CLINICAL IMPRESSIONS AND CARDIORESPIRATORY EFFECTS OF A NEW FLUORINATED INHALATION ANAESTHETIC, DESFLURANE (I-653), IN VOLUNTEERS

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SUMMARY

The new volatile anaesthetic, desflurane (I-653), was administered to 10 healthy, unpremedicated young male volunteers in order to determine its cardiorespiratory effects and the characteristics and acceptability of its inhalation. All volunteers breathed either sub-anaesthetic (1.8% inspired) or anaesthetic (5.4% inspired) concentrations of the anaesthetic without coughing, breath-holding, salivation or other untoward respiratory response. Respiratory minute volume and alveolar ventilation decreased and ventilatory rate increased. Systemic arterial pressure decreased (diastolic more than systolic) and heart rate remained unchanged. Cardiac rhythm remained unaltered, except in one volunteer who experienced a single premature atrial contraction. Volunteers stated that the odour of desflurane was not irritating or unpleasant. Exposure to the agent for approximately 90 min resulted in rapid and clear-headed recovery.

KEY WORDS


In the first study in man, we have exposed volunteers to desflurane in order to examine some of its cardiorespiratory effects and the characteristics and acceptability of its inhalation.

METHODS AND MATERIALS

After institutional Ethics Committee approval and written informed consent were obtained, we studied 10 young unpremedicated male volunteers all of whom were ASA class I and had not smoked for 5 or more years and had taken no medication for the previous 14 days. Before the study, all volunteers abstained from alcohol and caffeine-containing drinks for 24 h. They were screened before test drug exposure for the Australia antigen and evidence of illicit drug taking. Routine blood chemistry, haematology and urinalysis were performed and a physical examination performed including temperature, arterial pressure and heart rate measurements. A 12-lead ECG was recorded. It was necessary for all results to be normal before accepting a volunteer into the study. An experienced anaesthetist also examined the volunteers for evidence of potential airway problems and for ability to breathe through the nose without obstruction. Volunteers were admitted to Guy’s Hospital (London) the day before anaesthesia. All screening data and pretreatment tests were checked by the principal investigator (R. M. J.) before exposure to desflurane was permitted.

Before administration of the test drug, the volunteer rested supine and breathed room air for 20 min and then underwent 10 min denitro-
genation breathing 100% oxygen from an anaesthetic breathing system incorporating soda-lime for carbon dioxide absorption. Control values for arterial pressure (Riva-Rocci), heart rate, ECG, oximetry and temperature (toe) were recorded at 5-min intervals whilst the volunteer breathed room air and in addition, minute volume and end-tidal carbon dioxide concentration were noted during denitrogenation. After denitrogenation, subjects held their breath following a normal exhalation and then breathed in (time zero) from a second anaesthetic breathing system, identical to the first, which had been primed with 1.8% (n = 5 group I) or 5.4% (n = 5 group II) desflurane in oxygen. Inspired and expired concentrations were monitored using a Datex Multi-gas anaesthesia monitor modified to measure desflurane and calibrated before and after each trial exposure with known standard concentrations (gravimetric measurement) of 1.5, 3.0 and 6.0% of the agent. The anaesthetic was delivered by a modified Ohio DM 5000 anaesthesia machine with an electrically heated, temperature controlled vaporizer. The flowmeters were calibrated in ml min⁻¹ of vapour output (direct metering vaporization). The vaporizer temperature was maintained at 23–25°C.

Volunteers breathed via a cuffed clear plastic mask; an adaptor with a side port allowed the attachment of a catheter which was linked to the gas analysers. The inspired gas was delivered to the adaptor from a Y-connector and this deadspace (approximately 50 ml) protected the end-tidal sample from contamination with inspired gas.

The inspired concentration of desflurane was maintained for 30 min (by adjusting vaporizer and fresh gas flow), then increased (group I) to produce anaesthesia or decreased (group II) to sub-anesthetic values in a step-wise fashion, each step being maintained for at least 15 min. All control measurements, in addition to inspired and expired desflurane concentrations, were recorded at 1, 2, 3, 5, 7 and 10 min and thereafter at 5-min intervals. The ECG was monitored continuously by a dedicated observer and any disturbance of rhythm noted and a hard copy recorded. The subject’s response to breathing the test drug was categorized in terms of the presence or absence of breath-holding, cough, laryngospasm or bronchospasm, secretions or other untoward response. The response to the insertion of an oral airway was recorded. Time to responding correctly to command (“squeeze my fingers”) was recorded after discontinuing anaesthetic concentrations of desflurane. Side effects after exposure were noted and categorized in terms of their likely relationship to test drug exposure. The subjects were questioned specifically for their memory for events and asked if the experience had been unpleasant and to comment on their impression of the odour of the test drug.

RESULTS

Data are expressed as mean (SD). All subjects entered into the study completed the trial, and the average exposure to the test drug was 89 (17) min.

Respiratory effects

Exposure to either anaesthetic (5.4% inspired) or sub-anaesthetic (1.8% inspired) concentrations of desflurane for 30 min was tolerated well by all subjects and there was no breath-holding, coughing, salivation, laryngospasm or bronchospasm during this period. After the initial 30 min one subject (No. 2) coughed twice at an end-expiratory concentration of 4.9% and twice again at 4%. On the former occasion a small amount of saliva appeared at the lips. No other subject coughed on any occasion, including during the insertion of an oral airway. Subject No. 3 sneezed (once at 4.8% end-tidal agent), as did subject 4 (twice at 4.9% end-tidal) and subject 8 (once at 3.3% end-tidal). After 7 min exposure to an inspired concentration of 1.8% desflurane (end-tidal 1.5%), subject 4 complained of feeling dizzy. An oral airway was inserted in order to overcome some respiratory obstruction in six subjects and was tolerated well.

Ventilation was often irregular, in both rate and volume, at end-tidal concentrations of 1.6–3.2%, associated sometimes with a brief excitement phase (typical of that which occurs during gaseous induction of anaesthesia with other agents), and airway support was usually necessary in this range as the laryngeal and pharyngeal musculature relaxed. As noted previously, an oral airway was used in six subjects; it was inserted at end-tidal concentrations of 4.0–4.9% when the volunteer was asleep and relaxation of pharyngeal musculature made the maintenance of a clear airway difficult. In the five subjects exposed initially to an inspired concentration of 5.4% (group II) this was accomplished smoothly during a single expiration and without respiratory disturbance at 10.6 (1.9) min after initiating exposure to the agent. Minute volume did not change signifi-
TABLE I. Mean (sd) changes from control (pre-exposure values) in measured cardiorespiratory variables and skin temperature at the highest steady state concentration of desflurane to which all volunteers were exposed. Typically, this was 5.4% inspired, which corresponded to an end-tidal concentration of 4.8 (±0.1)%.

* Significantly different from control (P < 0.05) (paired t test)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Desflurane</th>
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<tbody>
<tr>
<td>Minute volume (litre min⁻¹)</td>
<td>8.1 (2.2)</td>
<td>7.8 (1.9)</td>
</tr>
<tr>
<td>Ventilatory rate (b.p.m.)</td>
<td>9 (2)</td>
<td>19 (4)*</td>
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<tr>
<td>End-tidal CO₂ (%)</td>
<td>5.0 (0.7)</td>
<td>6.2 (0.5)*</td>
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<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>119 (12)</td>
<td>110 (10)</td>
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<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>68 (7)</td>
<td>58 (8)*</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>59 (5)</td>
<td>57 (7)</td>
</tr>
<tr>
<td>Rate-pressure product (L)</td>
<td>6984 (847)</td>
<td>6299 (830)</td>
</tr>
<tr>
<td>Skin temperature (°C)</td>
<td>26.6 (1.0)</td>
<td>34.1 (1.3)*</td>
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Post-exposure data

In group I, after anaesthetic concentrations of desflurane were discontinued, the time taken to respond to command ("squeeze my fingers") varied from 1 to 4 min (mean 2.7 (1.17) min). Side-effects and likely association with exposure to desflurane are listed in table II. All subjects drank water within 1 h of discontinuing the test drug. In all subjects, including the five who were exposed initially to the low concentration of desflurane, amnesia developed rapidly and subjects remembered very little of the subsequent events, including those occurring during excitement. No subject found the experience unpleasant and all agreed they would readily undergo again a similar investigation with the agent. When specifically questioned, all stated that the agent had a noticeable odour, but none thought that it was unpleasant. One subject, a department member who has taken part in several trials of inhalation agents (including nitrous oxide) as sedatives, stated that breathing low concentrations of desflurane compared favourably with his previous experiences.

**DISCUSSION**

In common with isoflurane, enfurane and halothane, desflurane is halogenated with fluoride but not with chlorine (halothane, enfurane and isoflurane) or bromine (halothane) (fig. 1). In this respect, it resembles sevoflurane, which is a methyl isopropyl ether halogenated entirely with fluoride. Structurally, it differs from isoflurane only by substitution of fluoride for chlorine on the...
Our study suggests that, although some of the cardiorespiratory effects of desflurane in man are similar to those of isoflurane, there are important differences. Of particular significance is the observation that unpremedicated, healthy young men breathing either sub-anaesthetic (1.8%) or anaesthetic (5.4%) concentrations of desflurane for 30 min had no episodes of breath-holding, cough, salivation or other untoward respiratory disturbance. All the subjects stated that the agent was not unpleasant to breathe and some volunteered that it was quite pleasant. Thus, at the concentrations used in this study, desflurane appears devoid of irritant respiratory effects. This lack of pungency and irritation, coupled with the low solubility in blood (blood/gas partition coefficient 0.42) suggests that desflurane may be a useful anaesthetic for inhalation induction. This property would be of particular value in paediatric anaesthesia.

The agent produces respiratory depression in unstimulated volunteers, as indicated by an increase in end-tidal carbon dioxide concentration. Despite an increase in rate of ventilation, it appears that alveolar minute volume decreases. In this respect, desflurane resembles other potent halogenated anaesthetics. Airway support was necessary after more than 2–3% of the agent was breathed and at concentrations greater than 4% an oral airway could be inserted easily and was well tolerated.

Systemic arterial pressure was reduced, with a greater change in diastolic arterial pressure. In general, changes in systolic pressure relate to changes in cardiac output and changes in diastolic pressure relate to changes in systemic vascular resistance. Thus, in common with isoflurane, desflurane may decrease systemic vascular resistance more than cardiac output. In swine, these two agents have similar effects on cardiac output and systemic vascular resistance. However, in distinction to isoflurane, which increases heart rate especially in younger subjects, desflurane was not associated with any significant change in this study (mean values: control 59; 4.9% end-expired desflurane 57). In combination with a small reduction in systolic arterial pressure (statistically insignificant), the stable heart rate resulted in little overall change in rate–pressure product (mean values: control 6984; 4.9% end-expired desflurane 6299). The lack of an increase in heart rate was unexpected, and is at variance with the findings in swine. This may have implications for
use of desflurane in patients with ischaemic heart disease, in whom an increase in myocardial oxygen demand and a decrease in supply would be deleterious.

The stability of cardiac rhythm during desflurane exposure was a notable property of the drug. The single premature atrial contraction occurred in a volunteer who was known to have a marked (physiological) bradycardia at the screening visit (he was a keen sportsman) and in whom a short sequence of junctional rhythm was recorded before exposure to desflurane. Stability of cardiac rhythm has been demonstrated also in the presence of increased plasma concentrations of adrenaline in swine [7], and implies that desflurane lacks a significant effect on cardiac impulse initiation and conduction (electrophysiologically, changes in these factors are prerequisites for the initiation of rhythm disturbances caused by altered automaticity or impulse re-entry). During induction, several subjects had a brief period of excitement during which endogenous catecholamines may be expected to be released. In none of these was there any rhythm disturbance other than sinus tachycardia.

All subjects awoke within a few minutes of discontinuing anaesthetic concentrations of the agent and all side effects were short-lived; none required active treatment. All volunteers stated that the experience had not been unpleasant and that they would readily undergo a similar trial in the future.

In conclusion, desflurane appears to be a promising new inhalation anaesthetic agent. It may not have the respiratory irritant properties and effect on heart rate that isoflurane has and may, therefore, more closely approximate the properties of an "ideal" inhalation agent [8]. In addition, its low solubility in blood may permit especially rapid recovery from anaesthesia and its molecular stability should minimize the potential for end-organ toxicity.

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REFERENCES