ACCIDENTAL INTRAVENOUS INJECTION OF HALOTHANE

Case Report

BY

J. SUTTON, G. A. HARRISON AND J. B. HICKIE

SUMMARY

A case is described of the accidental administration of halothane intravenously. Severe pulmonary oedema and right heart failure occurred. Hypoaxaemia was marked and transient mild changes occurred in hepatic, renal and haemopoietic functions. Treatment was based on the administration of oxygen by positive pressure ventilation via an endotracheal tube, together with considerable additional medical therapy.

The majority of drugs have side effects when given in the correct dosage by the recommended route of administration. The administration of such drugs by another route can result in complications very different from those usually encountered.

This report is the case history of a patient accidentally given an intravenous injection of the inhalational anaesthetic, halothane. Whilst this is a rare event it is known to have occurred in the past (Sandison et al., 1970, reporting Langtry) and two other probable cases are known to the authors. A short account of this case has been published elsewhere (Sutton, Harrison and Hickie, 1971).

CASE HISTORY

A 16-year-old girl was admitted to St Vincent's Hospital, Sydney, from another hospital, 24 hours after receiving 2.5 ml of halothane intravenously during induction of anaesthesia for the reduction of a Colles fracture of the wrist. It was alleged that the halothane had been placed inadvertently in a multidose bottle labelled Brevital (methohexitone).

The patient complained of pain in her arm as the injection began and within 30 seconds became unconscious and ceased breathing. Her trachea was intubated and the lungs were ventilated with 100 per cent oxygen. Within 1–2 minutes she began to breathe spontaneously. No observations are known of her blood pressure or pulse at that time. She started to awaken but was receiving nitrous oxide and oxygen whilst the reduction of the fracture was performed and she awoke normally when the administration of nitrous oxide ceased. The endotracheal tube was removed without difficulty.

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Four hours later it was found that the patient had developed respiratory difficulty and cyanosis. Haematuria was present. A chest radiograph revealed bilateral pulmonary mottling, and the e.c.g. showed sinus tachycardia and an incomplete right bundle branch block.

On admission she was drowsy and cyanosed. The respiratory rate was 50 b.p.m. There was marked drawing of the ribs and sternum during inspiration and widespread crepitations and rhonchi were present in both lungs. The pulse was 140 beats/min, the blood pressure 100/60 mm Hg, and the jugular venous pressure was raised to 10 cm. There was a palpable right ventricular impulse and a marked gallop rhythm. A chest radiograph showed bilateral pulmonary mottling (fig. I). The e.c.g. appearance suggested acute cor pulmonale: sinus tachycardia 140 beats/min, peaked P waves in leads II and aVF, and RSR' pattern in V1, V2, and V3, and R axis deviation and S-T depression with T-wave inversion in leads II, III and AVF, V1, V2, V3 (fig. 2).

The Pao2 was 30 mm Hg after a few minutes air breathing and 60 mm Hg on intranasal oxygen at 5 l./min. There was a neutrophil leucocytosis (90 per cent of a total white cell count of 19,600/mm3) and microscopic haematuria (20–25 red cells/h.p.f.). The serum bilirubin was 1.0 mg/ml and the s.g.p.t. 30 units. Her serum electrolyte concentrations were Na+ 136 m.equiv/l, K+ 4.0 m.equiv/l, and Cl− 98 m.equiv/l. The blood urca was 45 mg/100 ml and the creatinine 0.8 mg/100 ml.

TREATMENT

From the time of admission to this hospital (4 p.m. on day 2, i.e. approx. 24 hours after the injection), the patient was treated with intranasal oxygen 5 l./min, betamethasone 4 mg i.v. 4-hourly, digitalis, frusemide, methicillin and penicillin.

Over the subsequent 24 hours (day 3) the patient showed no clinical improvement; the Pao2, was 58 mm Hg and her chest X-ray appearances were unchanged. Therefore she was intubated with an 8-mm Rusch endotracheal tube and frothy bloodstained pulmonary oedema fluid was aspirated. The patient was then ventilated by means of a Bird Mark 7 automatic ventilator. The lungs were difficult to ventilate adequately at first and inspiratory pressures of 25–30 cm H2O were...
necessary to achieve a tidal volume of 500 ml. This produced a PaO\(_2\) of 76 mm Hg whilst she was being ventilated with 100 per cent oxygen.

Twenty-four hours later (day 4) the frothy sputum was reduced in quantity, the chest sounds were clear on auscultation, but tachycardia, right ventricular heave and gallop rhythm persisted. The PaO\(_2\) had now risen to 163 mm Hg on 100 per cent oxygen but the chest radiograph showed no significant change. It was now considered possible to use the "Air Mix" control on the ventilator at a pressure and flow setting which would deliver approximately 50-60 per cent oxygen. Nine hours later the PaO\(_2\) exceeded 200 mm Hg but there was clinical evidence of subcutaneous emphysema and radiological evidence of both subcutaneous and mediastinal emphysema (fig. 1B). Mechanical ventilation was discontinued. The endotracheal tube was retained in place and she was allowed to breathe oxygen spontaneously through an Ayre T-piece system. Forty-eight hours after intubation (day 5) the sputum was clear, her pulse rate was 90 beats/min and right ventricular heave and gallop rhythm persisted but were less marked. The PaO\(_2\) was 80 mm Hg when breathing air. The chest radiograph showed minimal evidence of pulmonary oedema. The endotracheal tube was removed. After a further 24 hours (day 6) the PaO\(_2\) was 93 mm Hg when breathing air.

Her subsequent progress was uneventful and she remained asymptomatic for the duration of her stay in hospital, with a gradual return to normality of blood counts, liver function tests, cardiac enzymes and micro-urine studies.

**FIG. 1**

Chest X-rays

A (day 2): On admission widespread pulmonary mottling (heart appears displaced to the left but patient had a congenitally depressed sternum).

B (day 4): Decreased pulmonary oedema, but subcutaneous and mediastinal emphysema.

C (day 6): Normal chest X-ray (patient has depressed sternum).
The data in tables I—III summarize the changes in blood-gas, haematological and biochemical values. Figures 1–4 show the changes in radiological appearances of the chest, and in the electrocardiogram.

**DISCUSSION**

To the authors' knowledge this is the first case report documenting the consequences of accidental intravenous injection of halothane in man. The results of ingestion of halothane in man have been reported by Spencer and Green (1968) and Curelaru and associates (1968).

The initial loss of consciousness and apnoea which occurred within 30 seconds of the intravenous injection were probably related to a bolus of halothane reaching the brain on its first circulation through the body. The return of spon-
Transient respiration and the tendency to awaken within 2-3 minutes would correspond to a lowering of the cerebral concentration of halothane as mixing, redistribution, and excretion occurred.

Transient damage to the liver, kidneys and bone marrow appear to have occurred, as assessed by the subsequent disturbance of the liver function tests, the development of haematuria, and of a neutrophil leucocytosis. These effects were, however, greatly overshadowed by pulmonary oedema and secondary right heart failure. The severe hypoxaemia may also have contributed to these biochemical changes.

It seems somewhat paradoxical that halothane, an anaesthetic which produces virtually no pulmonary irritation when inhaled, should cause predominant and severe pulmonary pathology when given intravenously. However, when 2.5 ml of halothane is given intravenously to a girl weighing 45 kg, a blood concentration 5-10 times that found

Fig. 3
Electrocardiograph (day 4).
Sinus tachycardia, 100 beats/min. Non-specific S-T and T-wave changes.
in clinical anaesthesia (15–20 mg/100 ml) would probably be reached for a short period. Furthermore, during the first passage through the pulmonary vascular bed it would tend to travel as a bolus because it is poorly soluble in water (Raventós, 1956) and only slightly more soluble in blood (Larsen, Eger and Severinghaus, 1962). Hence the concentration of halothane initially traversing the pulmonary vascular bed would be very high indeed.

The clinical features of intravenous injection of halothane, as seen in this case, were probably accounted for by a toxic pulmonary vasculitis, causing necrosis of arteriolar and capillary walls, and alveolar haemorrhage and oedema, and possibly a release of histamine causing subsequent bronchoconstriction.

Since this case occurred, Sandison and associates (1970) have reported pulmonary damage associated with intravenous injection of halothane in dogs. Six anaesthetized dogs became unconscious and apnoeic within a few seconds of injection of halothane 0.1 mg/kg. They observed pulse irregularities and commented that "the apnoeic period lasted 2–3 minutes and was followed by rapid shallow breathing and a gradual lightening of the
### Table I
**Blood gases**

<table>
<thead>
<tr>
<th>Day</th>
<th>Sample time</th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pH</th>
<th>Base excess (m.equiv)</th>
<th>Buffer base</th>
<th>Standard bicarbonate (m.equiv)</th>
<th>Inspired gas</th>
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</thead>
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<tr>
<td>Day 2 (Transfer—St Vincent's Hospital)</td>
<td>4.30 p.m.</td>
<td>30</td>
<td>40</td>
<td>7.36</td>
<td>-3</td>
<td>47</td>
<td>22</td>
<td>Air</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>34</td>
<td>7.43</td>
<td>-3</td>
<td>34</td>
<td>22</td>
<td>O₂ 5 l./min, intranasal</td>
</tr>
<tr>
<td>Day 3</td>
<td>10.00 a.m.</td>
<td>58</td>
<td>34</td>
<td>7.46</td>
<td>+1</td>
<td>51</td>
<td>25</td>
<td>O₂ 5 l./min, intranasal; 100% O₂, Bird ventilator</td>
</tr>
<tr>
<td>Day 4</td>
<td>11.00 a.m.</td>
<td>163</td>
<td>39</td>
<td>7.48</td>
<td>+5</td>
<td>51</td>
<td>28</td>
<td>100% O₂, Bird ventilator</td>
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<tr>
<td></td>
<td>1.30 p.m.</td>
<td>84</td>
<td>39</td>
<td>7.51</td>
<td>+5</td>
<td>51</td>
<td>28</td>
<td>50-60% O₂ Bird ventilator</td>
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<td></td>
<td>7.00 p.m.</td>
<td>200</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>60% O₂, Bird ventilator</td>
</tr>
<tr>
<td>Day 5</td>
<td>10.00 a.m.</td>
<td>80</td>
<td>36</td>
<td>7.48</td>
<td>+4</td>
<td>50</td>
<td>27</td>
<td>Air—off ventilator</td>
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<tr>
<td>Day 6</td>
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<td>93</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Air—extubated</td>
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### Table II
**Biochemistry**

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<thead>
<tr>
<th>Day</th>
<th>Na (m.equiv/L)</th>
<th>K⁺ (m.equiv/L)</th>
<th>Cl⁻ (m.equiv/L)</th>
<th>Urea (mg/100 ml)</th>
<th>Creatinine (mg/100 ml)</th>
<th>Bilirubin (mg/100 ml)</th>
<th>Alkaline p'ase (N=3-13 units)</th>
<th>SGPT (N=4-13 units)</th>
<th>HBDH (N=55-125 units)</th>
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<td>136</td>
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<td>—</td>
<td>45</td>
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<td>1.0</td>
<td>—</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>138</td>
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<td>98</td>
<td>58</td>
<td>0.8</td>
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<td>4</td>
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<td>0.7</td>
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### Table III
**Haematology**

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<th>Day</th>
<th>Hb</th>
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<th>Hct</th>
<th>WCC</th>
<th>N</th>
<th>Segmented</th>
<th>L</th>
<th>M</th>
<th>E</th>
<th>Platelets</th>
<th>ESR</th>
<th>Anisocytosis—polychromasia</th>
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<td>N</td>
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<td>Slight</td>
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<tr>
<td>4</td>
<td>15.0</td>
<td>32</td>
<td>47</td>
<td>10,500</td>
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<td>94</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>N</td>
<td>7</td>
<td>Slight</td>
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<tr>
<td>5</td>
<td>14.5</td>
<td>—</td>
<td>—</td>
<td>14,500</td>
<td>90</td>
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<tr>
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<td>9,200</td>
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<td>90</td>
<td>6</td>
<td>4</td>
<td>—</td>
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<td>15</td>
<td>Slight</td>
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<tr>
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<td>9,500</td>
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<td>5,200</td>
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comatose state, most dogs being fully awake in 15 minutes". Two dogs were given halothane 0.3 mg/kg in divided doses at 0, 30 and 54 minutes and both died within 3 minutes of the final increment. Macroscopic pulmonary findings showed the lungs to be heavy and congested. Frothy oedema was found in the trachea and bronchi. Microscopic examination revealed distended oedematous alveoli containing extravasated red blood cells. The dogs receiving the highest dosage of halothane had the most severe pulmonary haemorrhage and oedema. The identical features of our case and the experimental findings of Sandison and associates (1970) on dogs strongly suggest a cause-and-effect relationship between intravenous halothane and the subsequent pulmonary pathology in man.

There are other possible explanations for the clinical features, and the radiographic and electrocardiographic changes described in our case, for example Mendelson's syndrome (Mendelson, 1946), multiple pulmonary emboli or acute left ventricular failure. Of these the Mendelson syndrome, with the inhalation of gastric juice, can produce the closest similarities to those seen in this case. However, this patient did not appear to have regurgitated, intubation was performed immediately and no gastric contents were aspirated from the endotracheal tube.

Multiple pulmonary emboli in the ordinary sense would be most improbable. However, Sandison and associates have proposed multiple halothane emboli as a possible explanation for the peripheral subpleural distribution of the congested areas seen in dogs. They also found nodular areas suggesting healed infarcts in the dog sacrificed 22 days following injection.

Acute left ventricular failure may have been an additional factor in the production of the pulmonary oedema but the clinical and electrocardiographic findings indicated predominantly right and not left ventricular failure. This is supported by the studies on dogs undertaken by Sandison and associates (1970). They recorded an average decrease of 6 cm H₂O in the left atrial pressure but a 10 cm H₂O rise in the pulmonary artery pressure.

In the established case of accidental intravenous halothane, oxygen and positive pressure ventilation have an obvious place. The use of digitalis and a diuretic can also be justified on the basis of heart failure. Antibiotics were used prophylactically, although no specific indication for their use existed. The value of steroids to decrease inflammatory oedema is debatable. No bronchodilator, such as isoprenaline, was used in this instance because we felt it contraindicated by the risk of arrhythmias in the presence of marked hypoxaemia, tachycardia and possible cardiac pathology.

Prevention is obviously the most important measure needed to avoid such an occurrence and this report is a further indictment of the use of multidose bottles and of the storage of liquids in anything but the correct container properly labelled.

ACKNOWLEDGEMENT

We are indebted to the Nursing Staff of the Intensive Care Unit, St Vincent's Hospital, Sydney, whose skill and care contributed immeasurably to the successful outcome of this patient.

REFERENCES


Intravenous halothane. (Correspondence). Lancet, 1, 345.
INJEKTION VON HALOTHAN

ZUSAMMENFASSUNG


BRITISH JOURNAL OF ANAESTHESIA

INYECCION INTRAVENOSA ACCIDENTAL DE HALOTANO

RESUMEN

Es descrito un caso de administración accidental de halotano por vía intravenosa. Se desarrolló un edema pulmonar intenso e insuficiencia cardíaca derecha. La hipoxemia fue acusada y hubo cambios ligeros y transitorios en las funciones hepática, renal y hematopoyética. El tratamiento estuvo basado en la administración de oxígeno mediante ventilación a presión positiva por un tubo endotraqueal junto con una considerable terapia médica adicional.

DEPARTMENT OF ANAESTHETICS CARDIFF TRUST FUND

Registrars Prize

Two prizes of £25 and £10 will be awarded to registrars working in Wales for the two best papers of sufficient merit either published or delivered in the Department of Anaesthetics, Cardiff, between October 1, 1971, and October 1, 1972. Those wishing to read a paper or submit published work should apply to the Chairman of the Trust, Dr Barbara Roberts, Department of Anaesthetics, University Hospital of Wales, Cardiff.

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