Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: elimination from the head


Summary
We describe the first human experiments to demonstrate wash-out of isoflurane using fluorine magnetic resonance spectroscopy. Using a surface receive coil, we found two-compartment kinetics within the head with decay half-times of 9.5 and 130 min, but the signal was too weak to localize the compartments. If the fast compartment is assumed to be the brain then our results match the predictions of the classical perfusion-limited pharmacokinetic model of inhalation anaesthesia. (Br. J. Anaesth. 1997; 79: 581–585).

Key words

In the classical pharmacokinetic theory of inhalation anaesthesia, an inhaled anaesthetic is considered as an inert gas, the partial pressure of which slowly equilibrates throughout the body. The partial pressure in each tissue approaches arterial partial pressure exponentially with a rate constant proportional to the perfusion of that tissue and to the ratio of blood solubility to tissue solubility for that anaesthetic. Inter-tissue diffusion and specific tissue binding are not usually considered. Published values of brain perfusion and isoflurane solubility predict a half-time for the equilibration between arterial blood and brain of 2–3 min. There are no specific binding sites of quantitative significance in the brain, and no evidence of chemical bonding to body tissues, so wash-out kinetics should match wash-in. The overall elimination of isoflurane from the brain at the end of an anaesthetic is slower than this because the concentration in arterial blood declines gradually (clearance by the lungs is imperfect), and the longer the anaesthetic, the slower the elimination from the brain as a greater drug load must also be cleared from the remainder of the body. One model of this process predicts an elimination half-time of 7 min after 30 min of anaesthesia.

Fluorine magnetic resonance spectroscopy (19F MRS) allows pharmacokinetic investigation in vivo because all modern inhalation anaesthetics are fluorinated. The first animal MRS experiments with halothane demonstrated very slow elimination of halothane from the brain, incompatible with the classical model. Some of that MRS signal probably arose from fluorinated metabolites, and there has been debate over the identity of the tissue source of the signal. Later animal studies demonstrated fast and slow compartments within the head (usually assumed to be brain and extra-cerebral tissue, respectively), but even in recent studies of isoflurane, estimates of the faster half-time have been greater than predicted by theory (36 min, 25 min with only one exception (8 min)). A persistent problem with these studies is that the 19F signal is too weak to allow dynamic imaging, and the location of the signal source has been estimated indirectly.

The question of delayed cerebral elimination of anaesthetics has obvious implications both for the recovery of “street fitness” in patients after anaesthesia and the validity of the standard perfusion-limited model of anaesthetic distribution. We have investigated this problem by undertaking the first 19F MRS studies of isoflurane kinetics in humans. In this part of the study we have examined elimination of isoflurane from the head; in part II the data are re-examined to estimate the rate of equilibration between end-expired gas and brain.

Subjects and methods
We studied healthy volunteers, aged 30–41 yr. Subjects gave written informed consent and the study was approved by the Medical Research Ethics Committee of Hammersmith Hospital and the Royal Postgraduate Medical School. Subjects lay in the left lateral position in the bore of the spectrometer and breathed oxygen via a Mapleson A system incorporating a non-ferromagnetic valve venting outside the magnet bore to eliminate trace concentrations of isoflurane in the air around the subject’s head. The nares were occluded and subjects breathed through a...
snorkel-style mouthpiece. There was no $^{19}$F MR signal from the apparatus used. Pulse oximeter and ECG leads were passed through low pass filters to shield the spectrometer from radio frequency interference. End-tidal carbon dioxide and isoflurane concentrations were measured throughout using an infrared monitor (Capnomac, Datex, Finland) sampling via a catheter 6 m long. The monitor was calibrated before each experiment using QuickCal Standard (Datex, Finland). Digital output from the Capnomac was logged onto a computer and the analogue output of the volatile anaesthetic channel was recorded on paper. Subjects were attended by two anaesthetists: one remained outside the spectrometer’s radio frequency screening enclosure watching the electronic monitors, the other was inside the enclosure monitoring respiration. Baseline measurements were made, and then a constant concentration of isoflurane (0.6% or 1%) was introduced into the inspired gas.

The spectrometer was a prototype Picker system operating at 1.5 T corresponding to a frequency of 64 MHz for fluorine and 60 MHz for protons. The transmitter coil was of saddle shape geometry, 52 cm in diameter, and could be tuned independently to both required operating frequencies. Radio frequency pulses of 200 ms could be generated for both $^1$H and $^{19}$F components of the study with this transmitter system and had sufficient bandwidth to excite equally all resonances of the $^{19}$F spectrum. A 6 cm coil, also tuneable to both 64 and 60 MHz, was positioned over the subject’s occipital region. This combination of coils gave a homogeneous transmit pulse over the whole head of the subject together with the improved sensitivity of a closely coupled receiver coil. The system was shimmed using the proton signal before acquisition of the $^{19}$F spectra. The radio frequency pulse was calibrated by an operator-selectable plane. They were checked visually to ensure that true minima had been found.

Continuous data collections were made, each comprising 128 averages (256 for the initial study), with collection starting within 400 μs of the pulse and a repetition time of 1 s. During the sequence of experiments, presaturation sequences were designed which would eliminate the magnetic resonance signal from an operator-selectable plane. They were used in the last two experiments, interleaved with the standard sequences, in an attempt to eliminate the signal from the superficial tissues.

The MRS peak height data collected during the period of elimination were normalized to peak height before isoflurane was stopped and modelled by one, two and three exponential equations. The $F$ test criterion advocated by Boxenbaum, Riegelman and Elashoff was used to decide which model was supported best by the data. Conventionally, the significance of such curve fitting can be improved by pooling data from different subjects: the number of data points is increased but the number of variables to be fitted is unchanged. The coefficients and rate constants of the curve derived from the pooled data are then group coefficients and group rate constants. Unfortunately, our data were in arbitrary units which differed between subjects because the signal strength was so sensitive to the position of the surface coil, and there was no prospect of obtaining meaningful group coefficients. None the less, individual curve fitting can be undertaken simultaneously with the constraint that they all have the same rate constants (the group rate constants) with individual coefficients and group rate constants chosen to provide the best fit. The fit of single and biexponential equations to the pooled data can then be tested by the same $F$ test criterion used for individual data sets. All curve fitting was performed by iteration using the Solver function of a Microsoft Excel v4 spreadsheet, with least squares solutions approximated from several initial variable values and checked visually to ensure that true minima had been found.

### Results

A total of eight studies were undertaken on five volunteers (see table 1, fig. 1). Only five studies produced wash-out data. The other studies were terminated prematurely because the subject became restless before regaining consciousness. When this happened the subject was withdrawn immediately from the magnet bore and wash-out data were lost.

When each experiment was analysed individually, a biexponential equation was a significantly better fit to the data than a single exponential in only two experiments (table 1). However, when the data sets were pooled, there was strong overall support for biexponential decay ($P<0.00001$). No data set supported a three-exponential equation.

Presaturation pulses were used in two studies but

### Table 1

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Concentration and duration of isoflurane</th>
<th>Wash-out data points</th>
<th>$T_{1D}$ fast</th>
<th>$T_{1D}$ slow</th>
<th>Signif. of 2 exponentials</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25%, 10 min + 0.5%, 35 min</td>
<td>8</td>
<td>—</td>
<td>57 ns</td>
<td></td>
<td>Initial study. 5-min data acquisition</td>
</tr>
<tr>
<td>2</td>
<td>0.6%, 25 min</td>
<td>17</td>
<td>4.7</td>
<td>92</td>
<td>0.002</td>
<td>2-min data acquisition for this and all following studies</td>
</tr>
<tr>
<td>3</td>
<td>1%, 30 min</td>
<td>30</td>
<td>5.9</td>
<td>74</td>
<td>0.00001</td>
<td>Presaturation pulses obliterated all signal</td>
</tr>
<tr>
<td>4</td>
<td>1%, 30 min</td>
<td>12</td>
<td>—</td>
<td>25 ns</td>
<td></td>
<td>Presaturation pulses obliterated all signal</td>
</tr>
<tr>
<td>5</td>
<td>1%, 35 min</td>
<td>12</td>
<td>—</td>
<td>121 ns</td>
<td></td>
<td>The best fit when the model for each data set was constrained to share group half-times</td>
</tr>
<tr>
<td>Group</td>
<td>79</td>
<td>9.5</td>
<td>130</td>
<td>0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the signal was so diminished that peak heights could not be distinguished from noise.

Discussion

This study was undertaken because of inconsistencies in results from animal experiments and their deviation from the theoretical prediction of an elimination half-time of 5–10 min. In 1983, Wyrwicz and colleagues made the first in vivo observations of the kinetics of inhalation anaesthesia in rabbits using 19F MRS. They reported prolonged elimination of halothane from the brain with a half-time of several hours. These results were challenged by Strum, Johnson and Eger, arguing from in vitro studies, but it was not until 1987 that further 19F MRS studies appeared. Wyrwicz's group found biexponential elimination kinetics for halothane and isoflurane (the faster having a half-time of 25 min for both agents), but as both components were detected after surgical removal of extracranial tissues it was still concluded that there was a slow component to the elimination of anaesthetics from the rabbit brain with a half-time of 3–5 h. Litt and colleagues, using a different MRS technique to eliminate the signal from surface tissues, also found biexponential elimination kinetics of halothane from rat brain, but the half-times were only 6 and 23 min. The same group also studied the elimination of isoflurane from rabbit brain. They found that elimination had a single component (half-time 36 min) when the skull was removed and a small surface coil applied directly to the brain, but two half-times of 55 min and 5 h in a single animal when a larger coil (matching that used by Wyrwicz and colleagues) was applied to the intact head. Their conclusion was that the long elimination half-time found by Wyrwicz and colleagues arose from tissue outside the brain, but their fast component results still disagreed with theory. They later compared the kinetics of halothane, isoflurane and desflurane in cranietomized rabbits, producing data compatible with perfusion-limited kinetics (half-times of approximately 8 and 60 min for all agents). Litt's group also produced images showing halothane exclusively in non-brain structures within the rabbit head, although the MRS collection variables biased this study towards these areas. The opinions of these two groups remained unresolved, with each still vigorously defending their position in 1991, but others were prepared to accept the fast component of halothane elimination from the rat head as an indicator of cerebral blood flow.

Recently, Xu and co-workers found two-compartment kinetics for sevoflurane in the rat head with half-times of 14 and 100 min. Sequential fluorine images showed initial accumulation of sevoflurane in brain, and one MRS characteristic of the two compartments (their T2) provided further evidence that the fast compartment was the brain. Although the weight of evidence from animal work may now suggest that elimination of fluorinated anaesthetics from the brain is rapid, Wyrwicz and colleagues maintain that there is slow elimination from the brain, and the studies from Litt's group have not been consistent. Even the results of Xu and colleagues, although technically impressive, give a half-time of sevoflurane elimination from the rat brain which is twice that expected from simple pharmacokinetic theory.

This is the first 19F MRS study of the kinetics of inhalation agents in humans. Inhalation of isoflurane to the point of unconsciousness, and subsequent recovery, may be associated with restlessness, confusion and loss of airway control. It is therefore difficult to perform these experiments in the bore of a magnetic resonance spectrometer because the subject lies within a tunnel 6 ft long and 30 inches in diameter. Restlessness demands that the experiment be terminated so that the subject can be withdrawn from the magnet bore for safety, but any change in position of the subject's head relative to the receive coil invalidates further data collections. The studies therefore have some risk and a poor data yield. Nevertheless the investigation was pursued because human studies alone allow anaesthetic effects on consciousness to be related to tissue compartment concentrations: animal experiments are performed with background i.v. anaesthesia. This aspect of the study is reported in part II of the study.

We have found evidence of biexponential wash-out of isoflurane from the head. The longer averaging used in the pilot study precluded the identification of a fast component of elimination, but the next two studies produced consistent data supporting two compartments. The improvement obtained by fitting a two- rather than a one-compartment model was not statistically significant in the last two subjects. This may be because fewer data points were collected from these experiments (the experiment was terminated when the subject became too restless), but there is another possible explanation. During this series of experiments the spectrometer was overhauled and modified, which included installation of electronic decoupling between receive and transmit coils (the previous decoupling was geometrical). An incidental result of the improved decoupling was to reduce the...
sensitivity of the surface coil to deeper tissues and if, as we believe, the fast component is deep, it would be more difficult to identify in the total signal. The timetable for hardware modifications to the spectrometer was unfortunately not under our control. In order to determine the overall significance of our evidence for biexponential elimination, we argued that regional perfusion of the head (which determines the kinetics of the underlying compartments) would be similar between subjects and that the more variable parameters would be the relative strength of the signal from the compartments because this depends critically on the exact position of the coil relative to the scalp, cranium and brain. We therefore re-computed the best fitting single and biexponential equations for all of our subjects simultaneously, subject to the constraint that all five shared the same half time(s). This analysis gave strong support for biexponential elimination.

The presaturation pulses were intended to resolve the two components spatially. Ideally the plane of the pulse obliterating the MR signal would have been so sharply defined that signal from adjacent areas was unaffected. Some encroachment into brain tissue was inevitable, but we thought that enough signal would remain to estimate isoflurane kinetics in purely brain tissue. In the two studies for which pre-saturation sequences were available there was no significant fast component and it is not surprising that almost all the signal was lost after presaturation of the superficial plane. This part of the study therefore only enables us to say that most of the signal is superficial, as is inevitable with a surface coil, and in particular we cannot refute the claim that there is a slow component in the deeper structures. None the less, the match of experimental and computer-generated results suggests that the fast compartment is brain and the slow is superficial tissue.

Our half-times were substantially shorter than those reported from most animal studies. This may be explained by species differences, but there were experimental differences which may also have contributed. Our subjects were exposed to isoflurane for relatively short durations; slow compartments would not have absorbed much isoflurane and their contribution to the MRS signal would be modest even though the 19F signal from non-cerebral tissues decays more slowly and can be collected more efficiently (technically, it has a longer T2 in these tissues). In a longer experiment the signal from a small, fast compartment could be drowned by the signal from slower compartments with greater affinity for isoflurane, lying closer to the surface coil. Our 6 cm surface coil was smaller relative to the brains used in animal experiments so that it should have relatively more brain in its region of sensitivity, and our sampling rate of 2 min was shorter, making it easier to identify faster processes. Indeed, if we had continued to average over 4 min as in the pilot study, we may not have obtained statistical justification for biexponential elimination.

Thus although the underlying kinetics in humans and animals are probably similar, different experimental designs have been biased towards different subprocesses.

Although we have data from only a few studies, our results match the expectation of practising anaesthetists and support the classical perfusion-limited pharmacokinetic theory of inhalation anaesthesia. We feel that because of the inherent risks of the study and the low yield, further human experiments should await improvement in the MRS technique.

References

Wash-out of isoflurane from brain


