AUTONOMIC REFLEXES AND THE CARDIOVASCULAR EFFECTS OF PROPYLENE GLYCOL

D. AL-KHUDHAIRI AND J. G. WHITWAM

Propylene glycol (1-2 propanediol) was described by Wurtz in 1859 and is now widely used in the food and drug industries (Heine, Parker and Francke, 1950; Ruddick, 1972). Moreover, awareness of the modifications to the acute effects of drugs, when propylene glycol is used as the solvent, is increasing (Zarolinski, Browne and Possley, 1971; Osterlin, Akesson and Wahlstrom, 1979). The few previous studies on the hemodynamic effects of propylene glycol describe decreases in heart rate and arterial pressure, and implicate vagal reflexes without suggesting their origin or the detailed nature of the evoked responses (Louis, Kutt and McDowell, 1967; Sharer and Kutt, 1971; Gross, Kitzman and Adams, 1979).

The present study was directed to the nature and duration of the hemodynamic response to propylene glycol and the contribution of changes in activity in both the cardiomotor vagus and efferent sympathetic nerves.

MATERIALS AND METHODS

Observations were made in 16 mongrel dogs. Anaesthesia was induced with methohexitone 10 mg kg\(^{-1}\), administered as an i.v. bolus, and maintained with a 1% solution of \(\alpha\)-chloralose, initially as a bolus of 30 mg kg\(^{-1}\) and subsequently, by a continuous infusion of 20 mg kg\(^{-1}\) h\(^{-1}\) i.v. Following tracheal intubation, the lungs were ventilated mechanically with oxygen-enriched air (Starling pump). Once anaesthesia was established with \(\alpha\)-chloralose, neuromuscular blockade was induced and maintained with suxamethonium 1-2 mg kg\(^{-1}\) h\(^{-1}\).

Catheters were inserted to a femoral artery and vein. When required, a further catheter was passed through either the external jugular or the femoral vein into the superior vena cava or the right atrium for the measurement of central venous pressure and the injection of dye for the determination of cardiac output.

Sympathetic nerves were exposed either retroperitoneally close to the renal artery, or in the thorax by removal of the second and third ribs, part of the right subclavian vein and the upper lobe of the right lung. They were dissected free from surrounding tissues, desheathed and cut distally, and immersed in mineral oil. Efferent activity was recorded using bipolar silver-silver chloride electrodes and processed through a preamplifier

SUMMARY

The effect of i.v. propylene glycol in doses of 160-800 mg kg\(^{-1}\) on heart rate, arterial pressure and efferent sympathetic activity were observed in anaesthetized paralysed, artificially ventilated dogs. Within 3-5 s of the commencement of the injection of propylene glycol there was an immediate mean decrease in heart rate of 22.7 and 72.1 beat min\(^{-1}\) and in arterial pressure of 27.2 and 58.8 mm Hg at doses of 400 mg kg\(^{-1}\) and 800 mg kg\(^{-1}\), respectively, together with a gross reduction of sympathetic activity and a subsequent increase in heart rate above control values. All these effects were transient and at a dose of propylene glycol 800 mg kg\(^{-1}\), heart rate and arterial pressure returned to control values by 1 min, and sympathetic activity by 2 min. Blocking the vagus nerves with atropine prevented the observed changes in heart rate and arterial pressure, whereas sympathetic blockade with bretylium tosylate had little effect. It was concluded that propylene glycol causes powerful reflex stimulation of the cardiomotor vagus and transient inhibition of efferent sympathetic activity within 5 s of injection, and that the origin of the reflex is likely to be intrathoracic.
TABLE I. Changes in heart rate (beat min⁻¹) (mean ± SEM) in response to the injection of propylene glycol i.v.: A = 160 mg kg⁻¹; B = 400 mg kg⁻¹; C = 800 mg kg⁻¹. Phase 1 minimum heart rate; phase 2 maximum heart rate (fig. 1)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Control</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>1 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>110.7 ± 9.8</td>
<td>105.5 ± 9.35</td>
<td>123.6 ± 11.8</td>
<td>108.0 ± 12.98</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>113.1 ± 10.46</td>
<td>90.4 ± 7.77</td>
<td>136.7 ± 10.1</td>
<td>126.7 ± 14.33</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>113.8 ± 9.05</td>
<td>41.7 ± 4.96</td>
<td>142.9 ± 10.92</td>
<td>122.0 ± 10.56</td>
</tr>
</tbody>
</table>

*P* values for comparisons between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>1 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A v. B</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>A v. C</td>
<td>ns</td>
<td>&lt; 0.001</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>B v. C</td>
<td>ns</td>
<td>&lt; 0.001</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Fig. 1. Effect of propylene glycol on heart rate (HR) (beat min⁻¹), mean femoral arterial pressure (AP) (mm Hg) and effenter activity in renal sympathetic nerves. Each section from above down: integrated sympathetic activity; directly-recorded sympathetic activity; heart rate (HR); mean femoral arterial pressure (AP). Consecutive doses of propylene glycol i.v., to one animal injected at the arrows: 
A = 160 mg kg⁻¹; B = 400 mg kg⁻¹; C = 800 mg kg⁻¹; D = 160 mg kg⁻¹.
PROPYLENE GLYCOL AND AUTONOMIC REFLEXES

(Tectronic Type 122 filters 80–1000 Hz) the output of which was either displayed directly or integrated (Neurolog type NL 703 Digitimer).

\( P_{\text{a}CO_2}, P_{\text{a}CO_2}, \text{ and pH} \) were measured in arterial blood samples (collected anaerobically in heparinized syringes) using a Radiometer system (ABL 1), and maintained in the ranges 23.9–33.3 kPa, 4.7–6.0 kPa and 7.31–7.38, respectively. Core temperatures were maintained in the range 37–38 °C.

Intravascular pressures were measured using resistance strain gauges (S. E. Laboratories type 488) and the recording system was calibrated for gain and linearity using a column of mercury.

The ECG was recorded and used to display the beat-by-beat heart rate using a Devices ratemeter (type 4522).

Cardiac output was measured by dye dilution (indocyanine green: Guilford 140 system); the coefficient of variation between replicates was within 3.5%.

Arterial and central venous pressures, the ECG, beat-by-beat heart rate, intratracheal pressure, and efferent activity in sympathetic nerves were displayed on either an oscilloscope (Tektronix type RN 5 265) or an ultraviolet recorder (S. E. Laboratories type 2112) using conditioning amplifiers and galvanometers with a frequency response of 3000 Hz.

In some preparations, activity in efferent sympathetic nerves was blocked by the administration of bretylium tosylate 10 mg kg\(^{-1}\) i.v. (Ledsome and Linden, 1964) and that in the cardiomotor vagus with atropine 0.5 mg kg\(^{-1}\) i.v.

Propylene glycol was injected to the inferior vena cava as a 40% solution in one of three doses. Group A: 160 mg kg\(^{-1}\) (0.4 ml kg\(^{-1}\)); Group B: 400 mg kg\(^{-1}\) (1 ml kg\(^{-1}\)); Group C: 800 mg kg\(^{-1}\) (2 ml kg\(^{-1}\)). A concentration of 40% propylene glycol is frequently used in the formulation of drugs (for example diazepam, diphenylhydantoin) and these doses were selected as they are equivalent to the amount of propylene glycol in the formulation of equivalent doses of diazepam (Roche): 2 mg kg\(^{-1}\), 5 mg kg\(^{-1}\) and 10 mg kg\(^{-1}\), respectively. In all the preparations the same volumes of saline as the highest volume of propylene glycol were injected to establish that the effects observed were attributable to propylene glycol.

Statistical analyses were performed using Student's \( t \) test, and the Wilcoxon sum rank test.

**RESULTS**

**Haemodynamic effects**

**Heart rate** (table I). The biphasic pattern of the changes in heart rate (HR) caused by the injection of propylene glycol is clearly illustrated in figures 1 and 2. Within 3–5 s of the commencement of an injection of propylene glycol to the inferior vena cava, there was a reduction in heart rate which reached its minimal value within 2–3 beats. The mean reduction in HR was not statistically significant following a dose of 160 mg kg\(^{-1}\), but increased to 22.7 beat min\(^{-1}\) (\( P < 0.05 \)) and 72.1 beat min\(^{-1}\) (\( P < 0.001 \)) at doses of 400 mg kg\(^{-1}\) and 800 mg kg\(^{-1}\), respectively (table I). Thereafter, during the time when there was a decrease in mean arterial pressure (figs 1 and 2), it increased above the resting rate, but even at the largest dose

![Fig. 2. Effect of propylene glycol on heart rate (HR) (beat min\(^{-1}\)), mean femoral arterial pressure (AP) (mm Hg) and central venous pressure (CVP) (mm Hg). Three consecutive doses of propylene glycol 800 mg kg\(^{-1}\) i.v. injected to one animal: 1 = control; 2 = 1 h after bretylium tosylate 10 mg kg\(^{-1}\) i.v.; 3 = 10 min after the subsequent administration of atropine 0.5 mg kg\(^{-1}\) i.v.]
Table II. Changes in mean femoral arterial pressure and cardiac output (mean ± SEM) following the injection of propylene glycol i.v.: A = 160 mg kg⁻¹; B = 400 mg kg⁻¹; C = 800 mg kg⁻¹

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Control</th>
<th>Minimum pressure</th>
<th>Duration of response (s)</th>
<th>1 min</th>
<th>P</th>
<th>n</th>
<th>Control</th>
<th>1-8 min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>126.7</td>
<td>±7.66</td>
<td>6.68</td>
<td>123.1</td>
<td>ns</td>
<td>7</td>
<td>2.02</td>
<td>2.2</td>
<td>ns</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>133.9</td>
<td>±10.1</td>
<td>±1.5</td>
<td>±6.91</td>
<td></td>
<td>7</td>
<td>±0.27</td>
<td>±0.31</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>131.1</td>
<td>±6.21</td>
<td>±3.1</td>
<td>±9.41</td>
<td></td>
<td>7</td>
<td>2.26</td>
<td>2.35</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table III. The effect of bretylium tosylate 10 mg kg⁻¹ i.v. and atropine 0.5 mg kg⁻¹ i.v. on the initial phase (fig. 1; table I). Maximal changes in heart rate and mean arterial pressure in response to propylene glycol (PG) 800 mg kg⁻¹ i.v. Mean values ± SEM; n = 4. *P < 0.05; †ns

<table>
<thead>
<tr>
<th>Control</th>
<th>1 h after bretylium</th>
<th>10 min after atropine preceded by bretylium 1 h previously</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>Resting</td>
<td>After PG</td>
</tr>
<tr>
<td></td>
<td>132 ± 15.9</td>
<td>78.8*</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>105 ± 14.3</td>
<td>29*</td>
</tr>
</tbody>
</table>

of propylene glycol (800 mg kg⁻¹), heart rate had returned to control values within 1 min (fig. 1; table I).

Arterial pressure (table II). Propylene glycol caused a mean decrease in mean arterial pressure of 16.3 mm Hg at a dose of 160 mg kg⁻¹ (P < 0.05) and 58.8 mm Hg (P < 0.001) at the highest dose (800 mg kg⁻¹) (table I). This decrease showed a complex biphasic response (fig. 1: B and C), but recovered and was not significantly different from control values by 1 min (table II).

Cardiac output. Duplicate readings starting 1 min after the injection of propylene glycol, by which time heart rate and arterial pressure had returned to their resting values, were not significantly different from control (table II).

Sympathetic activity. Within 3-5 s of injecting propylene glycol in doses of 400 mg kg⁻¹ and 800 mg kg⁻¹, efferent activity in sympathetic nerves either ceased (fig. 1) or was reduced markedly (fig. 3). This, together with the acute decrease in HR, was associated with a decrease in arterial pressure. However, within 10-15 s there was a surge in sympathetic activity lasting approximately 20 s, after which spontaneous pulse-phased activity returned, initially at a lower level than in the control period but, even following a dose of propylene glycol 800 mg kg⁻¹, it had returned to resting values by 2 min (fig. 1: C).

Bretylium and atropine. Following bretylium tosylate 10 mg kg⁻¹ i.v. the injection of a dose of propylene glycol 800 mg kg⁻¹ caused an initial bradycardia of the same order of magnitude as in the control situation, but this was abolished by atropine (fig. 2; table III). In the presence of both bretylium and atropine, the injection of propylene glycol 800 mg kg⁻¹ i.v. caused a small increase in arterial pressure which was associated with a small decrease in HR (fig. 3). However, in the four preparations studied these changes did not reach statistical significance (table III).
The present study shows that, while large doses of propylene glycol cause profound effects on the autonomic nervous system, and hence on the cardiovascular system, these changes are transient and last less than 2 min, even at a dose of 800 mg kg\(^{-1}\). Propylene glycol undergoes oxidation in the body to lactic and pyruvic acids (Hanzlick et al., 1939; Ruddick, 1972): in this study there was never any evidence of a cumulative effect of propylene glycol, even with large repeated doses.

The evoked stimulation of the cardiomotor vagus and inhibition of sympathetic activity (figs 1 and 3) occurs within 3–5 s of commencing the injection of propylene glycol, that is well before the material could have reached the central nervous system. This implies that the observed phenomena are a reflex response to stimulation of some intrathoracic organ. This subject has been reviewed by Dawes and Comroe (1954), and Hainsworth, Kidd and Linden (1979). Louis, Kutt and McDowell (1967), Sharer and Kutt (1971), and Gross, Kitzman and Adams (1979) have also implicated vagal reflexes as a cause of the effects of propylene glycol, without offering any suggestion as to their likely origin. The complex nature of the response, for example the initial bradycardia followed by an increase in heart rate, has not been described before.

The immediate response is stimulation of the cardiomotor vagus, inhibition of efferent sympathetic activity and a decrease in arterial pressure. However, there is then an increase in sympathetic activity which could be mediated by a reduction of baroreflex activity as a result of the decrease in arterial pressure. The subsequent increase in heart rate above control values is also probably the result of decreased baroreceptor activity causing both inhibition of cardiomotor vagal activity and an increase in sympathetic activity.

Abel, Starosck and Reis (1969), suggested that diazepam, the vehicle of which contains propylene glycol, caused an increase in ventricular contractility and coronary blood flow in dogs undergoing cardiopulmonary bypass with a constant heart rate. Bianco and colleagues (1971), using a dog right-heart bypass preparation, described depression of left ventricular function by both diazepam and its vehicle. However, Yasaka, Eichbaum and Oga (1979b) suggested that propylene glycol has a negative inotropic effect on the atra, but a positive effect on the ventricles of the isolated rabbit heart. Yasaka, Eichbaum and Oga (1979a), showed that propylene glycol increases the duration of the refractory period of isolated rabbit atria and, hence, could have antiarrhythmic effects. Bianco and colleagues (1970) have shown also that vagal stimulation causes depression of left ventricular function. Thus the effect of propylene glycol on the heart is extremely complicated and the present study suggests that, while it may have a direct effect on the myocardium, in the intact animal a major component of its effects on the heart is mediated indirectly through the autonomic nervous system.

Following bretylium, propylene glycol still caused an initial decrease in heart rate of the same order of magnitude as in the absence of this drug, while the administration of atropine abolished both the depression in heart rate and also that in arterial pressure, which suggests that a vagal reflex was responsible for both events. The small increase in arterial pressure and the decrease in
heart rate seen in animals treated with both bretylium and atropine following the injection of propylene glycol did not occur when an equivalent volume, 35–45 ml in different preparations, of physiological saline solution was injected. This suggests that, in addition to the large autonomic reflex effects, propylene glycol may have a small direct effect on the myocardium. However, the observed changes did not reach statistical significance in the four preparations studied in this way.

In addition to these autonomic reflex effects affecting the cardiovascular system, Al-Khudhairi, Whitwam and Askitopoulou (1982) showed that propylene glycol, in doses as great as 1600 mg kg−1, had only a transient reflex effect on efferent phrenic nerve activity in artificially ventilated dogs, and this also could be the result of stimulation of some intrathoracic structure. The phenomena described here are toxic effects of propylene glycol and are not likely to be seen in such an exaggerated form during the normal clinical use of various drugs such as etomidate, diphenylhydantoin, diazepam and the tetracyclines, in which propylene glycol is used in the formulations. However, this study suggests that propylene glycol could modify transiently the immediate cardiovascular effects of drugs dissolved in this solvent.

ACKNOWLEDGEMENTS
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REFERENCES