Analysis of ethanol in expired air during low-flow isoflurane anaesthesia

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Summary
Monitoring of ethanol concentration in expired air is a method for assessing fluid absorption during transurethral prostatic surgery and endometrial resection, but the validity of this technique has not been studied in low-flow ventilation systems. For this purpose, we have compared the concentration–time profiles of ethanol in expired gas and in venous blood during an i.v. infusion of 0.4 g kg⁻¹ of ethanol over 30 min in 10 women during isoflurane anaesthesia and in the awake state. Anaesthesia increased the ethanol concentration in expired gas by 13% and in venous blood by 34%. The expired gas–blood difference during infusion was abolished, and the central volume of distribution for ethanol was reduced from 20.9 to 8.6 litre, on average. We conclude that breath sampling during low-flow isoflurane anaesthesia reflects an alcohol load well, but that a change in ethanol disposition makes the values slightly higher than in the awake state. (Br. J. Anaesth. 1996; 76: 85–89)

Key words

Measurement of ethanol in expired gas is performed most frequently in awake subjects who are suspected of driving offences in relation to drinking alcohol. In recent years, ethanol analysis in expired gas has been used as a marker of fluid absorption during transurethral resection of the prostate [1, 2] and transcervical resection of the endometrium [3, 4]. Ethanol monitoring was developed originally for spontaneously breathing patients under regional anaesthesia, but it has also been used under general anaesthesia [5, 6]. However, atelectasis and hypothermia would be expected to give lower values for ethanol in the breath [7] while tracheal intubation may increase them by reducing the reabsorption of ethanol in the oral cavity during expiration [6].

The aim of the present study was to evaluate the validity of measurement of ethanol in expired gas during isoflurane anaesthesia using a low-flow breathing system. This was done by comparing ethanol concentrations and pharmacokinetics of ethanol in blood and expired gas during and after an i.v. infusion of ethanol during surgery. The experiment was repeated on the same subjects in the awake state.

Patients and methods
We studied 10 healthy women, aged 24–62 (mean 44) yr and with a body weight of 50–83 (mean 67) kg. They were consecutive patients admitted for elective ENT surgery with an estimated duration of more than 2 h. The study was approved by the local Ethics Committee and all patients gave informed consent to participate in two studies, one during general anaesthesia and one in the awake state about 2–6 weeks later.

In the first study, subjects were premedicated with triazolam 0.25 mg by mouth. General anaesthesia was induced with thiopentone and fentanyl, followed by atracurium or vecuronium. The lungs were ventilated using a circuit system (Q-system, Anmedic AB, Vallentuna, Sweden) with a bag-in-bottle, soda lime absorber and a heat and moisture exchanger (Humid-Vent 2 Port, Gibeck Respiration AB, Upplands Väsby, Sweden) with isoflurane and nitrous oxide in oxygen. After preoxygenation and denitrogenation for 5 min, a fresh gas flow of 6 litre min⁻¹ was used during the first 5 min after tracheal intubation. During steady-state ventilation, the fresh gas flow was reduced to 1.5 litre min⁻¹. Body temperature was measured by an oesophageal probe (Datex/Instrumentarium Oy, Helsinki, Finland).

After general anaesthesia had been induced, we administered 0.4 g kg⁻¹ of ethanol at a constant rate over 30 min by infusing a solution containing 10% ethanol and 5% glucose (w/v) with an infusion pump (Ivac 560, Ivac Co., San Diego, CA, USA) through a venous cannula placed in one arm.

Starting from the onset of infusion, concentrations of ethanol in blood and expired gas were measured at 20 exactly timed occasions over 2 h. Venous blood was sampled from a cannula placed in the arm opposite to that used for infusion and ethanol concentration was measured by gas chromatography (GC 6000 Vega Series 2, Carlo Erba Instruments, Milan, Italy). To avoid the “salting-out” effect of sodium fluoride used as an anticoagulant for whole blood [8], we analysed plasma samples and converted the ethanol concentration to whole blood data based...
on a plasma–whole blood ratio of 1.10 [9]. Each sample was analysed twice and the mean value obtained. Duplicate analyses ensured a coefficient of variation of 1.7%.

Ethanol concentration in expired gas was measured by a fuel cell type alcohol sensor (Alcolmeter S-D2, Lion Laboratories Ltd, S. Glamorgan, Wales). The breathalyser was calibrated by alcohol-in-gas standards before each study. To facilitate comparison with the blood ethanol concentration, the Alcolmeter readings were expressed in grams per 2100 litre of air. Accuracy was within 0.01 g per 2100 litre of air. Before each measurement, fresh gas flow was shut off by closing the circuit for 30 s. A 1.5-ml sample of air was taken at the end of passive expiration by attaching the Alcolmeter to an adapter placed between the tracheal tube and the heat and moisture exchanger of the ventilation system [6].

The second study was also performed at the hospital and followed the same design for ethanol infusion and plasma sampling as the first. The patient was conscious and no drug other than alcohol was given. She was instructed to take a deep breath and to blow into the mouthpiece of the Alcolmeter. Body temperature was measured by an earprobe (First Temp Genius 3000 A, Sherwood Medical, Carlsbad, CA, USA) which was calibrated to show the same values as the oesophageal probe.

In five patients where the operation ended earlier than expected, only data obtained during low-flow anaesthesia (mean 15.5) are reported. The corresponding measurements obtained during the second experiment were also discarded. This allowed comparisons between the anaesthetized and awake patients to be made at all times.

To avoid problems associated with computing the variance of a ratio, the blood–expired gas partition coefficient of ethanol was calculated as the difference between logarithm-transformed individual expired gas and blood ethanol values. The data were converted to the original scale and then multiplied by 2100.

The pharmacokinetics of ethanol were studied by assuming that the ethanol concentration equals the sum of a first-order distribution function and a zero-order saturated Michaelis–Menten elimination function. The concentration ($C$) at any time after a bolus injection of ethanol was obtained as [10];

$$C = Ae^{-\alpha t} + B - \beta t$$

where $\alpha$ = first-order exponential rate constant, $\beta$ = zero-order elimination rate constant and $t$ = time after the start of infusion. $A$ and $B$ = concentrations of ethanol obtained when the first-order and the zero-order functions are extrapolated back to $t = 0$.

We curve-fitted the data by considering the effect of an i.v. infusion on the model variables according to the following equations [11]:

During infusion:

$$C = A\{1 - e^{-\alpha T}\} + B - \beta T$$

After infusion:

$$C = A\{1 - e^{-\alpha T}\}/\alpha T - e^{-\alpha (T-T)} + B - \beta T$$

where $T$ = infusion time.

The model variables were estimated by using a non-linear curve fitting program for a digital computer (Model-PK, McPherson Scientific, Rosanna, Victoria, Australia). No weighting factor was used as the error in the blood-ethanol analysis was constant within the concentration range studied. The ethanol values were consistently higher than the Michaelis constant for alcohol dehydrogenase, which is 0.05–0.10 g litre$^{-1}$ [12].

The volume of the central compartment ($V_c$) was obtained from the dose of ethanol divided by the sum of $A$ and $B$. The total distribution volume ($V_{trans}$) was obtained from the dose divided by $B$ [13].

Results are presented as mean (SD). The area under the concentration–time curve for ethanol ($AUC$) during the experiment was calculated by the linear trapezoidal method. The statistical calculations were performed on a Macintosh computer using StatView 4.01 (Abacus Concepts, Berkeley, CA, USA). Differences were evaluated by the paired $t$ test and Wilcoxon’s matched pair test, as appropriate, and reported to be significant when $P < 0.05$.

Results

The ethanol concentration in expired air was 13% higher during general anaesthesia than in the awake state.
Ethanol analysis during general anaesthesia

In venous blood, this difference was 34% (fig. 1). The agreement between expired air and blood samples was stronger during general anaesthesia than in the awake state (fig. 2).

The expired gas–venous differences in ethanol concentration were close to zero during infusions of ethanol in anaesthetized patients, while they were markedly positive when the patients were awake (AUC, \(P < 0.05\)). After infusion, these differences were reduced and remained slightly negative during the pseudolinear phase of ethanol elimination (fig. 3).

These relationships represented a blood–expired gas partition coefficient for ethanol of 2238 (356) during infusion of ethanol in anaesthetized patients, while it was only 1339 (411) when the patients were awake. After infusion, these coefficients were 2107 (275) and 2118 (257), respectively (fig. 4).

The pharmacokinetic rate constants describing the distribution and elimination of ethanol showed similar values, regardless of whether or not the subjects were anaesthetized (table 1). However, \(V_c\) for ethanol in blood was only half as large during general anaesthesia (Wilcoxon’s test, \(P < 0.03\)).

Body temperature was lower in anaesthetized compared with awake patients. The difference increased gradually from 0.5 °C and 1.5 °C but was significant at all times (table 2).

Discussion

We have found that breath sampling during isoflurane anaesthesia reflected the alcohol load well and with the same precision as in the conscious state. The slightly higher mean ethanol concentration obtained during anaesthesia must be considered in view of the markedly increased ethanol concentration in blood that returned to the lungs. This increase can be attributed to the reduction in central distribution volume \((V_c)\) for ethanol. That a reduction in \(V_c\) could be detected in venous blood but not in expired gas indicates that it occurred after the blood had passed the pulmonary circulation, namely at the capillary level in peripheral tissues.

The distribution of ethanol to and from the tissues implies that the expired gas–venous difference in concentration is positive during ethanol infusion and becomes negative when mixing is complete throughout the total body water [14, 15]. This pattern was seen when our patients were awake, but the positive difference observed during infusion was absent when they were anaesthetized. The negligible expired gas–blood difference is consistent with vaso-
Table 1 Pharmacokinetic variables of ethanol (mean (SD)) derived by curve fitting concentration–time data obtained from analysis of ethanol concentration in expired gas (×2100) and venous blood. A = Theoretical concentration of ethanol when distribution phase is extrapolated to time = 0. α = first-order exponential distribution rate constant. B = theoretical concentration of ethanol when elimination phase is extrapolated to time = 0. β = zero-order elimination rate constant

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>General anaesthesia</th>
<th>Awake</th>
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<tbody>
<tr>
<td></td>
<td>Expired gas</td>
<td>Blood</td>
</tr>
<tr>
<td>0</td>
<td>36.4 (0.5)*</td>
<td>37.0 (0.4)</td>
</tr>
<tr>
<td>30</td>
<td>36.0 (0.3)</td>
<td>37.0 (0.4)</td>
</tr>
<tr>
<td>90</td>
<td>35.6 (0.4)</td>
<td>37.0 (0.4)</td>
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<tr>
<td>120</td>
<td>35.5 (0.5)</td>
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Table 2 Body temperature (°C) during the experiments with ethanol infusions (mean (SD)). *Measured after anaesthesia had been induced

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The rationale for measuring ethanol in expired gas is based on the assumption of a fairly stable equilibrium between ethanol concentration in the capillary blood of the lungs and alveolar air. The agreement between the blood and expired gas data is usually reported after multiplying the expired gas concentration with the blood–expired gas partition coefficient. However, this coefficient tells us that the ethanol concentration is always about 2100 times higher in blood than in expired gas. Therefore, reabsorption of ethanol from the gas mixture in the breathing system is only a theoretical source of ethanol administration in anaesthetized patients.

Preliminary experiments showed that the heat and moisture exchanger and soda lime together absorbed about 30% of the ethanol in the breathing system. This suggests that sampling should be performed close to the tracheal tube for accurate analysis of end-expiratory ethanol concentration [6] and that the results are probably unaffected by ethanol in inspired gas. The confounding effect of using an extremely small fresh gas flow was challenged further by turning it off completely for 30 s before each breath sampling. However, our results imply no bias in the breath analysis from this practice. During both experiments, the blood–expired gas partition coefficient for ethanol during the pseudolinear phase of ethanol metabolism was 2113, on average, which was similar to that found in previous studies [6–8, 12]. On the other hand, this coefficient was markedly lower during infusion of ethanol in awake patients [14] which suggests that a close correlation between expired gas and venous blood samples during rapid absorption of irrigating fluid marked with ethanol cannot be expected. In fact, the agreement between expired gas and blood was closer during anaesthesia.

The present study suggests that anaesthesia-induced vasodilatation is the main confounder when measuring fluid absorption by ethanol monitoring during surgery. This view implies that the effects of atelectasis, tracheal intubation and moderate hypothermia on breath alcohol analyses are very small or cancel out. In particular, the lower body temperature in the anaesthetized patients would be expected to increase the blood–expired gas partition coefficient of ethanol by almost 10% during the pseudolinear phase of ethanol metabolism [7, 8]. However, this coefficient was almost identical in the groups at that time.

The pharmacokinetic model we used allows separate evaluation of the distribution and the elimination parts of the blood-ethanol concentration profile. A previous study showed that the half-time for distribution of ethanol into the total body water (T½α) averaged 6.6 min after i.v. infusion of ethanol at different rates in young men and women [10]. In our present report, T½α was 6.9 min in venous blood when the female subjects were awake. In the anaesthetized state, we expected that the higher venous return of ethanol would correspond to a prolonged T½α. Instead, it tended to be shorter. This result, and the fact that equilibration of ethanol requires as long as 30 min to become complete, supports the assumption that α represents equilibration between well perfused and poorly perfused anatomical regions of the body rather than across the cellular membranes [15].
References

11. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *Journal of Pharmacokinetics and Biopharmaceutics* 1976; 4: 443–467.