery of anesthetic in excess of the amount taken up. The present report describes the factors that must be considered in a comparison of the cost of inhaled anesthetics. To illustrate these factors, we compare costs associated with using desflurane, a recently approved inhaled anesthetic as an example, and contrast these costs with those associated with using isoflurane, the inhaled anesthetic most frequently used in North America. We supply a method for making specific cost comparisons. Our analysis does not consider other factors such as length of stay in the postanesthetic care unit. Though these issues may materially influence the cost of patient care, presently available data are insufficient to permit accurate analysis.

Methods and Results

The amount of anesthetic must be supplied taking three factors into account.

1. The need to supply sufficient agent to establish appropriate levels at the start of anesthesia (*i.e.*, enough anesthetic to load the anesthetic circuit and the patient's lungs). This is relatively small and will be ignored in the present analysis.
2. The need to replace anesthetic lost by uptake into blood and then into the tissues of the body. This translates into a requirement to sustain the alveolar concentration (F_A) at a level sufficient to meet clinical demands. Such a concentration is sustained by appropriate adjustment of the inspired concentration (F_I). In turn, the inspired concentration is controlled by adjustment of the concentration delivered from the vaporizer (F_D). It is this concentration (F_D) times the flow of gases (*i.e.*, oxygen, nitrous oxide, and/or air) that determines the amount of liquid anesthetic vaporized (consumed).

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3. Finally, there must be compensation for the anesthetic that is wasted consequent to the delivery of more gas and vapor than can be consumed by the patient. This factor also influences F_D. The last two factors are taken into account in the construction of the table and figures supplied with this report.

The volume of anesthetic vapor produced by 1 liquid ml of anesthetic differs slightly among anesthetics. Owing to differences in density and molecular weight, a given volume of liquid desflurane produces 7.4% more gas than does the same volume of liquid isoflurane. The table and figures take this into account.

For our analysis, we selected an alveolar concentration of 1 MAC. Further, the fractional inspired concentration (F_I) was calculated assuming an alveolar ventilation of 4 l/min, a volume sufficient in a normal adult to produce normocapnia (assuming a carbon dioxide production of 200–250 ml/min).

Our approach, determining the amount of uptake of an anesthetic at a constant alveolar concentration is similar to that of Eger and Saidman.[1] However, we have the advantage of being able to rely on actual uptake data obtained in humans by Yasuda *et al.*,[2] rather than having to make assumptions regarding body composition. We used kinetic constants defined by Yasuda *et al.*'s work to assemble a four-compartment model to define uptake at any time, assuming a constant alveolar concentration. We calculated F_D/F_A taking these data and considering data regarding anesthetic circuit mechanics (see Eger and Ethans[3] and Harper and Eger[4]), rather than make an assumption of instantaneous mixing within anesthetic circuits, as did Eger and Saidman.[1] (Please see appendix for determination of F_D.) This fraction is the ratio of the amount of anesthetic that must be vaporized (consumed) to that required to produce a given therapeutic effect (concentration in the patient). Several factors influence this ratio, the two most important being the solubility of the anesthetic and the background gas flow rate. Table 1 indicates the use and cost of desflurane and isoflurane anesthetics for 30- and 60-min procedures. The calculations assume a constant alveolar concentration of 6% desflurane and 1.15% isoflurane (1 MAC) and prices of $70.00 and $71.00 for a 240-ml bottle of desflurane and a 100-ml bottle of isoflurane, respectively.

Two other factors influence use and cost. A concentration greater than MAC may be needed (to meet surgical stresses or control hemodynamics), and thus the values may underestimate actual expense of both desflurane and isoflurane, although the proportionate expense should not change. Conversely, the common use of other drugs, such as nitrous oxide and opioids, decreases the required dose of inhaled anesthetic and thereby decreases use and cost of desflurane or isoflurane, also likely in a proportionate manner.

Table 1. Comparison of Cost: Desflurane *versus* Isoflurane

		Desflurane		Isoflurane	
Time (min)	Background Flow (l/min)	Volume (ml)	Cost ($)	Volume (ml)	Cost ($)
30	0.2	7.2	2.10*	4.7	3.10†
	1.0	15.8	4.62	6.3	4.44‡
	2.0	26.6	7.77	8.6	6.13
	4.0	48.3	14.08	13.4	9.49
	6.0	69.9	20.38	18.1	12.85
60	0.2	10.8	3.15*	6.8	4.82†
	1.0	27.8	8.12	10.4	7.41‡
	2.0	49.1	14.33	15.0	10.66
	4.0	91.7	26.74	24.2	17.15
	6.0	134.3	39.16	33.3	23.63

Based on prices of $70.00 for a 240-ml bottle of desflurane and $71.00 for a 100-ml bottle of isoflurane.

* Not clinically practical to deliver from a conventional vaporizer for the first 10 min of the anesthetic.

† Not clinically practical to deliver from a conventional vaporizer, although such delivery can be accomplished by directly injecting liquid anesthetic into the anesthetic circuit. Cost is calculated as if it were possible to deliver the anesthetic.

‡ Add $0.86 to this amount for the additional cost of the need to use higher background flows for several minutes to supply a sufficient quantity of isoflurane.

Comparisons of desflurane and isoflurane in closed circuits (a background flow rate of 0.2 l/min) at 1 MAC have a practical limitation: for the first hour of anesthesia of this analysis, vaporizers used to deliver isoflurane cannot supply a sufficient amount of isoflurane, whereas desflurane vaporizers cannot deliver sufficient agent for the first 10 min after the inception of anesthesia; the required delivered concentration (F_D) exceeds the capacity of the vaporizer (5% for isoflurane and 18% for desflurane) (fig. 1). With background flow rates of 1 l/min, current isoflurane vaporizers can deliver a sufficient quantity of anesthetic after 5 min of anesthesia, whereas the desflurane vaporizer has the capability to deliver sufficient anesthetic almost immediately (fig. 1). The additional flow greater than 1 l/min required to provide sufficient isoflurane for the first 5 min of the anesthetic when using isoflurane results in additional cost. This extra amount should be added to the cost indicated in the table for isoflurane given at 1 l/min.

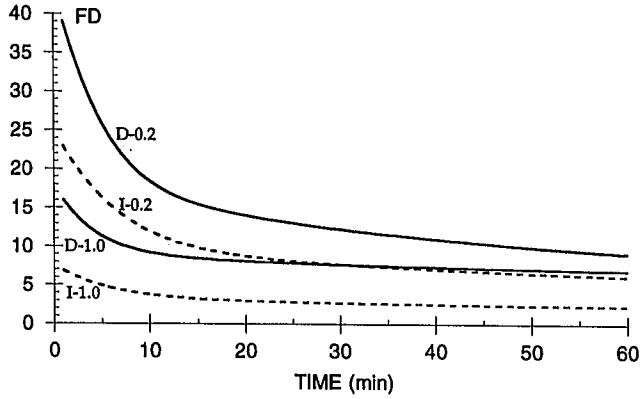

Fig. 1. Anesthetic concentration delivered from the vaporizer (F_D) required to maintain a constant anesthetic alveolar concentration of 1 MAC, with a background gas flow rate of 0.2 (closed system) or 1 l/min. Note that with a background flow rate of 0.2 l/min, the concentration of isoflurane (I) required exceeds that of currently produced vaporizers (5%) for a period of time beyond the period of this analysis (60 min). With a background gas flow rate of 0.2 l/min, the concentration of desflurane (D) required exceeds that of the current vaporizer (18%) for the first 10 min of the anesthetic. With a background gas flow rate of 1 l/min, the concentration of isoflurane required exceeds that of currently produced vaporizers (5%) for nearly the first 5 min of the anesthetic.

Figure 2 shows the ratio of volumes of liquid desflurane to liquid isoflurane used during 60 min of various constant background flow rates and constant, comparable (MAC) alveolar concentration of anesthetic. The figure allows a means of comparison of cost: calculate the cost of 1 ml liquid isoflurane, and divide it by the cost of 1 ml liquid desflurane. The current ratio is 2.43, indicated by the dashed line. Points on a given "flow rate" curve above this value (dashed line) represent times when isoflurane is less expensive to use; points below this value represent times when desflurane is less expensive to use. Presently, the cost of using isoflurane is approximately equal to that of desflurane at a background gas flow rate of 1 l/min. For procedures shorter than 15 min, the break-even background flow rate is approximately 1.5 l/min.

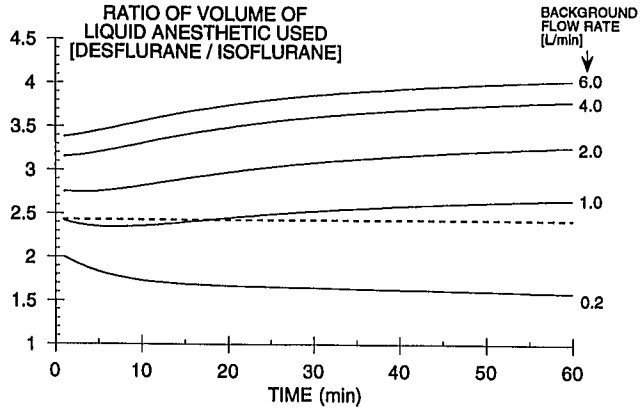

Fig. 2. The ratio of volumes of liquid desflurane and isoflurane during 60 min of anesthesia at a constant alveolar concentration of 1 MAC. The dashed line at 2.43 represents the current ratio of the cost of isoflurane to desflurane (per milliliter of liquid) for some institutions. Based upon current costs of $70.00 per 240 ml desflurane and $71.00 per 100 ml isoflurane, the cost of 1 ml isoflurane is 2.43 times the cost of 1 ml desflurane. This ratio is at the lower end of the current range of prices.

One other approach to comparison may be made. The isoflurane F_D/F_A ratio associated with commonly used inflow rates (3–4 l/min) is higher than that found with desflurane in a background flow of 1 l/min. That is, desflurane used with a background gas flow rate of 1–2 l/min offers the advantages of both smaller cost and a lower F_D/F_A than isoflurane with background gas flow rates of 2–4 l/min (table 1).

Discussion

Both anesthetic uptake and inflow rate determine the cost of an inhaled anesthetic. At low inflow rates, uptake (and the need to replace the amount taken up) may be the primary determinant of cost. At higher inflow rates, the inflow rate itself may be the primary determinant. The combination of the flow rate of background gas and concentration of anesthetic emanating from the vaporizer determines the total amount of liquid anesthetic vaporized (and thus, consumed). As table 1 indicates, over the range of inflow rates used in practice, the cost of delivering an inhaled anesthetic can change by tenfold or more.

The threefold difference in blood solubility and a further difference in tissue solubility between desflurane and isoflurane mean that more than 3 times as much isoflurane must enter the patient to produce a given anesthetic partial pressure in blood and tissue. Thus, although MAC for desflurane exceeds that for isoflurane by 5.2-fold (6% *vs.* 1.15%), at a 1-l/min inflow rate the actual concentration of desflurane that must be delivered from the vaporizer to provide 1 MAC exceeds that for isoflurane by approximately 2.5-fold.

As a multiple of the alveolar concentration (1 MAC), the vaporizer dial setting (F_D) for desflurane is much less than that for isoflurane (fig. 3). After approximately 10 min of anesthesia and an inflow rate of 1 l/min, the

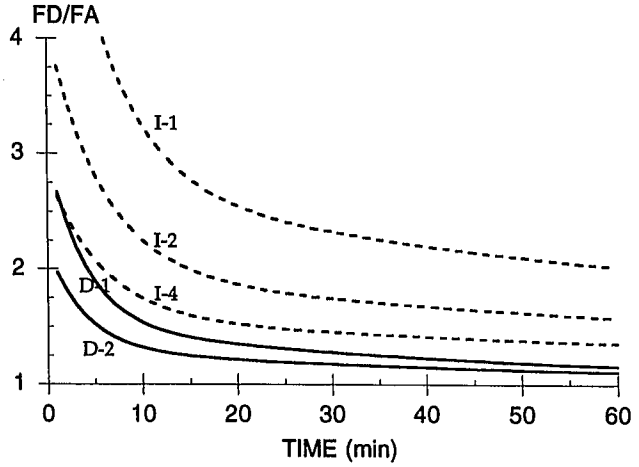

Fig. 3. F_D/F_A for desflurane (D) and isoflurane (I) with background gas flow rates of 1 and 2 l/min and of 1, 2, and 4 l/min, respectively. Note the lower ratio for desflurane than for isoflurane. The concentration required to be delivered from the vaporizer at any point can be calculated by multiplying F_D/F_A by MAC. For example, an F_D/F_A of 2.5 for isoflurane would require a vaporizer output of 2.5 × 1.15% = 2.88% to maintain MAC. Similarly, an F_D/F_A of 1.5 for desflurane would require a vaporizer output of 1.5 × 6% = 9.0% to maintain MAC.

required dial setting of the vaporizer for desflurane decreases to 40% above the concentration desired in the patient; for isoflurane, the dial setting must be 200% above the desired concentration. This relative difference is sustained over time.

The above ratios and vaporizer dial settings correlate inversely with background gas flow. A high background gas flow decreases rebreathing of the exhaled gas (gas partially depleted of anesthetic because of uptake) and thereby narrows the difference between delivered and alveolar gas concentrations. However, doing so greatly increases the amount of anesthetic vaporized and thus increases the cost of anesthesia. The anesthetic volume delivered in higher background flows largely is wasted because it is far in excess of the anesthetic volume taken up. The excess anesthetic is vented, usually to a scavenging system and thence into the atmosphere. With less soluble inhaled anesthetics, lower (and, thus, less costly) background gas flows are required to provide a narrow difference between alveolar gas and gas exiting the vaporizer. The lower solubility of desflurane allows a lower background gas flow to provide an equivalent difference between the gas exiting the vaporizer and the gas of the alveoli (fig. 3).

Two other factors require consideration in the arguments concerning costs. First, delivery of a new anesthetic requires the use of a new agent-specific vaporizer. Second, measurement of the anesthetic concentration respired by the patient may be desired. Analyzers for such a purpose may be purchased or analyzers for other anesthetics may be modified to permit analysis of the new anesthetic (note that modification is not possible in some cases—*e.g.*, the present manufacturer of the SARA analyzer does not intend to undertake such a modification). However, the need for analysis is decreased in the case of poorly soluble anesthetics (*e.g.*, desflurane). With poorly soluble anesthetics, the output of a precision vaporizer approximates the alveolar concentration and may be used as a surrogate measurement of that concentration: after the initial period of higher uptake, the concentration delivered closely approximates the concentration in the patient's alveoli (fig. 3).

We have provided a method of analyzing a major component of the cost of delivery of an inhaled anesthetic: the amount of anesthetic consumed. However, purchase prices and differences in anesthetic potencies are not the only factors governing relative costs of inhaled anesthetics. First, the fivefold greater MAC of desflurane implies that the use of desflurane will impose a greater expense than the use of generic isoflurane. In fact, the converse may be true because this implication ignores several factors. Cost does not derive from differences in alveolar concentrations but from the differences in the delivered (amount vaporized) concentrations needed to sustain the alveolar concentrations. What might be called the "effective potency" is not fivefold but roughly threefold different. The lower value results from the smaller differences between inspired and alveolar concentrations of desflurane and from the smaller impact of rebreathing of desflurane. Second, 1 ml liquid desflurane produces 7.4% more vapor than does 1 ml liquid isoflurane. Third, the cost comparisons assume application of equal inflow rates (table 1). However, if lower inflow rates are used with desflurane, the cost of desflurane anesthesia can decrease to less than the cost of isoflurane. This, of course, assumes that the relative costs of isoflurane and desflurane remain unchanged.

Appendix

We determined the concentration that must be delivered from the vaporizer (F_D) to provide a constant alveolar concentration (F_A) as follows: We calculated uptake (in ml/min) at a constant alveolar concentration

using values for tissue blood flow and volume obtained by Yasuda *et al.*[2,5] These values apply to four tissue groups: vessel rich group (VRG), muscle group (MG), fourth compartment (4th), and fat group (FG). For an individual tissue group, cumulative uptake (U_T) is given by:[6]

$$U_T = \lambda_T \cdot V_T \cdot C_B[1 - e^{-t((Q_T)/(\lambda_T \cdot V_T)}], \quad (1)$$

where λ_T is the tissue/blood partition coefficient,[7] V_T is the volume of the tissue (see table 5 of reference 2), C_B is the concentration of anesthetic in the blood (ml/ml), Q_T is the blood flow in ml/min to the tissue, and t is time in minutes. The exponential expression $[(Q_T)/(\lambda_T \cdot V_T)]$, is the reciprocal of the time constant. C_B is obtained as the alveolar concentration (*e.g.*, MAC as a fractional concentration) times λ_B, the blood/gas partition coefficient. Uptake for any minute may be calculated as the difference between the cumulated uptake at the start and at the end of the minute.

Uptake by individual tissues then may be summed to give the total uptake (V_U), which then may be used to calculate the fractional inspired concentration (F_I) required to sustain F_A. Apart from washin at the gas space, V_U must equal the difference between the amount of anesthetic inhaled and the amount exhaled:

$$V_U = F_I(V_A + V_U) - F_A \cdot V_A, \quad (2)$$

where V_A is alveolar minute ventilation. This also assumes a respiratory quotient (RQ) of 1; a smaller RQ may be accounted for as an additional input ventilation equaling $V_M(1\text{-}RQ)/RQ$, where V_M is the metabolic consumption of oxygen. Rearranging equation 2 yields:

$$F_I = (V_U + F_A \cdot V_A)/(V_A + V_U) \quad (3)$$

and

$$F_I/F_A = (V_U + F_A \cdot V_A)/[F_A(V_A + V_U)]. \quad (4)$$

The delivered gas volume (V_D) consists of the volume provided by the background flow (V_B) plus the volume of anesthetic added (V_{AN}):

$$V_D = V_B + V_{AN}. \quad (5)$$

Thus, the concentration in the delivered gas (F_D) must be V_{AN}/V_D or

$$F_D = V_{AN}/(V_B + V_{AN}). \quad (6)$$

The volume of anesthetic in the inflowing gases (V_{AN}) must replace that gas lost by uptake (V_U) and that lost through the overflow (V_L):

$$V_{AN} = V_U + V_L. \quad (7)$$

V_L, in turn, equals the product of the concentration of anesthetic in the outflow (F_O) and the volume of gas passing through the overflow (V_O). F_O results from the proportions of V_A and V_{DS} (dead-space ventilation) that respectively carry F_A and F_I. Note that this assumes that, until the inflow rate exceeds minute ventilation, the gases escaping through the overflow never include fresh gas.[3,4] The sum of V_A and V_{DS} is the minute ventilation (V_E). Thus,

$$V_L = F_O \cdot V_O. \quad (8)$$

Since

$$F_O \cdot V_E = F_I \cdot V_{DS} + F_A \cdot V_A,$$

then,

$$F_O = F_I(V_{DS}/V_E) + F_A(V_A/V_E). \quad (9)$$

As for V_O, it is part of the equation defining input of gas and output:

$$V_D = V_O + V_U + V_M \quad (10)$$

(the whole equals the sum of its parts) and

$$V_O = V_D - V_U - V_M. \quad (11)$$

Equation 9 defining F_O has known values or values calculable (*e.g.*, F_I) from the previous equations. The equation for V_O (11) requires further analysis because it contains the term V_D. Substituting equations 5 and 7 into equation 11 produces:

$$\begin{aligned} V_O &= V_B + V_U + V_L - V_U - V_M, \\ &= V_B + V_L - V_M, \end{aligned} \quad (12)$$

and equation 8 becomes

$$V_L = F_O(V_B + V_L - V_M) = F_O(V_B - V_M) + F_O \cdot V_L.$$

Rearranging,

$$V_L = [F_O(V_B - V_M)]/(1 - F_O). \quad (13)$$

Finally, substituting 7 and into 6:

$$F_D = (V_U + V_L)/(V_B + V_U + V_L). \quad (14)$$

All variables are now defined. V_U, F_I, and F_D, as well as F_I/F_A and F_D/F_A, may be estimated.

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