The cost of inhalation anaesthesia has received considerable study and is undoubtedly reduced by the use of low fresh gas flows. However, comparison between anaesthetics of the economies achievable has only been made by computer modelling. We have computed anaesthetic usage for MAC-equivalent anaesthesia with iso­flurane, desflurane, and sevoflurane in closed and open breathing systems. We have compared these data with those derived during clinical anaesthesia administered using a computer-controlled closed system that measures anaesthetic usage and inspired concentrations. The inspired concentrations allow the usage that would have occurred in an open system to be calculated. Our computed predictions lie within the 95% confidence intervals of the measured data. Using prices current in our institution, sevoflurane and desflurane would cost approximately twice as much as iso­flurane in open systems but only about 50% more than iso­flurane in closed systems. Thus computer predictions have been validated by patient measurements and the cost saving achieved by reducing the fresh gas flow is greater with less soluble anaesthetics.

Keywords: anaesthetic volatile, iso­flurane; anaesthetics volatile, desflurane; anaesthetics volatile, sevoflurane; anaesthetics, audits

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Methods

Computer predictions

A four-compartment patient was modelled using specially developed software, details of which are given in the Appendix. The usage of iso­flurane, desflurane, and sevoflurane to achieve 1.3 MAC at 0.2, 1, 2, 4, and 6 litre min⁻¹ was computed and plotted for the three possible pairwise comparisons according to the method of Weiskopf and Eger.³

Patient data

The computer predictions were compared with our database of patients anaesthetized using our completely closed, computer-controlled anaesthetic system.⁴ Many of these patients contributed results to our previous publications,⁵⁻⁷ and all gave written, informed consent with local Research

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Ethics Committee approval. All patients received controlled ventilation to maintain their end-expired $P_{CO_2}$ at 4.5±5 kPa. The system maintained end-expired concentrations of 1.5% isoflurane, 8% desflurane, or 2.4% sevoflurane by injection of liquid anaesthetic into the system. These were intended to represent 1.3 MAC for each agent, but in view of a recent meta-analysis, which recommended a value of 6.6% for desflurane MAC, the values of usage and inspired concentrations of desflurane for each patient were increased by 10%. The rate of anaesthetic usage in the closed system was measured directly by this breathing system. The rate of usage that would have occurred in an open system was estimated by multiplying a fresh gas flow of 6 litre min$^{-1}$ that would have been necessary by the measured inspired anaesthetic fraction and converting to volumes of liquid at 20°C.

Statistical analysis

There are two problems to be addressed. First, although we know the inter-patient variability of anaesthetic usage, we do not know the variability when individual patients are administered anaesthetics repeatedly. Anaesthetic usage is very variable between patients and so the variability of the ratio of usage of two anaesthetics in different patients will be huge, making agreement between modelling and experiment undemanding. However, we expect that a patient who had a large isoflurane usage would have had a large desflurane or sevoflurane usage if they had been used instead. We have assumed arbitrarily that half the overall variability in the usage of each anaesthetic is because of within-patient variability and half because of between-patient variability.

The second problem is that variability in the ratios of random variables, and confidence intervals around a central value, cannot in general be calculated exactly. We have undertaken Monte Carlo simulations of this problem, generating sets of artificial results as if from 1200 patients for each anaesthetic. The anaesthetic usage for the $i$th data set at each time point $t$ was given by $u_i(t)=\mu(t)+\varphi \sigma(t)/\sqrt{2}$, where $\mu(t)$ and $\sigma(t)$ are the mean and SD of the measured usages at time $t$, $\varphi$ is a random normal deviate, different for every artificial patient and every anaesthetic, and the $\sqrt{2}$ factor allows for the fact that half the population variance is assumed to be a result of within-subject variation. For each pair of anaesthetics, 1200 values of the ratio of usage were then calculated at each time point, enabling 95% confidence intervals to be determined numerically.

Results

The computer predictions of anaesthetic usage at different fresh gas flows are shown in Figure 1. The number of patients whose results were used for analysis are shown in Figure 2. Most of the patients in the isoflurane group were from our initial study of procedures lasting only an hour or so; longer data sets are available for desflurane and sevoflurane. There was instability in the rate of anaesthetic usage for the first few minutes as the target end-expired concentration was established, resulting in large variability of both the measured variables. After 5 min the SD calculated from the Monte Carlo experiments reduced to a value within 1% of an estimate of the SD of the ratio of two random variables that is said to be valid when variance in the denominator is small. The lower and upper 95% confidence intervals were then approximately −1.7 and +2.3 SD, respectively, from the mean value. These limits are drawn from our patient data and show the range within which the results of a randomly chosen patient would be expected to lie. The computed results are shown against
these 95% confidence intervals of the patient results for the open system in Figure 3 and for the closed system in Figure 4. These figures also show the break-even lines at our institution, which are at 1.7, 0.62, and 2.7 for isoflurane:desflurane, isoflurane:sevoflurane and sevoflurane:desflurane, respectively.

Discussion
The accuracy of the computer simulation is supported by the patient data. Comparison with Weiskopf and Eger’s original paper shows little difference between the model they used, based on ‘artificial’ pharmacokinetic compartments derived from Yasuda’s study of elimination kinetics,12 and the model we have used based on Eger’s original and ‘natural’ physiological compartmental model,13 allowing for the fact that we have taken a different value for the MAC of desflurane. This does not confirm that either represents patient uptake accurately, for if predicted usage was systematically in error, even in a time-dependent fashion, then the ratio of usage of two anaesthetics would be unaffected. In fact, the usage predicted by our model matches the clinical data (Fig. 5), so we conclude that it is good enough to be used as a guide to clinical expectation and that the computer-generated data in Figure 1 for flows other than open and closed systems are also likely to be correct.

We have no data on within patient variability of anaesthetic uptake. If it is less than our assumed value of half the total variability, then the confidence intervals shown in Figures 3 and 4 overstate the variability in the ratios of anaesthetic usage. The distribution of ratios is a troublesome problem in statistics for the variance may not be defined and, in general, only an approximate solution is available.10 We used a Monte Carlo simulation to produce a better estimate of the variance of our data and found that the use of the approximation would have underestimated variance, particularly for the early data but also when the number of patients in the isoflurane group was small. In spite of these efforts to be stringent, our conclusions are inevitably weakened by our arbitrary specification of within-patient variance.

Although the cost of drugs is a small part of the anaesthetic budget and an even smaller part of the total cost of an operation, many anaesthetists find it worthwhile to have some idea of comparative costs when planning their practice. We interpret our results as saying that when a patient is anaesthetized at our institution with an open system, isoflurane is almost certain ($P>0.95$) to be much less expensive than desflurane and sevoflurane, and that...

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{The shaded area shows the 95% confidence interval of the ratio of usage of anaesthetics in an open system. The continuous lines are the predictions of the computer model. The break-even lines for our institution are dotted and these lines should be adjusted to local costs. When the ratio of usage lies below this line then the anaesthetic in the numerator of the ratio is the less expensive.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{The shaded area shows the 95% confidence interval of the ratio of usage of anaesthetics in a closed system. The continuous lines are the predictions of the computer model. The break-even lines are dotted and these lines should be adjusted to local costs. When the ratio of usage lies below this line then the anaesthetic in the numerator of the ratio is the less expensive.}
\end{figure}
sevo¯urane would cost the same as des¯urane. If a closed system is used, iso¯urane is almost certain to be less expensive than sevo¯urane and would probably (\( P > 0.5; P < 0.95 \)) be less expensive than des¯urane, but des¯urane would probably be a little less expensive than sevo¯urane. Not only are the absolute costs of all the anaesthetics less in closed systems, but the relative cost differences are also reduced. The position of the break-even line will change as prices vary with time and between institutions, but the ratios of usage shown in Figures 3 and 4 are invariable and can always be used to determine relative expense.

**Appendix**

Narkup was a simple program, predicting the uptake of anaesthetics using a four-compartment model.\(^\text{14}\) It has been modified to make it run more accurately and efficiently over long simulations by integrating simultaneously variables representing all anaesthetics in all components of the model (from breathing system concentrations to tissue tensions), using a variable step length.\(^\text{15}\) The user places an upper limit on the step size throughout which the fresh gas composition and patient physiology cannot be changed, because they must be constant during an integration step. The price paid for these improvements is that the delays built in to the original Narkup program to represent circulation times are no longer included and so blood volume is no longer considered as a separate compartment. This is of no consequence when considering events on a time scale of 1 h. The servo-control algorithms that are used by our automated anaesthetic breathing system form the basis of the servo-control algorithms in the new version of Narkup. The compartment parameters used in the computer experiments we have reported in this paper are listed in Table 1, and the integration step size was limited to a maximum of 10 s to mimic the speed of updating in the real system.

**References**


<table>
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<tr>
<th>% Body weight</th>
<th>% Non-shunted cardiac output</th>
<th>( \lambda_{\text{tissue/gas}} )</th>
<th>Iso</th>
<th>des</th>
<th>sev</th>
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Fig 5 The shaded area shows the 95% confidence interval of the usage of anaesthetics in a closed system. The continuous lines are the predictions of the computer model.

