Emergence and recovery in children after desflurane and isoflurane anaesthesia: effect of anaesthetic duration


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Background. We hypothesized that increasing duration of inhalation anaesthesia is associated with slower emergence and recovery in children, and that this effect would be less marked with desflurane in comparison with isoflurane.

Methods. Fifty-four infants and children assigned in groups according to age and expected length of operation were prospectively randomized to receive either isoflurane (I) or desflurane (D) for anaesthesia. After standard induction, the anaesthesia was maintained using an age-related 1.0 minimum alveolar concentration (MAC) equivalent for either agent in air and oxygen. Local analgesia was used as appropriate. End-tidal volatile agent concentration was recorded until extubation. Clinical evaluation of recovery was made by observers, blinded to group allocation.

Results. For patients < 4 yr of age, the median (95% CI) times in minutes to first movement [5.27 (D), 9.22 (I)], eye opening [9.42 (D), 13.3 (I)] and extubation [7.18 (D), 12.5 (I)] were significantly shorter (P < 0.05) for desflurane. In the group > 4 yr of age, the median (95% CI) times in minutes to first movement [4.42 (D), 11.6 (I)], eye opening [8.55 (D), 18.0 (I)] and extubation [7.08 (D), 16.7 (I)] were significantly shorter (P < 0.001) for desflurane. Times to leave recovery were not significantly different for the group < 4 yr of age, but were significantly shorter for desflurane in the group > 4 yr of age (P < 0.01). The isoflurane, but not desflurane, had a time-dependent effect on arousal. There were no significant differences in incidence of airway irritation or emergence delirium between the two agents.

Conclusions. The rate of recovery in children after exposure to desflurane was faster than those patients receiving isoflurane; recovery from desflurane, but not isoflurane, was relatively unaffected by the duration of anaesthesia.

Keywords: anaesthesia, paediatric; anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; recovery, postoperative

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Recovery after anaesthesia is influenced by the choice of volatile agent. Agents with lower tissue and blood:gas solubility such as desflurane have been shown in adults to be associated with faster times to return of airway reflexes,1 exubtation2 and recovery.1–3 This effect may be relatively insignificant for some procedures,4 while others have failed to demonstrate any reliable time-related effect.5,6 In paediatric anaesthesia, time to recovery with desflurane has been shown to be quicker7–12 compared with other volatile agents, and is associated with a reduced incidence of postoperative apnoea in neonates.9,11 Its use, however, has been restricted by reported concerns relating to emergence delirium,7,12,13 airway irritation10,14 and respiratory depression.15 Adult computer simulation programs16,17 show increasing duration of anaesthesia can markedly delay recovery after isoflurane, compared with desflurane. However, there have been few objective studies on emergence and recovery after desflurane anaesthesia in children, with no specific data on the potential effects of anaesthetic duration on recovery characteristics. We therefore designed a study to compare emergence and recovery in children after either isoflurane or desflurane anaesthesia, and to evaluate the effects of anaesthetic duration.

Methods
Following institutional Ethics Committee approval and informed parental consent, we studied 54, ASA I and II, children aged 4 months to 12 yr undergoing elective surgery. Exclusion criteria included the need for postoperative

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ventilation and significant cardiovascular, respiratory or neurological abnormalities. A scheme of block randomization was undertaken to ensure equality for age and duration of operation between the isoflurane group (Group I) and desflurane group (Group D). Therefore, at enrolment, children were randomized within groups for age (>4 or <4 yr) or expected duration of surgery (>60 or <60 min). Random number tables were used for group allocation and codes were stored in sealed envelopes. Patient characteristics recorded included; weight, height, age and full medical history. The corresponding age-related 1.0 MAC value for the child for desflurane and isoflurane were transcribed on to the study group envelope.

Patients were premedicated with oral paracetamol (20 mg kg$^{-1}$). General anaesthesia was induced, at the discretion of the senior anaesthetist, with either i.v. propofol (2–5 mg kg$^{-1}$) or inhalational sevoflurane. Tracheal intubation was facilitated using atracurium (500 µg kg$^{-1}$). Before incision, diclofenac (1 mg kg$^{-1}$) was given rectally in addition to appropriate regional anaesthesia. The study anaesthetic agent was started at the earliest opportunity. The following timings were recorded: induction, start of study agent and start of surgery.

All patients were ventilated to normocapnia, using a Penlon Nuffield Series 200 ventilator and a Mapleson F/circle breathing system according to patient weight, with the calculated study agent end-tidal 1.0 MAC value in oxygen and air. Intra-operatively boluses of fentanyl were given as indicated clinically to a maximum dose of 2 µg kg$^{-1}$. The administration of i.v. fluids was left to the discretion of the anaesthetist. All patient data including end-tidal agent levels were monitored with the Datex AS/3 and saved for later analysis on a laptop PC running the Datex Collect software. The volatile anaesthetic agent was turned off with the last surgical stimulus and the patient was allowed to wake spontaneously with minimal handling. Ventilation was continued until establishment of spontaneous ventilation. An observer, blinded to the anaesthetic agent, observed and timed the patient’s emergence events including times to first gross limb movement, eye opening, establishment of regular breathing pattern, extubation (primary outcome), admission to and discharge from the recovery ward.

The sample size for the study had been set at 48 patients, with equal numbers in each age group and treatment combination. A study of this size was calculated to have a 90% power to detect a treatment effect, 84% power to detect an age and duration effect. In calculating the sample size we have assumed that the treatment effects will be large (0.4) and any interaction to be moderate (0.25). The data from our 15 patient pilot study had a large observed treatment effect (0.46) and we anticipated a similar effect here. The calculation assumed that the data would be analysed using ANOVA and that a two-tailed 5% significance level would be used. On completion of the main study we determined that our duration times were not normally distributed, therefore, the data were consequently treated as ordinal and analysed using the Mann–Whitney rank sum two-tailed test for comparison between the individual observations of Groups D and I. Comparisons of extubation times related to duration of anaesthesia were made using the Kruskal–Wallis non-parametric ANOVA.

**Results**

A total of 68 patients’ parents were approached during this study period (Fig. 1). Fifty-nine patients were consented and five patients were excluded due to deviation from the protocol. All data analysis were performed after exclusion of these cases; however, analyses—on those patients who had usable data—on an intention-to-treat basis made no difference. For each age group the two groups were similar in terms of age, weight, sex, duration of study agent and operation type (Tables 1 and 2). For the age range of <4 yr, the recovery milestones in median time in minutes after cessation of anaesthesia were significantly shorter for desflurane compared with isoflurane for time to first movement [5.27 (Group D), 9.22 (Group I) $P<0.05$], eye opening [9.42 (Group D), 13.3 (Group I) $P<0.05$] and extubation [7.18 (Group D), 12.5 (Group I) $P<0.05$]. Median times to leave recovery [28.2 (Group D), 33.1 (Group I) $P>0.05$] were not significantly different. For the age range of >4 yr the recovery milestones in median time in minutes after cessation of anaesthesia were significantly shorter for desflurane compared with isoflurane for time to first movement [4.42 (Group D), 11.6 (Group I) $P<0.001$], eye opening [8.55 (Group D), 18.0 (Group I) $P<0.001$], extubation [7.08 (Group D), 16.7 (Group I) $P<0.001$] and to leave recovery [29.9 (Group D), 38.0 (Group I) $P<0.05$] (Figs 2 and 3).

Figures 4 and 5 summarize the extubation data for both age groups. The positive correlation between exposure and time to extubation is apparent for isoflurane in both age groups demonstrating the time sensitive elimination characteristics of isoflurane. The time to extubation for desflurane in both age groups appeared to be independent of duration of anaesthesia exhibiting a relatively constant context-sensitive half life leading to a time to extubation of around 7 min throughout; actual median and interquartile range times were 7.18 (4.94–10.8) min in <4 yr and 7.08 (5.83–8.17) min in >4 yr group.

After cessation of anaesthesia, the median number of breaths to reach 0.5 MAC was found to be significantly less ($P<0.001$) in Group D for both age groups. It was 3.8 (3.2–4.0) [median (interquartile range)] in <4 yr group and 3.7 (3.2–4.2) in the >4 yr group. The values for Group I were 8.0 (6.7–8.8) in the <4 yr group and 8.3 (6.92–10.0) in the >4 yr group.

MAC at extubation was similar for all groups ($P>0.05$). Median value for desflurane was found to be 0.18 in the <4 yr and 0.17 in the >4 yr groups. Median MAC value at
extubation for isoflurane was 0.2 in the <4 yr group and 0.19 in the >4 yr group.

Most adverse events were similar between the two agents. These were agitation (one patient in Group D) and coughing (two patients in Group I and one in Group D). All were observed in the recovery area. The episodes of coughing were self-limiting; the patient classified as agitated was given rescue analgesia (fentanyl).

**Discussion**

In this study, we have confirmed that infants and children receiving desflurane achieve recovery milestones more quickly than isoflurane. However, we have gone on to demonstrate that while a positive correlation exists between duration of anaesthesia and time to extubation for the isoflurane group, recovery from desflurane remains independent of the duration of anaesthesia. The results indicate that with desflurane 1 MAC anaesthesia with delivered by endotracheal ventilation, the time to extubation is about 7 min independent of age or anaesthetic duration. Sub group analysis also indicates that the time-dependent recovery with isoflurane is more pronounced in older children compared with those under 4 yr of age.

Pharmacokinetic models of inhaled anaesthetics have suggested that duration of exposure and blood gas solubility affect washout and subsequent recovery.

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**Table 1** Characteristics for patients under 4 yr of age. Age and weight values are mean (range or sd). Duration of study agent values are median [interquartile range]

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=13)</th>
<th>Group I (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.68 (0.42–3.58)</td>
<td>2.05 (0.5–3.91)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.7 (3.62)</td>
<td>11.9 (3.41)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/2</td>
<td>12/2</td>
</tr>
<tr>
<td>Operation specialty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENT</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urology</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Duration of study agent (min)</td>
<td>69.1 [32.9–80.0]</td>
<td>57.1 [45.1–96.6]</td>
</tr>
<tr>
<td>Regional anaesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local infiltration</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Caudal</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 2** Characteristics of patients over 4 yr of age. Age and weight values are mean (range or sd). Duration of study agent values are median [interquartile range]

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=14)</th>
<th>Group I (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>7.99 (4.5–11.83)</td>
<td>7.51 (4.33–11.17)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30.9 (14.5)</td>
<td>27.5 (12.1)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/7</td>
<td>8/5</td>
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<tr>
<td>Operation specialty</td>
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<tr>
<td>ENT</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Urology</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>General</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Duration of study agent (mins)</td>
<td>33.7 [26.7–80.0]</td>
<td>43.6 [25.0–62.7]</td>
</tr>
<tr>
<td>Regional anaesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local infiltration</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Caudal</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Fig 2 Times to reach recovery milestones for patients for age range 4 yr and under in isoflurane (I) and desflurane (D) groups. Values are median, interquartile range and full range. Assessment times are from time of cessation of anaesthesia. Time for desflurane was significantly lower ($P<0.05$) for first movement, extubation and eye opening.

Fig 3 Times to reach recovery milestones for patients age range over 4 yr in isoflurane (I) and desflurane (D) groups. Values are median, interquartile range and full range. Assessment times are from time of cessation of anaesthesia. Time for desflurane was significantly lower ($P<0.05$).
have demonstrated that while increased duration of anaesthesia can markedly delay awakening for isoflurane, this effect is considerably less pronounced with desflurane. Eger and Shafer calculated that the time to an 88% decrement (time to reach 12% of the starting concentration) increased significantly after 90 min of isoflurane, yet there was little difference for desflurane anaesthesia for up to 240 min. Our clinical data support these findings, but demonstrate delayed recovery after only 60 min of isoflurane anaesthesia. The measured decrement was about

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**Fig 4** Times to extubation for patients aged 4 yr and under plotted against duration of anaesthetic including best fit line (linear). Extubation times are in minutes from time of cessation of anaesthesia. Anaesthetic duration times are in minutes.

**Fig 5** Times to extubation for patients aged over 4 yr plotted against duration of anaesthetic including best fit line (linear). Extubation times are in minutes from time of cessation of anaesthesia. Anaesthetic duration times are in minutes.
82% in end-tidal agent concentration rather than the effect site/vessel rich group concentration used in Eger and Shafer’s calculations.

The pharmacokinetic data reinforces the clinical results. The speed to decrease end-tidal anaesthetic agent concentration (number of breaths) to a predetermined point (0.5 MAC) was significantly less with desflurane than with isoflurane in both age groups and durations of anaesthesia. It is entirely predictable that desflurane with a blood/gas partition coefficient of 0.42, compared with 1.3 in isoflurane, washed out at a much faster rate resulting in faster wake up and earlier extubation as shown in previous studies.9 10

It is interesting to speculate why younger children are less susceptible to delayed recovery after longer exposure to isoflurane. Elimination of a volatile agent is dependent on the alveolar ventilation, and while the young infant breathing spontaneously may have greater ventilatory depression than older children because of increased sensitivity to central nervous system depressants; the ratio of alveolar ventilation to functional residual capacity is much greater.21 This latter property results in a more rapid exchange in alveolar gas, and therefore a faster elimination of the volatile agent. We would have expected that younger children, particularly if spontaneously ventilating, exposed to isoflurane would have a greater time-dependent effect on recovery compared with older children, but our results suggest the opposite. This result could be explained by the effect of enhanced alveolar gas exchange of the younger child with the technique of controlled normocapnoeic ventilation as used in the study. This would effect a larger gas exchange and bypass any age-related effects of central nervous system depressants on ventilatory drive.

We also examined MAC at extubation. Previous studies have looked at MACawake, defined as the level at which patients responded appropriately to command, finding this to be about a third of MAC.22 23 Cook and colleagues,24 however, looked at the threshold for impairment of cognitive function, found it to be about 0.1 MAC. Neither of these is particularly useful in paediatric anaesthesia, and it is not surprising that we found the end-tidal concentration at time to extubation to be between these two values. Both agents were found to have a MACextubation to be just below 0.2 MAC.

The incidence of complications from either anaesthetic agent was low. There were no incidences of respiratory depression15 and only three minor coughing spells (two in the isoflurane group and one in the desflurane group). Desflurane has been shown to be a marked irritant to the respiratory tract, and is, consequently, unsuitable for use during gaseous induction, regardless of premedication,10 and perhaps, its reputation has suffered for this. Our results support the view that desflurane is very unlikely to provoke airway complications on emergence.8 It is perhaps better to consider that respiratory complications correlate with patient risk factors and not with anaesthetic agent.11 Indeed, desflurane shows many characteristics that make it favourable in high-risk patients, especially pre-term neonates suffering from apnoeas.9

There was one incidence of agitation in comparison with a higher incidence in previous studies (24 12 to 55%7 in those patients receiving desflurane). Pain is a confounding factor, difficult to distinguish from what has been termed emergence delirium21 25 in other papers. We successfully treated the patient with a small dose of fentanyl.

Despite rigid protocols there still remain a large number of confounding factors that introduce potential errors into the observations. These include different induction methods, operations, surgeons, anaesthetists, analgesia, preoperative arousal and patient characteristics. It is difficult to account for all these and our protocol was designed to minimize them as much as possible. There remained little difference between the two groups in the major factors, for example analgesia method, type of operation and induction method. Although both i.v. and inhalational induction techniques were employed during this study they were not differentiated at data analysis. It is widely regarded, that the method of induction does not influence the recovery process which is more dependent on the agent used for maintenance of anaesthesia.11

To standardize the anaesthetic for this study, the volatile agent was maintained at 1 MAC until the end of surgery. Most anaesthetists do not practice in this fashion. Instead they decrease the fraction of inhaled anaesthetic agent as the anticipated end of surgery approaches. This approach might compensate for an expected difference between isoflurane and desflurane in daily practice. However, computer models seem to refute this. Eger and Shafer in an adult model looked specifically at decreasing the anaesthetic concentration by half for the last 30 min of anaesthesia. The results demonstrated that although this shortened recovery time, the relationship between different anaesthetic agents remained the same.

The recovery time between volatile agents and the effects of duration of anaesthesia is relevant in daily clinical practice, and the time-independent recovery of desflurane, particularly in the younger age group confers specific benefits over isoflurane.

In summary, desflurane was associated with a reproducible rate of recovery independent of anaesthetic duration, while isoflurane resulted in a slower time-dependent recovery. The incidence of postoperative respiratory complications and emergence delirium was low irrespective of agent. Further data are required particularly in the younger age group having longer procedures.

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