Clinical Investigation

A simple method for evaluation of the uptake of isoflurane and its comparison with the square root of time model

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ABSTRACT

Background: The square root of time (SqRT) model had been used to predict the uptake of volatile agents. **Methods:** We studied the rate of uptake of isoflurane in 10 patients using liquid isoflurane infusion through syringe pump into the closed circuit. The infusion rates were titrated to maintain a constant end tidal concentration of isoflurane of 1.5%. The predicted uptake values were also calculated from the square root principle and compared with the derived uptake. **Results:** The observed rate of uptake was higher than predicted from the Lowe and Ernst equation (P<0.001). There exists considerable inter-individual variability in uptake pharmacokinetics and it showed statistically significant correlation with ideal body weight, body weight (P<0.01), body surface area, and body weight$^{3/4}$ from 30 min of start of isoflurane infusion (P<0.05). **Conclusion:** SqRT model is inaccurate in predicting isoflurane uptake and underestimates it during closed circuit anaesthesia.

Key words: Anaesthetics, equipment, isoflurane, pharmacokinetic, volatile

INTRODUCTION

The uptake of anaesthetic agent is defined as the amount of vapours that is taken by the alveoli. It depends on the agent solubility, cardiac output (CO) and alveolar to mixed venous partial pressure difference of the agent.[1] Severinghaus (1954) postulated that the uptake of nitrous oxide is inversely proportional to the square root of time (SqRT).[2] Lowe and Ernst gave the SqRT, which was later utilized for predicting the uptake of commonly used volatile agents.[3] It indicates that uptake is related to patient's weight$^{3/4}$ and gradually decreases according to the SqRT. However, recent clinical observations have shown that the observed rate of isoflurane uptake differ from that predicted from the SqRT model.[4-6] In addition, there exists a large inter-individual variation in the uptake.[4,7,8]

Addition of liquid volatile agent (ether) into the circuit was first used by William Morton in 1847.[9] Subsequently, a series of dosage tables according to patient's body habitus have been predicted for use during closed circuit anaesthesia.[10,11] The derivations of these complex formulae and mathematical models have deterred anaesthesiologists from using low flow anaesthesia. The anaesthesiologist is more interested in attaining a desired minimum alveolar concentration (MAC) as the parameter and not the pharmacokinetics of the agent.[5]

By studying the rate of uptake of isoflurane during our pilot cases, we modified the dosages derived from Lowe and Ernst equation into a simplified form of rate of liquid isoflurane injection into the circle system using low flow anaesthesia. We hereby present the implementation of those derived rates in 10 patients.

METHODS

After approval by the hospital ethics committee, 10 patients of either sex undergoing elective surgeries for 1 h to 3 h duration of anaesthesia were enrolled. Patients with American Society of

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Anaesthesiologists (ASA) physical status I, aged between 22 years and 55 years were included after informed consent. The surgeries performed were varicose vein stripping ($n=3$), modified mastectomies ($n=4$), inguinal hernia repair ($n=1$) and superficial parotidectomy ($n=2$). Patients with pregnancy, cardio-pulmonary pathology, any history of central nervous system disease, chronic use of psychoactive medication; with a body mass index (BMI) less than 15 and greater than 30 were excluded from the study.

General anaesthesia was induced with IV fentanyl 2 μg/kg, propofol 1-2 mg/kg followed by 150 μg/kg/min infusion, and vecuronium 0.1 mg/kg. Bag and mask ventilation was performed for 4 min using the circle system with oxygen flows of 10 L/min (the circle system was flushed prior to this with 100% oxygen for 5 min for de-nitrogenation). The circle system was closed after ascertaining the correct position of the endotracheal tube with initiation of controlled ventilation and propofol infusion was discontinued. Isoflurane infusion was started into the expiratory limb of the circle absorber at 0.47 ml/kg ideal body weight (IBW) h^{-1} and later titrated to attain and maintain end-tidal isoflurane concentration (Et-Iso) of 1.5% (MAC 95). The expiratory limb had a specialised connection with two luer lock ports, one for attachment to isoflurane infusion and the other for return of sampling gases (150-200 ml/min) by the multigas analyzer (Datex-Ohmeda S/5, Instumentarium Corp, Helsinki, Finland), which was calibrated before every case. Isoflurane was injected in 50 ml Plastipak (polyethylene BD) syringe with polyethylene tubing using a syringe pump (Fresenius vial SA, France). The dead space of the tubing (2 ml) was pre-filled with liquid isoflurane and the stated volumetric accuracy of the pump was ±2%. The entire apparatus was kept at a lower level than the circle system to avoid accident spillage of liquid agent into the circuit [Figure 1]. Ohmeda 7000 Anaesthesia Ventilator (Ohmeda, BOC Health Care Division, Madison, WI) with soda lime canister, corrugated rubber tubing and ascending bellows were used to provide pre-set volume ventilation. The volume of the circle system was determined individually for all the components and was 2.2 L, the volume of the connecting hose to the ventilator being 0.5 L. The amount of acceptable leak in the circuit was ≤50 ml/min determined during ventilation of a test lung at 30 cm peak inspiratory pressure. The same apparatus and ventilator was used for all cases. Oxygen was used as the sole carrier gas

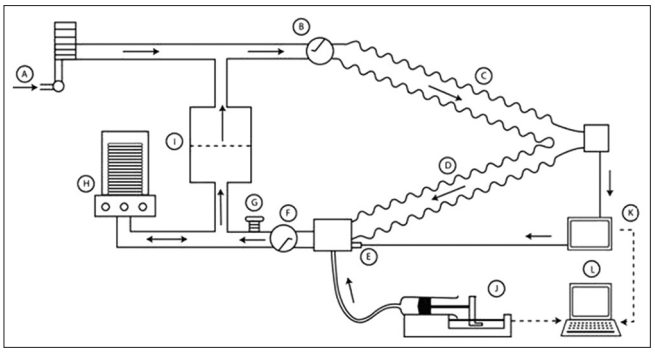

Figure 1: Arrangement of the closed circuit. A – Oxygen flow meter; B and F – Unidirectional valves; C – Inspiratory limb; D – Expiratory limb; E – Specialised connector for isoflurane infusion and return of sampling gases; G – Adjustible Pressure Limiting valve; H – Ventilator bellows; I – Soda lime canister; J – Isoflurane infusion; K – Agent analyser; L – Computer for data recording

with fresh gas flow (FGF) to maintain a constant circuit volume. The incision was given after 30 min of the start of the isoflurane infusion to study isoflurane uptake in un-stimulated conditions. This time was utilised for surgical cleaning and draping. Intra-operative analgesia was maintained with fentanyl infusion of 1 μg/kg/h IV. Patients requiring vasopressor or cardiac medication for haemodynamic changes of ≥or ≤20% of baseline values were excluded from the study. Patient's temperature was maintained strictly around 36-37°C. Additional fentanyl (apart from infusion) and vecuronium boluses were given as clinically indicated.

Rate of uptake and cumulative uptake of isoflurane was determined from the difference between the isoflurane administered and the system leaks (see appendix). Similarly, the expected rate of uptake and cumulative uptake was calculated using Lowe and Ernst's SqRT model for comparison with our study.

Throughout the procedure bispectral (BIS) index, non-invasive blood pressure, heart rate, haemoglobin oxygen saturation (SpO_2), temperature, end-tidal carbon dioxide (Et-CO_2), inspired isoflurane (FI-Iso), and Et-Iso were recorded continuously. A computer interphased to the syringe pump and the monitor recorded the data continuously.

Statistical analysis

Results are given as mean±SD. Pearson correlation coefficient was obtained between the cumulative uptake of isoflurane in the first 30 min of start of isoflurane infusion with the patients variables; body Weight, IBW[13], height, body surface area (BSA), and (body weight).[3/4] BMI was correlated with cumulative

uptake per kilogram body weight. The mean cumulative rate of uptake per kg derived from the Lowe and Ernst equation was compared with the observed rates at 10 min interval, from 10 min onward using repeated measured ANOVA. The mean rate of uptake per kg per minute were averaged at 10 min intervals and also compared with that estimated from Lowe and Ernst equation using repeated measures ANOVA. Statistical significance was assumed for values of $P<0.05$.

RESULTS

Patients' characteristics (six male/four female) and anaesthesia details are given in Table 1. Perioperative haemodynamics were stable in all cases with no patient requiring cardiac medication, vasopressors and/or additional doses of fentanyl or vecuronium. Intra-operative surgical conditions were described satisfactory by all the surgeons. No patient got excluded during the study.

The mean FGF used was 250±10 ml/min (equal to leaks and patients oxygen consumption) to maintain the circuit volume. Isoflurane vapour was detected in 63±20 s and 1.5% concentrations achieved by 8.2±2.3 min. After attainment of 1.5% Et-Iso, it was maintained between 1.4% and 1.6%. The rate of injection used did not result in liquid droplet formation in the circuit as seen by a glass window in the specialised connector. The infusion rate stabilised at 0.15-0.10 ml IBW/kg/h at 15-20 min. The observed cumulative uptake of isoflurane vapours by 30 min was 20.5±2.8 ml/kg/min. Since the target Et-Iso (1.5%) was achieved by 10 min in all the patients, we compared the predicted and the observed uptake after 10 min. Observed cumulative uptake was high as compared to Lowe's equation, the difference gradually increased with time. This difference was statistically significant ($P=0.042$ from 60 min onwards from the start of isoflurane infusion [Figure 2]. As compared to Lowe's equation the mean observed uptake per kg per min was significantly higher after initial 10 min ($P<0.05$). Rate of observed uptake relatively stabilized after 30-40 min [Figure 3] with a mean of 0.37±0.47 ml/kg/min vapour requirement for keeping a mean end-tidal isoflurane concentration of 1.51±0.1%. There was inter-individual variability in the uptake [Figure 4] and it showed statistically significant correlation with IBW, Wt, BSA, body weight$^{3/4}$ from 30 min of start of isoflurane infusion ($P<0.05$) [Table 2]. The significance was maximum with IBW ($P=0.01$). Cumulative uptake kg^{-1}

Table 1: Patient and anaesthesia details

Patient and anaesthesia characteristics	Range	Mean	SD
Age (years)	21-50	37.5	11.5
Weight (kg)	45-90	60.8	13.5
Ideal body weight (kg)	47-80	64.37	11
BMI	19.91-28.1	22.22	2.4
Isoflurane infusion time (min)	60-180	104	43.3
Liquid isoflurane used in the first hour (ml)	6.1-10.7	9.2	2.5
Surgical time (min)	30-160	85.8	50

BMI – Body mass index

Table 2: Correlation of cumulative isoflurane uptake (at 30 min) and measured patients variables. BMI has been correlated to cumulative uptake kg^{-1}. Value in parenthesis shows the actual *P* value

Variable	Correlation coefficient (*r*)	*P*
Body weight	0.713	<0.05 (0.021)
Ideal body weight	0.785	<0.01 (0.007)
Height	0.724	<0.05 (0.018)
BMI	−0.595	>0.01 (−0.053)
Body surface area	0.736	<0.05 (0.015)
Body weight$^{3/4}$	0.728	<0.05 (0.017)

BMI – Body mass index

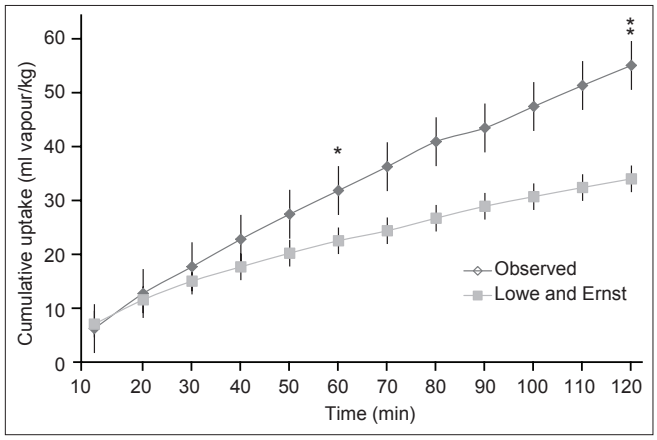

Figure 2: Cumulative rate of uptake of isoflurane (vapour) per kg body weight (mean±SD). *$P<0.05$; **$P<0.01$

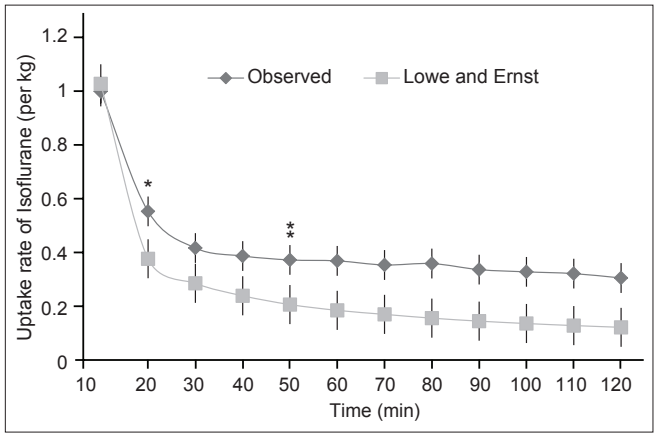

Figure 3: Mean rate of uptake (±SD) of isoflurane vapour per kg actual body weight per min. Also shown is that derived from Lowe and Ernst equation. Note the stability from 40 min onwards. *$P<0.05$; **$P<0.01$

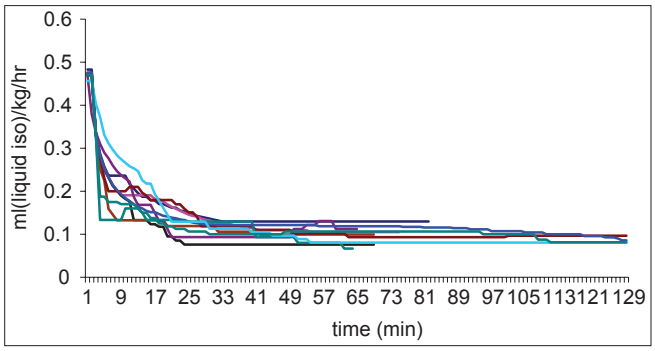

Figure 4: Individual rates of infusion of isoflurane per kg ideal body weight per h. The different rates of infusion depict inter-individual variability for the same end tidal after functional residual capacity and circuit wash in

varied inversely with BMI ($r=-0.53$), but the relation was not statistically significant ($P>0.05$).

BIS index was in the range of 25-30 and Et-CO_2 was maintained at 32.4±2.1 mm Hg during the study. The mean expired oxygen concentration at the end for the longest duration of surgery (160 min) was 78±5%.

DISCUSSION

We had derived isoflurane infusion rates [Figure 4] from our pilot cases by modification of Lowe and Ernst's equation of uptake (1 ml of liquid isoflurane produces 205 ml vapours at 37°C).[12] Our aim was to provide enough vapours to wash-in the circuit volume and patients' functional residual capacity (FRC) to 1.5% vapour concentration and in addition 3 unit doses (according to SqRT principle) within 9 min. We had decided to achieve Et-Iso of 1.5% within 5-10 min for gradual build-up of concentration, avoiding excess over pressurization and hypotensions in anaesthetized patients thus try to maintain a stable CO to study uptake. Though the rate of observed uptake in the initial period was lesser than predicted by the Lowe's equation, we compared uptake after 10 min; by the time1.5% Et-Iso was attained in all patients.

SqRT and 4-compartment models have been compared before with a lot of discrepancies with actual clinical observational studies on volatile agent uptake. Changes in CO with surgical stimulation were speculated as the main factor for the differences. However, even after substitution of measured CO values in the formulae both models had differences between observed and calculated uptake.[13] The same differences were observed when invasively measured fluctuating CO was used to calculate and compare uptake.[14] We tried to maintain stable haemodynamic to maintain a stable CO as our FGF were near metabolic flows and did not fluctuate much. Measurement of CO invasively would have been unethical in our ASA-I subjects. Moreover when using closed-loop feedback technique to maintain constant end expired concentration, the rate of increase and consequently the uptake becomes independent of CO and ventilation; and depends on the infusion rate of the volatile agent.[13] The other reasons to explain the difference of isoflurane requirement from the SqRT model are; isoflurane metabolism, loss from the surgical site, body surface, anaesthetic circuitry, and absorption into soda lime. Isoflurane is mainly exhaled unchanged from the body and only 0.2% of absorbed isoflurane undergoes oxidative metabolism.[15] Percutaneous and transvisceral losses do not appreciably affect isoflurane uptake.[1] Surgical losses become significant if they are from large and highly perfused wound surfaces.[16] Anaesthetic loss into the circuitry depends on the rubber/gas (49) and plastic/gas (58) partition coefficients;[17] however, this depot will be saturated with time and cannot explain the progressive increasing in the difference of cumulative uptake. Inter-individual variation is also a factor affecting uptake kinetics.[4,7,8] On plotting the infusion requirements over time, we found that it varied for similar Et-Iso in different patients [Figure 4]. This can be due to individual differences in the factors determining uptake i.e., CO, blood/gas partition coefficient ($\lambda_{B/G}$). The tissue and blood solubility coefficients have been derived from tissue homogenates and vary by as much as 150%.[18] Solubility is also influenced by changes in body temperature, blood and tissue composition, genetic pre-disposition, and other unknown physiological variables.[19] Hence, it may be difficult to predict completely what is happening *in vivo*.[7] Brody's equation has been derived from a large 'normal' sample population under resting conditions. It does not necessary predict the output for the individual patient and might be different from the measured CO in clinical situations. Moreover, changes in CO do not cause proportional changes in tissue perfusion to various compartments.[20]

Previous comparative studies state that isoflurane uptake is overestimated and later on underestimated by SqRT model.[13,14] Our study shows similar results with a simpler methodology to calculate the rate of uptake. The constant difference after 30 min between the uptake curve [Figure 3], imply that the

difference of cumulative uptake between the observed and that from the SqRT model would gradually increase [Figure 2]. Severinghaus had described the uptake of nitrous oxide in only 6 patients with primitive monitors.[2] Lowe and Ernst also relied on computer simulations themselves when describing the SqRT model.[3] Arterial to end expired gradient due to ventilation-diffusion mismatch, different exponential organ uptake time constants, inter tissue diffusion of volatile agents and regional blood flow variability may cause inaccuracy in calculating uptake.[13] Even current computer programs simulating anaesthetic uptake may not be correct because they are based on theoretical models, although they may be still useful to teach basic principles of uptake. Therefore, anaesthesia techniques with low flows continue to rely on anaesthetic monitoring. Nevertheless, the fact that authors have repeatedly come back to SqRT model as a benchmark suggests that it still might have some underlying validity.[14]

Different studies have shown weak correlations of uptake of the agent with all patient characteristics better with body weight,[3/4] BSA and actual body weight.[8,21] Thus, predicting anaesthetic uptake and its delivery at pre-determined rates derived from anthropometric measurements might not be accurate.[22] We used IBW for calculating the infusion rate of isoflurane because it correlates better with lean body mass.[23]

Since, this was an open labelled study the observer was not blinded. Data were simultaneously being recorded intra-operatively in a computer logged on to the monitor. Isoflurane uptake was based on oxygen requirement, which were derived from nomograms (Appendix).[11] The decreased requirement under anaesthesia was taken care of by further decrease in FGF progressively to metabolic flows. Isoflurane infusion was not connected to the inspiratory limb to avoid any accidental exposure of liquid isoflurane to patient's airway. Moreover, at the expiratory limb warm expired gases assist to maintain near body temperature and ensure vaporization. Vapour loss due to system leaks and venting was evaluated based on the FGF and patient's oxygen consumption. Alveolar uptake proceeds simultaneously with wash in therefore the actual rate of uptake cannot be separated from that of the system. The rate of infusion stabilized by 15-20 min (0.15-0.10 ml IBW/kg/h) in all subjects and remained the same throughout.

CONCLUSION

Anaesthetic requirements are higher than predicted by the SqRT model. There is inter-individual variability in the pharmacokinetics of isoflurane in humans. During the initial period rate of uptake is actually lower than predicted by the square root model. The rate of uptake correlates more with IBW than body weight alone.

REFERENCES

1. Eger EI. Uptake and distribution of anesthetic agents. In: Miller RD, editor. Anaesthesia. 5th ed., Vol. 1. Philadelphia: Churchill Livingstone; 2001. p. 74-95.
2. Severinghaus JW. The rate of uptake of nitrous oxide in man. J Clin Invest 1954;33:1183-9.
3. Lowe HJ, Ernst EA. The Quantitative Practice of Anesthesia – Use of Closed Circuit. Baltimore: London, Williams and Wilkins; 1981. p. 118-9, 194, 201-2.
4. Bengtson JP, Bengtsson A, Stengvist O. Uptake of enflurane and isoflurane during spontaneous and controlled ventilation. Anaesth Intensive Care 1992;20:191-5.
5. Lockwood GC, Chakrabarti MK, Whitmam JG. The uptake of isoflurane during anesthesia. Anaesthesia 1993;48:148-52.
6. Walker TJ, Chakrabarti MK, Lockwood GC. Uptake of desflurane during anesthesia. Anaesthesia 1996;51:33-6.
7. Hendrickx JF, Soetens M, Van der Donck A, Meeuwis H, Smolders F, De Wolf AM. Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled mechanical ventilation. Anesth Analg 1997;84:413-8.
8. Westenskow DR, Jordan WS, Hayes JK. Uptake of enflurane: A study of the variability between patients. Br J Anaesth 1983;55:595-601.
9. Morris LE. Closed carbon dioxide filtration revisited. Anaesth Intensive Care 1994;22:345-58.
10. el-Attar AM. Guided isoflurane injection in a totally closed circuit. Anaesthesia 1991;46:1059-63.
11. Lowe HJ, Viljoen JF. Nomogram for anaesthetic uptake. Anaesth Intensive Care 1994;22:374-5.
12. Weir HM, Kennedy RR. Infusing liquid anaesthetics into a closed circuit. Anaesth Intensive Care 1994;22:376-9.
13. Hendrickx JF, Van Zundert AA, De Wolf AM. Sevoflurane pharmacokinetics: Effect of cardiac output. Br J Anaesth 1998;81:495-501.
14. Hendrickx JF, Dishart MK, De Wolf AM. Isoflurane and desflurane uptake during liver resection and transplantation. Anesth Analg 2003;96:356-62.
15. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975;43:325-32.
16. Stoelting RK. Inhaled anesthetics. In: Stoelting RK, editor. Pharmacology and Physiology in Anaesthetic Practice. 3rd ed. Philadelphia: Lippincott Raven; 1999. p. 36-74.
17. Targ AG, Yasuda N, Eger EI 2nd. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. Anesth Analg 1989; 69:218-25.
18. Yasuda N, Targ AG, Eger EI 2nd. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989;69:370-3.
19. Eger EI 2nd. Respiratory and circulatory factors in uptake and distribution of volatile anaesthetic agents. Br J Anaesth 1964;36:155-71.
20. Hoffman WD, Banks SM, Alling DW, Eichenholz PW, Eichacker PQ, Parrillo JE, *et al*. Factors that determine the

hemodynamic response to inhalation anesthetics. J Appl Physiol 1991;70:2155-63.
21. O'Callaghan AC, Hawes DW, Ross JA, White DC, Wloch RT. Uptake of isoflurane during clinical anesthesia. Anaesth 1983;55:1061-4.
22. Vermeulen PM, Kalkman CJ, Dirksen R, Knape JT, Moons KG, Borm GF. Predictive performance of a physiological model for enflurane closed-circuit anaesthesia: Effects of continuous cardiac output measurements and age-related solubility data. Br J Anaesth 2002;88:38-45.
23. Fukuda K. Intravenous opiod anesthetics. In: Miller RD, editor. Anaesthesia. 6th ed., Vol. 11. Philadelphia: Churchill Livingstone; 2001. p. 379-438.

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APPENDIX

1. Derivation of the rate of uptake
   a. Rate of infusion of isoflurane vapours (ml/min) = rate of infusion (ml/h) × 205/60
   b. FGF vented or leaks = Total FGF (ml/min) − VO_2 (ml/min)
   c. Amount of isoflurane vapours leaking (assuming a constant circuit concentration of average of Fi-Iso and Et-Iso) = {(Fi + Et)/2 × 100} × (b)
   d. Rate of uptake = (a) − (c) (ml vapours/min)

2. IBW (Devine and Robinson) (lbs)
   Men = 106 + 6(H − 60) (H = height in inches)
   Women = 105 + 5(H − 60)

3. Lowe and Ernst's SqRT model of anaesthetic uptake[3,13]

   During closed circuit anaesthesia, the uptake of a potent inhaled anaesthetic has been predicted by the SqRT model. The body takes up a 'unit dose' during the first min and during each subsequent time interval (3 min, 5 min, 7 min etc.,) in addition the "prime dose" is required to saturate the circuit, patients' FRC and arterial delivery system. The addition of prime dose and unit dose over time result in the 'cumulative dose'
   1. Unit dose (L of vapour) =2. f. MAC. $\lambda_{B/G}$. Q
   2. Prime dose (L of vapour)=f. MAC. $\lambda_{B/G}$. Q+V. f. MAC
   3. Cumulative dose (L of vapour)=prime dose + unit dose. $t^{-1/2}$ = (f. MAC. $\lambda_{B/G}$. Q+V. f. MAC) (+2. f. MAC $\lambda_{B/G}$. Q. $t^{-1/2}$)
   4. Conversion of vapour into liquid: 1 L vapour = MW/(D 24) L liquid

   The abbreviations used are f = fraction of MAC administered: MAC = minimum alveolar anaestheticconcentration;$\lambda_{B/G}$=blood/gaspartition coefficient (for isoflurane, 1.38); Q = CO (L/min, based on Brody's: CO = 0.2 × weight (kg)¾; t = time (min); V = volume of circuit and FRC (L); MW = molecular weight (for isoflurane, 184.5 g); and D = density (for isoflurane $1.496.10^3$ g. L^{-1} at 25°C).