HAEMODYNAMIC EFFECTS OF INFUSIONS OF DIISOPROPYL PHENOL (ICI 35 868) DURING NITROUS OXIDE ANAESTHESIA IN MAN

C. PRYS-ROBERTS, J. R. DAVIES, R. K. CALVERLEY AND N. W. GOODMAN

SUMMARY

The haemodynamic effects of diisopropyl phenol in cremophor EL at infusion rates of 50–55 and 100 μg kg⁻¹ min⁻¹ in combination with inhalation of 67% nitrous oxide have been studied during spontaneous and controlled ventilation in patients premedicated with morphine and atropine. Under all the conditions studied diisopropyl phenol supplementation of nitrous oxide anaesthesia was associated with a decreased arterial pressure (−20% to −31%) compared with the awake patient, related to a decrease in cardiac output (−27% to 29%) and an increase in systemic vascular resistance (+8% to +30%) during surgery, but to a decrease in cardiac output (−19%) and a decrease in systemic vascular resistance (−17%) during anaesthesia without surgery. Doubling the infusion rate of diisopropyl phenol caused no significant haemodynamic changes during either spontaneous or controlled ventilation. The haemodynamic manifestations of sympathetic nerve activity in response to laryngoscopy and intubation were poorly suppressed by diisopropyl phenol.

Diisopropyl phenol in Cremophor EL (ICI 35 868) was introduced as a short-acting agent for the induction of anaesthesia (Kay and Rolly, 1977). Its pharmacokinetic profile (Adam, Glen and Hoyle, 1980; Adam, Kay and Douglas, 1982) indicated that it was suitable for continuous infusion, either alone or as a supplement to nitrous oxide anaesthesia. Preliminary studies (Prys-Roberts, Sear and Adam, 1981) indicated that, in conjunction with 66% nitrous oxide in patients who had been premedicated with morphine 0.15 mg kg⁻¹, an infusion of diisopropyl phenol at a rate of 51.3 ± 3.8 μg kg⁻¹ min⁻¹ was required to prevent movement in response to the initial surgical incision in 50% of patients. We have studied the haemodynamic responses to induction of anaesthesia with diisopropyl phenol (ICI 35 868) and to two infusion rates during both spontaneous and controlled ventilation during surgery.

PATIENTS AND METHODS

Haemodynamic studies were performed in 13 patients presenting for peripheral arterial surgery (femoro-popliteal bypass grafting or profundoplasty). Ten male and three female patients aged between 49 and 77 yr, and weighing 67.2 kg (±3.2 SEM) were selected for study on the basis that their atheromatous vascular disease had not produced signs or symptoms referable to the coronary or cerebral circulations, they had no diabetes or hypertension (diastolic pressure < 90 mm Hg), and were not receiving β-adrenoceptor antagonists, antihypertensive therapy or cardiac glycosides. Each patient consented to the studies and the administration of diisopropyl phenol after a full explanation of the proposed procedures.

All patients received morphine 150 μg kg⁻¹ and atropine 10 μg kg⁻¹ 1 h before the start of the studies. Under local analgesia an 18-gauge Teflon cannula was placed in a brachial artery and an 18-gauge drum cartridge catheter (Abbott Laboratories) was advanced centrally from an antecubital or basilic vein and satisfactory placement in the superior vena cava was monitored by the pressure waveform. A 16G Abbocath cannula was placed in a forearm vein and connected to a calibrated syringe pump (Fresenius) for infusion of diisopropyl phenol. A 14G Abbocath cannula was placed, after induction of anaesthesia, for infusion of a solution of Dextran 70 in 5% dextrose (Fisons) at a rate of 2 ml kg⁻¹ h⁻¹ to replace insensible fluid losses.

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Arterial and central venous catheters were connected to Gould–Statham P231a transducers and the appropriate pressures were amplified with Hewlett-Packard 78205 modules and recorded on an eight-channel ink-jet recorder (Siemens–Elena EM81). The electrocardiogram was recorded from leads in a CM5 configuration. Instantaneous heart rate was obtained from the ECG with a Neilson tachometer (Devices Instruments). The arterial pressure signal was processed with an analog differentiator (Gersh, Hahn and Prys-Roberts, 1971) to yield a continuous signal of arterial dP/dt. Cardiac output was measured intermittently by the indocyanine green dilution method (Prys-Roberts, 1980) and stroke volume and systemic vascular resistance were derived using standard formulae. Rate–pressure product (RPP) was derived as an indication of increased myocardial oxygen uptake to greater than baseline values (Nelson et al., 1974). Samples of arterial and central venous (SVC) blood were analysed for PO2, PCO2 and pH using an ABL-1 blood-gas analyser (Radiometer, Copenhagen), and the values were corrected for any temperature difference between the patient and the electrodes, and for elapsed time between sampling and analysis. At some stages (5 and 6) of the study, arterial blood was sampled and analysed for the concentration of diisopropyl phenol by high performance liquid chromatography (Adam et al., 1981).

Before the induction of anaesthesia, a set of baseline measurements (stage 1) was recorded with the patient lying supine and relaxed. Anaesthesia was induced with diisopropyl phenol 1.5 mg kg\(^{-1}\) at a rate of 200 mg min\(^{-1}\), and the infusion of diisopropyl phenol was commenced immediately at a nominal infusion rate of 50 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). This infusion rate was chosen following preliminary studies which indicated that during anaesthesia with 66% nitrous oxide in oxygen the infusion rate which prevented movement in response to the initial surgical incision was 51.3 ± 3.8 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). For the subsequent 3 min the patients breathed room air. Continuous records were made of the ECG, arterial and central venous pressures and, at the end of the 3rd min following induction, a cardiac output measurement was made and arterial blood was sampled. Subsequently, the patients breathed 100% oxygen from a mask and Bain system. Suxamethonium was administered and, after the vocal cords and trachea were sprayed with 4 ml of 4% lignocaine, the trachea was intubated and controlled ventilation was instituted pending the return of the patient’s spontaneous ventilation. Anaesthesia was subsequently maintained with 67% nitrous oxide in oxygen supplemented by the continuing infusion of diisopropyl phenol.

Immediately before the first surgical incision (not less than 25 min after induction) a set of haemodynamic and blood-gas measurements was recorded (stage 2). If the patient moved in response to the surgical incision, a single incremental dose of diisopropyl phenol 10 mg was administered and the infusion rate increased by 5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). Fifteen minutes after the first incision, and during continuing surgical activity, a further set of haemodynamic and blood-gas measurements was made (stage 3) following which the infusion rate of diisopropyl phenol was doubled. Provided that the patient’s spontaneous ventilation was not grossly depressed, the doubled infusion rate was maintained for at least 30 min before a further set of measurements (stage 4) was performed. After this set of measurements, or earlier if the spontaneous breathing of the patient was inadequate, intermittent positive pressure ventilation (IPPV) was established with a Penlon–Oxford ventilator set to provide a tidal volume of 15 ml kg\(^{-1}\) at a frequency of 12 b.p.m. The ventilator was situated in a circle system without a carbon dioxide absorber (Suwa and Yamamura, 1970) and the total fresh gas flow (67% nitrous oxide in oxygen) was adjusted to maintain \(P_{\text{ACO}_2}\) within the range 5.05–5.59 kPa. The infusion of diisopropyl phenol was continued at 100 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) for a further 30 min before the next set of measurements was made (stage 5). After this, the rate of infusion of diisopropyl phenol was decreased to the previously established infusion rate (50–55 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) and a final set of measurements (stage 6) obtained 30 min after the decrease in infusion rate.

The infusion of di-isopropyl phenol was continued at the same rate to the end of surgery. Following the re-establishment of spontaneous breathing by a 5% carbon dioxide challenge, the trachea was extubated, and the infusion and nitrous oxide were discontinued simultaneously. The times were recorded from the end of surgery to the first response to command, and to the recall of complex numbers such as date of birth, the patient’s home or office telephone number and vehicle registration number. The data were analysed for normality of distribution, and subjected to a repeated measures analysis of variance (ANOVA) and paired two-tailed Student’s \(t\) test. The distributions of postoperative
recognition times were found to be skewed and the t tests were performed on logarithmically transformed values.

RESULTS

Induction and early maintenance of anaesthesia

Figure 1 shows the haemodynamic responses recorded during the first 3 min after induction of anaesthesia in 12 of the 13 patients and the subsequent changes in response to laryngoscopy and intubation.

Following the administration of diisopropyl phenol, systolic and diastolic arterial pressures decreased rapidly during the first 2 min to average values of 79% and 84% respectively of the awake baseline values. These changes were partly related to a 12% decrease of cardiac output and a 9% decrease of systemic vascular resistance. Minimal and variable changes of heart rate occurred, thus the rate-pressure product decreased by 24% (P < 0.001). The cardiovascular responses to induction were accompanied by decreases in ventilation to the extent that $P_{\text{aCO}_2}$ values increased from $5.0 \pm 0.2 \text{ kPa}$ to $5.7 \pm 0.2 \text{ kPa}$ (P < 0.001).

In response to laryngoscopy and endotracheal intubation, systolic arterial pressures increased from $105 \pm 3$ to $155 \pm 10 \text{ mm Hg}$ (P < 0.001) and diastolic arterial pressures from $58 \pm 3$ to $85 \pm 5 \text{ mm Hg}$ (P < 0.001), resulting in an increase of rate-pressure product from $8215 \pm 502$ to $14605 \pm 1584 \text{ mm Hg beat min}^{-1}$ (P < 0.001). No electrocardiographic evidence of arrhythmia or myocardial ischaemia was observed even though peak values of RPP in excess of 24 000 occurred in two patients.

Maintenance anaesthesia and surgery

The durations of infusion ranged from 128 to 203 min (mean 156 min), during which time the total dose of diisopropyl phenol, including the induction dose, ranged from 310 to 1030 mg (mean dose $11.0 \pm 0.7 \text{ mg kg}^{-1}$). During steady-state maintenance anaesthesia with spontaneous breathing before surgery (stage 2), systolic and diastolic arterial pressures were respectively 69% and 73% of the awake baseline values (table I; fig. 1). Cardiac output decreased by 19% and systemic vascular resistance by 17% to account for the arterial pressure

![Graph of hemodynamic effects](https://academic.oup.com/bja/article-abstract/55/2/105/249983)
changes. Heart rate decreased by an average of 7 beat min\(^{-1}\) (−9%) and rate–pressure product was decreased to 62% of the awake values. Central venous pressure was significantly increased \((P<0.001)\), and ventilation was impaired to the extent that \(P_{\text{ACO}_2}\) increased to 6.5±0.2 kPa \((P<0.001)\).

The initial surgical incision was associated with slight limb movement in five patients, but no further movement occurred after the increase in the rate of infusion. The other patients made no movement at any stage of the study. Continued surgical stimulation was associated with an increase of systolic (+12.5 mm Hg) and diastolic (+10.8 mm Hg) arterial pressures compared with stage 2, but no significant change of heart rate. In view of the further decrease of cardiac output and stroke volume (73% of awake value), the increased arterial pressure reflected a 30% increase of systemic vascular resistance \((P<0.01)\). Increased ventilation in response to surgery resulted in a significant decrease \((P<0.001)\) of \(P_{\text{ACO}_2}\) (0.4 kPa). Spontaneous ventilation at an infusion rate of 100 µg kg\(^{-1}\) min\(^{-1}\) was studied in only four of the 13 patients. No significant changes in any haemodynamic variable were observed (table II), although ventilation was further impaired as judged by a significant increase of \(P_{\text{ACO}_2}\) from 6.2±0.3 to 7.0±0.3 kPa \((P<0.001)\).

In the eight of the 13 patients in whom two infusion rates of diisopropyl phenol were studied during IPPV (stage 5), no significant changes were found in any haemodynamic variables (table III), when compared with stage 6.

During surgery at a diisopropyl phenol infusion rate of 50–55 µg kg\(^{-1}\) min\(^{-1}\), controlled ventilation to maintain a normal \(P_{\text{ACO}_2}\) (table I, stage 6) was associated with greater systolic and diastolic pressures when compared with stage 3, despite lower cardiac outputs and stroke volume, reflecting further increases of systemic vascular resistance.

At a mean infusion rate of 51.9±0.7 µg kg\(^{-1}\) min\(^{-1}\) \((n=10)\), the whole blood concentration of diisopropyl phenol was 1.55±0.14 µg ml\(^{-1}\), and at an infusion rate of 100 µg kg\(^{-1}\) min\(^{-1}\) \((n=7)\) the whole blood concentration was 3.26±0.54 µg ml\(^{-1}\).

**DISCUSSION**

A number of i.v. anaesthetic agents have pharmacokinetic profiles which make them suitable for maintenance of anaesthesia by continuous infusion; or for continuous sedation either in association with local or regional anaesthesia, or in the intensive therapy unit. Althesin (du Cailar, 1972; Savege et al., 1975) or methohexitone (Hunter, 1972) were used clinically some time ago, and minaxolone,
etomidate and diisopropyl phenol have been introduced more recently.

In order that the results of the present studies could be comparable to previous studies (Sear and Prys-Roberts, 1979a; Sear et al., 1981; Prys-Roberts et al., 1982) a specific longitudinal programme was devised, allowing comparisons of the effects of spontaneous and controlled ventilation, the former with and without the influence of surgery.

During the planning of haemodynamic studies during the infusion of Althesin (Sear and Prys-Roberts, 1979b) it was proposed that an index of potency should be established comparable to MAC for gaseous and volatile anaesthetics. The minimum infusion rate (MIR) was introduced (Sear and Prys-Roberts, 1979a) as such an index and was defined as the steady-state infusion rate of an i.v. agent which was sufficient to suppress movement to the initial surgical incision in 50% of patients. Such an index will have values which will be modified by the nature and amount of premedication, and the use of nitrous oxide. In order to provide comparisons of one i.v. agent against another, the selection of patients, premedication and combination of i.v. agent with nitrous oxide in the present study conformed to that used for Althesin (Sear and Prys-Roberts, 1979b), minaxolone (Sear et al., 1981) and methohexitone (Prys-Roberts, 1982).

Studies of the haemodynamic effects of i.v. anaesthesia can be performed under two conditions, those

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**TABLE II. Comparisons of haemodynamic values (mean ± SEM; n = 4) during spontaneous breathing at two infusion rates of diisopropyl phenol**

<table>
<thead>
<tr>
<th>Stage</th>
<th>50–55 µg kg⁻¹ min⁻¹</th>
<th>100 µg kg⁻¹ min⁻¹</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>100.0 ± 8.5</td>
<td>99.5 ± 9.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>54.0 ± 4.5</td>
<td>56.0 ± 5.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>67.8 ± 3.5</td>
<td>72.3 ± 5.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rate–pressure product (mm Hg beat min⁻¹)</td>
<td>6791 ± 762</td>
<td>7380 ± 1129</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiac output (litre min⁻¹/70 kg)</td>
<td>3.7 ± 0.4</td>
<td>3.5 ± 0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stroke volume (ml/70 kg)</td>
<td>55.0 ± 7.4</td>
<td>48.4 ± 4.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s cm⁻³)</td>
<td>1336 ± 119</td>
<td>1421 ± 110</td>
<td>n.s.</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>5.0 ± 0.8</td>
<td>4.9 ± 1.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>P₅CO₂ (kPa)</td>
<td>6.2 ± 0.3</td>
<td>7.0 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**TABLE III. Comparisons of haemodynamic values during IPPV at two infusion rates of diisopropyl phenol. Mean values ± SEM (n = 8)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>6</th>
<th>5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood diisopropyl phenol (µg ml⁻¹)</td>
<td>1.55 ± 0.14</td>
<td>3.26 ± 0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>117.5 ± 6.7</td>
<td>109.9 ± 11.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>64.8 ± 2.8</td>
<td>63.0 ± 6.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>68.9 ± 2.8</td>
<td>68.1 ± 2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rate–pressure product (mm Hg beat min⁻¹)</td>
<td>8129 ± 621</td>
<td>7521 ± 855</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiac output (litre min⁻¹/70 kg)</td>
<td>3.5 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stroke volume (ml/70 kg)</td>
<td>50.5 ± 6.5</td>
<td>50.0 ± 5.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s cm⁻³)</td>
<td>1874 ± 144</td>
<td>1777 ± 174</td>
<td>n.s.</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>5.9 ± 0.9</td>
<td>6.1 ± 1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>P₅CO₂ (kPa)</td>
<td>5.1 ± 0.2</td>
<td>5.3 ± 0.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
of rapidly changing blood concentrations following induction of anaesthesia, or those during steady-state maintenance anaesthesia when the infusion rate, plasma concentration of the drug and its pharmacodynamic effect are unchanging. Studies with Althesin (Sear and Prys-Roberts, 1981) indicated that the plasma concentration reached 95% of the final steady-state value at 25–30 min and, as the pharmacokinetic profile of disopropyl phenol was stated to be very similar to that of Althesin (Prys-Roberts, Sear and Adam, 1981), a minimum period of 30 min was allowed before any steady-state measurements were made.

Perhaps the most striking feature of i.v. anaesthetics, by contrast with volatile anaesthetics, when either is used to supplement nitrous oxide anaesthesia, is the relative lack of arterial hypotension and the associated effects on the myocardium.

The haemodynamic values measured at both infusion rates, during either spontaneous or controlled ventilation, were similar to those measured under comparable conditions in patients infused with Althesin (Sear and Prys-Roberts, 1979b), minaxolone (Sear et al., 1981) or methohexitone (Prys-Roberts et al., 1982). Thus, unlike the volatile agents, which exert widely differing effects on the cardiovascular system, disopropyl phenol and the other i.v. infusion agents appear to exert minimal but consistent effects on cardiovascular performance (Prys-Roberts, 1982) allowing greater cardiac outputs and stroke volumes than normally observed with volatile anaesthetics, such as halothane, in comparable patients (Prys-Roberts et al., 1974).

The haemodynamic response to laryngoscopy and endotracheal intubation was not effectively suppressed by disopropyl phenol, although the marked sympathetic nervous response, typified by systolic hypertension, tachycardia and a dramatic increase of rate–pressure product, was less pronounced than that found following methohexitone induction and infusion (Prys-Roberts et al., 1982). None of the patients in the present study showed evidence of hypertension or coronary artery disease before operation; indeed their haemodynamic responses to laryngoscopy suggest that they belong to a class, identified by their haemodynamic status, as having arteriosclerosis (Prys-Roberts, 1981).

By contrast, the lack of somatic response to surgical incision in eight of the 13 patients, the ease with which the others were settled with a small increase of infusion rate, and the minimal haemodynamic response to continued surgical stimulation, suggest that disopropyl phenol is a good maintenance anaesthetic agent. Limb relaxation was apparent in every patient throughout the administration.

ACKNOWLEDGEMENTS

We thank Professor J. H. Peacock and Mr R. N. Baird, F.R.C.S., for their co-operation in the conduct of these studies on their patients. We are grateful to Dr Malcolm Peet and Miss Sue Binks of I.C.I. Pharmaceuticals Division for support of the studies and supplies of disopropyl phenol, and to Dr H. K. Adam and Dr I. Cockshott for the assay of blood concentrations of the drug. We are also grateful to Mr J. Dye, Mrs A. Dye and Miss J. Harvey for technical assistance with the study.

REFERENCES


HAEMODYNAMIC EFFECTS OF ICI 35 868


ZUSAMMENFASSUNG
Bei mit Morphin und Atropin prämedizierten Patienten wurde während Spontanatmung und kontrollierter Beatmung die hämodynamische Wirkung von Di-isopropyl-Phenol in Cre- mophor EL bei Infusionsgeschwindigkeiten von 50–55 und 100 μg kg⁻¹ min⁻¹ kombiniert mit Inhalation von 67% Lachgas untersucht. Bei allen Untersuchungen war die mit Di-isopropyl-phenol ergänzte Lachnarkose mit einem um 20% bis 30% niedrigeren arteriellen Druck als beim wachen Patienten verbunden, verursacht durch einen Abfall des Herzminutenvolumens (−27% bis −29%) und einen Anstieg des systemischen Gefäßwiderstandes (+8% bis +30%) während Operation, aber einen Abfall von Herzminutenvolumen (−19%) und einen Abfall von systemischen Gefäßwiderstand (−17%) während Anästhesie ohne Operation. Die Verdopplung der Infusionsgeschwindigkeit von Di-isopropyl-phenol verursachte keine signifikanten hämodynamischen Veränderungen bei Spontanatmung oder kontrollierter Beatmung. Die hämodynamische Auswirkung der sympathischen Nervenaktivität nach Laryngoskopie und Intubation wurden durch Di-isopropyl-phenol kaum unterdrückt.

SUMARIO
Se han estudiado los efectos hemodinámicos del fenol de diisopropilo en cremofor EL bajo regímenes de infusión 50–55 y de 100 μg kg⁻¹ en combinación con la inhalación de óxido nitroso al 67%, durante la ventilación espontánea y controlada de pacientes premedicados con morfina y atropina. Bajo todas las condiciones estudiadas, el suplementar la anestesia de óxido nitroso con fenol de diisopropilo vino asociado con una disminución de la presión arterial (−20% a −31%) en comparación con el paciente despierto, en relación a una disminución de la producción cardíaca (−27% a 29%) y a un incremento de la resistencia sistémica vascular (+8% a +30%) durante la intervención quirúrgica, al tiempo que también vino asociada a una disminución de la producción cardíaca (−19%) y a una disminución de la resistencia sistémica vascular (−17%) durante la anestesia sin intervención quirúrgica. El doblar el régimen de infusión de fenol de diisopropilo no ocasionó cambios hemodinámicos significativos durante la ventilación controlada ni durante la espontánea. Los efectos hemodinámicos de la actividad del nervio simpático como respuesta a la laringoscopia y a la intubación quedaron deiblemente suprimidos por la presencia del fenol de disopropilo.