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Washin and washout of isoflurane during cardiopulmonary bypass

To help decide when an inhalational agent should be discontinued during cardiopulmonary bypass (CPB), its rate of washin and washout must be known. Isoflurane one per cent was administered to 14 patients undergoing CPB and isoflurane blood concentrations were measured to determine the time course of washin and washout of this agent. Bubble oxygenators were used for seven patients and membrane oxygenators for the remaining seven. During the administration of isoflurane, isoflurane blood concentrations rose slowly and did not reach a steady state during the time available for washin. Isoflurane blood concentrations decreased by at least 50 per cent within two minutes of turning off the vaporizer, and by 15 minutes the concentration had dropped by 75 per cent. There was a tendency for more rapid elimination of isoflurane in patients undergoing rewarming during this period. There did not appear to be an important difference between bubble and membrane oxygenators in the rate of washin and washout of isoflurane. Within 15 minutes of turning off the vaporizer only 25 per cent of the original blood concentration of isoflurane will remain. The anaesthetist must decide what concentration of isoflurane is acceptable during separation from CPB. Knowledge of the time course of isoflurane washout will allow more accurate determination of when to discontinue its administration in order to reach an acceptable concentration by the time separation from CPB occurs.

Key words

ANAESTHETICS, VOLATILE: isoflurane; ANAESTHESIA: cardiovascular; SURGERY: cardiopulmonary bypass.

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Volatile anaesthetics are commonly used during cardiopulmonary bypass (CPB) both to maintain anaesthesia and to control blood pressure. There is very little known about the pharmacokinetics of volatile agents during CPB. The agent is often discontinued early in the period of rewarming for fear that a cardiodepressant effect will make separation from CPB difficult.¹ This practice may result in inadequate anaesthesia and patient awareness.

To determine when the volatile agent should be discontinued, the anaesthetist must decide what residual concentration is associated with an acceptable degree of myocardial depression during separation from CPB. The time required for the anaesthetic concentration to fall to this residual concentration from that present when the vaporizer is turned off is determined by the elimination characteristics of the anaesthetic under the conditions of CPB. This study was designed to describe the washin and washout of isoflurane in patients during CPB in order to provide guidelines for its use in that setting.

Methods

Following approval by the Hospital Research Ethics Committee, informed consent was obtained from 14 patients, 37 to 73 years of age, scheduled for surgery requiring CPB.

Anaesthesia was induced with high-dose narcotic (fentanyl or sufentanil), and maintained with further doses of narcotic and isoflurane up to one per cent delivered concentration, as needed. Isoflurane was discontinued at least 20 minutes prior to initiation of CPB, and more than 40 minutes before the study. Bubble oxygenators (Bentley Bio™) were used for seven cases and membrane oxygenators (Terumo Capiox™) for the remaining seven. The oxygenators were primed with 2000 ml of lactated Ringer's solution.

Study protocol

Once on CPB, the patients were cooled to 28–30°C core temperature. Following application of the aortic cross clamp and administration of a cardioplegic solution, time was allowed for pump flow, mean arterial pressure and the haemoglobin concentration, to reach stable levels (2.2–3.0 L·m⁻², 54–95 mmHg and 63–86 g·L⁻¹ respectively). Gas flows were maintained between 3 and 7

$L \cdot \text{min}^{-1}$. Uncorrected values for arterial blood gases were maintained within normal limits. Isoflurane one per cent was then delivered from a previously calibrated vaporizer to the gas inlet port of the oxygenator. The same isoflurane vaporizer was used throughout the study and stability of output was verified by a BeckmanTM infrared gas analyser. Washin of isoflurane occurred in all patients during this cold phase, with the temperature maintained at $28\text{--}30^\circ\text{C}$ (measured at the blood sampling site on the oxygenator). The patients were then divided into two groups: cold washout and warm washout. In the cold washout group ($n = 8$, four bubble and four membrane oxygenators), the isoflurane was discontinued after 24 to 32 minutes and washout of isoflurane occurred while the temperature remained stable at $28\text{--}30^\circ\text{C}$. In the warm washout group ($n = 6$, three bubble and three membrane oxygenators), the isoflurane was continued until the aortic cross clamp was removed (24–40 minutes), and the rewarming phase began. The vaporizer was then turned off and the washout of isoflurane took place as the temperature increased from 30 to 38°C .

Blood sampling

Blood samples were taken from the arterial sampling port of the oxygenator. A baseline sample was obtained prior to starting the isoflurane, and at 2, 4, 8, 16, and 24 to 48 minutes later. These measurements were used to describe isoflurane washin. Following discontinuation of the isoflurane, samples were taken at 2, 4, 8, 16, and 24 to 32 minutes. These measurements described isoflurane washout. The 2 ml samples were immediately inserted into 6 ml gas-tight vials.

Measurement of isoflurane concentration

The isoflurane concentration was determined by head-space gas chromatography. Carbon tetrachloride (1 ml of a $0.5 \mu\text{l} \cdot \text{ml}^{-1}$ solution in water) was added to the vial containing the sample and served as the internal standard. Samples were incubated for 20 minutes at 45°C to allow optimum gas/liquid equilibration. The gas phase ($200 \mu\text{l}$) was then injected into a Perkin-Elmer 3920 gas chromatograph equipped with a flame ionization detector. The column ($2.1 \text{ m} \times 4 \text{ mm ID}$), filled with three per cent OV-17 on 80–100 mesh Chromosorb W, was conditioned at 280°C for 24 hours before use with a helium gas flow rate of $30 \text{ ml} \cdot \text{min}^{-1}$. The operating conditions were: column temperature 70°C ; injector temperature 100°C ; and detector temperature 250°C . Carrier gas flow rate was $90 \text{ ml} \cdot \text{min}^{-1}$. Under these conditions the retention times of isoflurane and its internal standard were 1.0 and 1.5 minutes, respectively. Appropriate standard curves ($0\text{--}30 \mu\text{g} \cdot \text{ml}^{-1}$) were constructed for each patient and from these the concentration of isoflurane determined. Each

FIGURE 1 Isoflurane washin during CPB. Isoflurane one per cent was delivered to the gas inlet port of the oxygenator during CPB while patients' temperatures were maintained at $28\text{--}30^\circ\text{C}$. The arterial blood concentrations ($\mu\text{g} \cdot \text{ml}^{-1}$) at each time interval are plotted as mean $\pm$ SD. The sample size is written above the SD bars. Data from the four groups were combined (see Results).

standard curve showed a coefficient of determination greater than 0.99 with an interday variation of less than five per cent at the concentrations studied.

Data analysis

A washin curve was constructed using the mean isoflurane blood concentrations measured in patients receiving isoflurane one per cent during CPB (mean $\pm$ SD). The ratio of C_a to C_o (C_a/C_o) was used to describe the washout of isoflurane. In this study C_a is the isoflurane concentration in arterial blood at a given time and C_o is the concentration present when the vaporizer is turned off.

The per cent decrease in isoflurane blood concentration in the first two minutes following discontinuation of isoflurane administration and the elimination half life ($t_{1/2}$) are described using means and 95 per cent confidence limits. The $t_{1/2}$ was estimated from the slope of the terminal phase of isoflurane washout, ignoring the small effect that deeper compartments such as fat might have after such a short exposure to isoflurane.

Results

In all cases, during isoflurane washin there was an initial rapid increase in isoflurane blood concentration followed by a steady but slower increase (Figure 1). The isoflurane concentrations did not reach a steady state during the time available for washin and therefore pharmacokinetic parameters for this phase could not be determined.

After the isoflurane was discontinued, there was an initial rapid washout followed by a slower terminal elimination. Isoflurane blood concentrations dropped too rapidly in the first few minutes of the washout phase to allow calculation of the half life ($t_{1/2}$) for this period. The decrease in isoflurane concentration in the first two

FIGURE 2 Washout of isoflurane during CPB expressed as the ratio of the blood concentration at a given time (Ca) to the blood concentration immediately before discontinuation of isoflurane administration (Co), plotted against time (mean $\pm$ SD). Data from the four groups were combined ($n = 14$, see Results).

minutes after the vaporizer was turned off ranged from 50.5 per cent in the bubble oxygenator, warm washout group, to 71.4 per cent in the membrane oxygenator, warm washout group (Table). A technical problem in the measurement of a blood sample in the bubble oxygenator, warm washout group, made it impossible to calculate the per cent decrease of isoflurane in the first two minutes for one patient. The $t_{1/2}$, calculated from isoflurane blood samples measured during the time on CPB, ranged from 9.4 minutes in the bubble oxygenator, warm washout group, to 14.9 minutes in the membrane oxygenator, cold washout group (Table).

Differences between groups were not large. Combining the four groups, the average decrease in isoflurane concentration in the first two minutes was 61 per cent, and the $t_{1/2}$ was 13.1 minutes. Figure 2 illustrates the washout (Ca/Co) using the combined data.

Discussion

We have described the washin and washout of isoflurane during CPB. Previously, information on the use of volatile anaesthetics in this situation was lacking.

In order to represent the clinical situation, isoflurane blood concentrations were measured without strict control for variables which may affect the solubility and uptake of volatile anaesthetics in blood. For instance, gas and pump flows, and degree of haemodilution, were adjusted as needed to maintain patient stability, despite the fact that these may affect isoflurane solubility and therefore uptake.^{2,3} The effect of different gas and pump flow rates on anaesthetic uptake and elimination via bubble oxygenators has been examined in an *in vitro* study.⁴ Increasing gas flow rates from 3 to 6 to 12 L $\cdot$ min⁻¹ resulted in faster uptake and elimination but this effect was no longer significant after the first 16 min. Altering pump flow rate did not appear to affect anaesthetic washin or washout.

Consistent trends were demonstrated in the isoflurane blood concentrations. First, a steady state for the washin of isoflurane was not reached within the 40 minute washin period. This indicates that the isoflurane blood concentration is slow to reach inspired levels. Second, washout was rapid in all cases. Isoflurane concentrations decreased by at least 50 per cent within two minutes of turning off the vaporizer, and by 15 minutes the concentration had dropped by 75 per cent. There was a tendency for more rapid elimination in patients undergoing rewarming during this period. Third, although the number of patients studied was relatively small, there did not appear to be an important difference between bubble and membrane oxygenators in the rate of washin and washout of isoflurane.

The $t_{1/2}$ was calculated from isoflurane blood concentrations measured during washout on CPB. The maximum

TABLE Isoflurane blood concentration during washout. Values presented as mean and 95% confidence limits

Oxygenator-washout temperature	% decrease in 2 minutes	95% confidence limits for % decrease	$t_{1/2}$ * (minutes)	95% confidence limits for $t_{1/2}$
Bubble - cold	58.8	54.3-63.3	14.6	9.6-19.6
n	4		4	
Membrane - cold	60.6	45.6-75.7	14.9	7.5-22.4
n	4		4	
Bubble - warm	50.5	†	9.4	6.0-12.8
n	2		3	
Membrane - warm	71.4	70.6-72.2	12.2	6.9-17.5
n	3		3	
Average	61.0	55.4-66.5	13.1	11.0-15.2
n	13		14	

*Approximate, see methods.

†Confidence limits not presented due to small n, see Results.

time available for washout was 32 minutes. Washout of isoflurane following administration for two hours continues for days,⁵ due to contributions from muscle and fat. Although the $t_{1/2}$ we report ignores these deeper compartments their contribution is likely unimportant after the short exposure to isoflurane in the present study.

Usually, volatile anaesthetic concentration in the body is reported as the partial pressure. To convert from blood concentration to partial pressure, the constant relating concentration to partial pressure, the blood/gas coefficient, must be known. We did not measure the blood/gas coefficients in our patients. Previously published values are not useful as they have not been determined at the temperatures and haematocrit values of the present study.

Results from a study⁶ examining isoflurane uptake and excretion via the lungs are presented as an example of a more familiar situation. Following the inhalation of isoflurane in subanaesthetic concentrations for 32 minutes, washout occurred rapidly from normal volunteers. By two minutes the partial pressure had decreased by 63.0 per cent, and by 16 minutes it had dropped by 89.8 per cent, from the partial pressure immediately prior to the beginning of washout.

The present data indicate that when isoflurane is administered during CPB the blood concentration rises slowly and does not reach a steady state within 40 minutes. Within 15 minutes of discontinuing administration of isoflurane the blood concentration will have fallen to less than 25 per cent of the concentration present when the vaporizer was turned off. Once the anaesthetist decides what constitutes a safe delivered concentration of isoflurane during separation from CPB this information can be used to determine when to discontinue its administration. For example, if 0.5 per cent isoflurane is chosen, then up to two per cent isoflurane can be safely administered so long as it is discontinued 15 minutes before separation from CPB. Knowledge of the time course of washin and washout of isoflurane during CPB can allow the anaesthetist to more confidently use this agent to maintain anaesthesia during this critical period of cardiac surgery.

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Résumé

Afin d'aider à décider quand un agent d'inhalation doit être discontinué durant la CEC (CPB), son taux de captation et de lavage doit être connu. L'isoflurane un pour cent a été administré à 14 patients subissant une CEC et les concentrations plasmatiques d'isoflurane ont été mesurées afin de déterminer les temps de captation et de lavage de cet agent. Les oxygénateurs à bulles ont été utilisés pour sept patients et des oxygénateurs à membrane furent utilisés pour les sept autres. Les concentrations plasmatiques de l'isoflurane ont diminué d'au moins 50 pour cent en dedans de deux minutes après la fermeture du vaporisateur et 15 minutes plus tard la concentration fut diminuée de 75 pour cent. Il y avait une tendance à une élimination plus rapide de l'isoflurane chez les patients subissant un réchauffement durant cette période. Il n'y avait aucune différence importante entre les oxygénateurs à membrane et les oxygénateurs à bulles dans le taux de captation et de délimination de l'isoflurane. Quinze minutes après la fermeture du vaporisateur seulement 25 pour cent de la concentration plasmatique originale de l'isoflurane était demeurée. L'anesthésiste doit décider quelle concentration d'isoflurane est acceptable lors du sevrage de la CEC.