CARDIOVASCULAR EFFECTS OF I.V. INDUCTION IN CHILDREN: COMPARISON BETWEEN PROPOFOL AND THIOPENTONE

C. S. T. AUN, R. Y. T. SUNG, M. E. O'MEARA, T. G. SHORT AND T. E. OH

SUMMARY
We have compared the haemodynamic responses to i.v. propofol 2.5 mg kg\(^{-1}\) with those to thiopentone 5.0 mg kg\(^{-1}\) in 41 healthy Chinese children at induction of anaesthesia. They were allocated to four groups according to their age and induction agent received: group I < 2 yr, propofol, n = 9; group II < 2 yr, thiopentone, n = 9; group III 2–12 yr, propofol, n = 12; group IV 2–12 yr, thiopentone, n = 11. Anaesthesia was maintained by spontaneous ventilation with 70% nitrous oxide and 0.5% halothane in oxygen. Arterial pressure and heart rate were monitored by automatic oscillotonometer. Stroke volume was measured by two-dimensional echocardiography and pulse Doppler. Measurements were made before induction and at 1-min intervals for 5 min after induction. The reduction in mean arterial pressure was significantly greater after propofol (28–31%) than after thiopentone (14–21%) (P = 0.001). The reduction in cardiac index (10–15%) after induction was not significantly different between the two agents (P = 0.122). Baroreflex mediated increases in heart rate and systemic vascular resistance were less after propofol than after thiopentone. The baroreceptor reflex was more attenuated in children aged less than 2 yr than in older children. (Br. J. Anaesth. 1993; 70: 647–653)

KEY WORDS

Induction of anaesthesia with propofol is associated with a significantly greater reduction in arterial pressure than with thiopentone, both in adults [1–4] and in children [5–7]. This is one of the main criticisms of the use of propofol. In adults, the mechanism of hypotension has been studied by the invasive thermodilution method [2, 4, 8, 9]. The primary mechanism appears to be a reduction in systemic vascular resistance. There is controversy about its direct cardiovascular effects. However, it appears to exert a mild negative inotropic effect. Because of ethical and technical constraints, haemodynamic data in children are limited to non-invasive measurements of heart rate and arterial pressures [5–7], but these peripheral haemodynamic measurements are inadequate to describe the myocardial effects of anaesthetic agents [10]. With the development of echocardiography it is now possible to measure cardiac output non-invasively with accuracy by combining the technology of echocardiography and the Doppler principle. Measurement of cardiac output using the technique of pulsed Doppler echocardiography has been shown to have a high correlation coefficient (r = 0.90–0.98) compared with the dye dilution technique [11, 12]. In this study, this technique was used to compare the cardiovascular effects of i.v. induction of anaesthesia with either propofol or thiopentone in Chinese children.

PATIENTS AND METHODS
The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. We studied 45 healthy Chinese children aged between 8 months and 12 yr (ASA I or II) scheduled for elective surgery. Informed consent was obtained from their parents. Children with a history of allergy, or of any adverse reactions to previous anaesthetics were excluded. Those children in whom pre-induction haemodynamic variables or venous cannulation could not be obtained were withdrawn from the study. All patients were premedicated with oral diazepam syrup 0.4 mg kg\(^{-1}\) and EMLA cream (lignocaine 25 mg g\(^{-1}\) and prilocaine 25 mg g\(^{-1}\), Astra pharmaceuticals, Sweden) applied to the dorsum of both hands approximately 2 h before anaesthesia. The children were grouped into two age groups: less than 2 yr and between 2 and 12 yr. Children in each age group were allocated randomly in a double-blind manner to receive either propofol 2.5 mg kg\(^{-1}\) or thiopentone 5 mg kg\(^{-1}\).


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The velocity of the blood flow was calculated by averaging the measurements obtained from three consecutive cardiac cycles. All Doppler recordings and measurements were performed by a single observer (R.Y.T.S.), who was blind to the medication given. Derived haemodynamic variables calculated from the measured variables included cardiac output, stroke volume index and cardiac index. Cardiac output was calculated as the product of stroke volume and heart rate. Surface area was derived from a nomogram for infants and children [13]. Systemic vascular resistance (SVR) was calculated using the following formula [14]:

$$SVR \text{ (dyn s cm}^{-2}\text{)} = \frac{\text{mean arterial pressure}}{\text{cardiac output}} \times 80$$

In order to compare the effects of two agents in two age groups of children, the patients were allocated to four groups:

- **group I**: toddlers younger than 2 yr who received propofol;
- **group II**: toddlers younger than 2 yr who received thiopentone;
- **group III**: children aged 2–12 yr who received propofol;
- **group IV**: children aged 2–12 yr who received thiopentone.

Patient data between the same age groups were compared using a two-tailed Student's *t* test. The number of agitated children and the incidence of side effects were analysed by chi-square test. The haemodynamic measurements after induction were analysed using repeated measures analysis of variance for the difference from the baseline values. The factors included were time after induction, anaesthetic agents and age interaction. In the absence of statistically significant age-by-anaesthetic agent interactions, data from the four groups were compared simultaneously in the results. *P* < 0.05 was considered as statistically significant.
TABLE I. Patient characteristics (mean (range or SD)). Group I = less than 2 yr, propofol; group II = less than 2 yr, thiopentone; group III = 2-12 yr, propofol; group IV = 2-12 yr, thiopentone. BSA = Body surface area; Mood (a:c) = number of children agitated or calm. * P < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 9)</th>
<th>Group II (n = 9)</th>
<th>Group III (n = 12)</th>
<th>Group IV (n = 11)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>1.2 (0.7-2)</td>
<td>1.1 (0.7-2)</td>
<td>5.2 (2-12)</td>
<td>4.4 (2-12)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>9:0</td>
<td>7:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.6 (1.3)</td>
<td>9.7 (1.3)</td>
<td>18.8 (8.5)</td>
<td>16.4 (6.4)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>0.46 (0.04)</td>
<td>0.44 (0.06)</td>
<td>0.78 (0.24)</td>
<td>0.70 (0.20)</td>
</tr>
<tr>
<td>Mood (a:c)</td>
<td>7:2</td>
<td>5:4</td>
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TABLE II. Measured and derived haemodynamic variables before induction (mean (SEM)). Group I = less than 2 yr, propofol; group II = less than 2 yr, thiopentone; group III = 2-12 yr, propofol; group IV = 2-12 yr, thiopentone. SAP = Systolic; DAP = diastolic; MAP = mean arterial pressures; HR = heart rate; SVI = stroke volume index; CI = cardiac index; SVR = systemic vascular resistance. **P < 0.01; ***P < 0.001

<table>
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<tr>
<td>SAP (mm Hg)</td>
<td>104.6 (5.3)</td>
<td>104.6 (5.3)</td>
<td>106.7 (5.0)</td>
<td>96.3 (3.9)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>71.6 (3.6)</td>
<td>70.4 (4.6)</td>
<td>67.9 (3.0)</td>
<td>61.2 (3.3)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>85.7 (3.4)</td>
<td>85.3 (3.0)</td>
<td>85.3 (3.8)</td>
<td>75.5 (2.9)</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>162.0 (12.3)</td>
<td>143.7 (10.1)</td>
<td>101.1 (5.7)</td>
<td>102.5 (4.2)***</td>
</tr>
<tr>
<td>SVI (ml beat⁻¹ m⁻²)</td>
<td>33.5 (3.8)</td>
<td>34.1 (2.5)</td>
<td>41.7 (1.6)</td>
<td>43.9 (3.8)</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>5.2 (0.5)</td>
<td>4.9 (0.5)</td>
<td>4.2 (0.2)</td>
<td>4.6 (0.3)</td>
</tr>
<tr>
<td>SVR (dyn s cm⁻⁵)</td>
<td>3129.7 (332.9)</td>
<td>3413.7 (289.6)</td>
<td>2290.6 (186.1)</td>
<td>2203.6 (226.9)**</td>
</tr>
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</table>

Fig. 1. Cardiovascular responses (HR = heart rate; AP = arterial pressure) during induction of anesthesia in the children younger than 2 yr (groups I and II) and children aged 2-12 yr (groups III and IV). BL = Baseline (before induction); Time = time after induction; S = systolic pressure; M = mean arterial pressure; D = diastolic pressure. --- = Propofol; ---- = thiopentone.

older children (groups III and IV). The differences in arterial pressures, systemic vascular resistance and cardiac index among the four groups were not statistically significant.

After induction, systolic, mean and diastolic arterial pressures decreased significantly (P < 0.001) in all four groups (fig. 1). In the toddlers, the maximum reduction in mean arterial pressure was 31% after propofol (group I) and 21% after thiopentone (group II). In the older children, the maximum reductions were 28% after propofol (group III) and 14% after thiopentone (group IV). For both age groups, the differences were significantly more after propofol than after thiopentone (P = 0.011).

Heart rate decreased significantly in toddlers who received propofol (24%); the decrease was significantly more than for those who received thiopentone (11%) (P = 0.024). The mean heart rate was stable in the older children who received either propofol
(group III) or thiopentone (group IV) (fig. 1). There was a significant difference ($P < 0.001$) in the magnitude of heart rate changes for the two age groups.

There was an increase in stroke volume index after induction up to a maximum of 12% in the toddlers both after propofol (group I) and after thiopentone (group II). In the older children, stroke volume index decreased maximally by 13% after propofol (group III) and 15% after thiopentone (group IV). These changes were not statistically different (fig. 2).

Cardiac index, which is a reflection of the combined effects of heart rate and systemic vascular resistance, decreased significantly ($P = 0.005$) in all four groups (fig. 2). In the toddlers, the maximum decrease in cardiac index was 15% after propofol and 3% after thiopentone. In the older children, the maximum reduction was similar (10%) after each agent.

Systemic vascular resistance decreased significantly ($P = 0.001$) after induction in all four groups (fig. 2). The maximum reduction was similar for the toddlers who received propofol (15%) and those who received thiopentone (16%). The decrease in systemic vascular resistance in older children who received propofol was almost three times as much (19%) as the reduction in children after thiopentone (7%). The differences between the four groups were not significant.

None of the children showed signs of waking
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during the study period. There were no differences between the groups in the incidence of side effects (table III).

DISCUSSION

We have shown that i.v. induction of anaesthesia in children using propofol was associated with more cardiovascular depression than an equipotent dose (see below) of thiopentone. The degree of cardiovascular depression in toddlers was similar to that in older children.

This study used the non-invasive technique of pulsed Doppler and two-dimensional echocardiography to determine the stroke volume and cardiac output. The measurements are highly reproducible [11, 15] and can accurately detect relative cardiac output changes in individual patients. It has been shown to correlate well with thermodilution and dye dilution outputs in infants and young children [12, 15, 16]. Determination of cardiac output using M-mode echocardiography calculates volume from a measurement in a single dimension, and therefore any error made during the measurement could be magnified in the subsequent calculations [17]. M-mode identifies the aortic root area only during valve motion, whereas two-dimensional echocardiography can identify both aortic annulus (orifice) and root area. Aortic annulus diameter does not change during systole and therefore calculation of cardiac output using measurement at this site agrees more closely with invasive techniques than using aortic root measurements. Pulsed Doppler has been suggested to be a better technique than continuous Doppler. Pulsed Doppler permits measurement of flow velocity by range-gating at the specified location of the aortic orifice, whereas continuous wave Doppler measures velocity along the entire beam path and may include an area with a parabolic velocity profile which may give a misleading mean spatial velocity [12].

Equipotent doses are required for comparison of cardiovascular responses between two agents. We chose the dose of thiopentone 5 mg kg\(^{-1}\) as being equipotent with propofol 2.5 mg kg\(^{-1}\). This ratio was based on previous work on their relative potencies [18, 19].

To our knowledge, no previous study has compared in children the cardiovascular effects of propofol and thiopentone during induction of anaesthesia. In this study we found that mean arterial pressure reduction after propofol was significantly greater than after thiopentone in both toddlers and older children (\(P = 0.011\)). This is similar to the finding in adults that propofol is more depressant on the cardiovascular system than thiopentone [2, 4]. Our magnitude of arterial pressure reduction after propofol was similar to that found in previous studies [7, 20, 21].

In healthy adults, thiopentone characteristically produces a reduction in arterial pressure and cardiac output, with or without a compensatory increase in total systemic vascular resistance [22–24] and a decrease in baroreflex sensitivity, associated with tachycardia [25]. The cardiovascular depression caused by thiopentone is caused by a combination of depression of the vasomotor centre [26] and direct myocardial depression [27, 28]. Venodilatation leading to a sequestration of blood volume in the venous side of the circulation and a reduction in the left ventricular diastolic filling and stroke volume have also been suggested [29]. The effect on arterial resistance vessels is variable as demonstrated by the inconsistent changes in systemic vascular resistance with barbiturates.

The children receiving thiopentone in our study had a significant reduction in arterial pressure and cardiac index. However, systemic vascular resistance decreased rather than increased. The changes in heart rate were different between the two age groups. Mean heart rate increased in the older children, but decreased in the toddlers (fig. 1). A comparative study of thiopentone in infants and children, observed a greater degree of myocardial depression than that in the present study [30], probably because of the larger dose of thiopentone (7.5–8.5 mg kg\(^{-1}\)) in that study.

Studies of the mechanism of propofol-induced hypotension in adults have produced conflicting results [31]. Lippmann and colleagues, using the thermodilution technique, observed a reduction in left ventricle stroke work index (35 %) and cardiac index (18 %), with no significant decrease in systemic vascular resistance and pulmonary vascular resistance [4]. Gauss and co-workers, using echocardiographic assessment and end-systolic quotient as an indicator of inotropy, found that propofol induced hypotension as a result of simultaneous negative inotropy and reduction in afterload [32]. Grounds and colleagues, using the thermodilution technique, observed a significant decrease in total systemic vascular resistance (18 %) with minimal changes in heart rate and cardiac output [2].

In this study, the magnitude of hypotension after propofol was similar to that found in adults [2]. It was associated with a significant reduction in both cardiac index (10–15 %) and systemic vascular resistance (15–19 %). Heart rate in the older children did not change, but it decreased significantly in the toddlers (fig. 1). More toddlers were crying on arrival in the operating theatre than among older children and this may have caused an increase in sympathetic tone. We suspect this was reflected in their greater heart rates and systemic vascular resistance. Anaesthesia attenuates sympathetic tone and this may have contributed to the greater reduction in heart rate in the toddlers. However, heart rates were all within the physiological range (fig. 2). Baroreceptor reflexes have been found to be more attenuated in both young animals and humans anaesthetized with halothane [33, 34] or nitrous oxide [35] compared with adults. It is possible, therefore, that the difference in reduction in heart rate was a reflection of a more significant baroreceptor impairment in the toddlers than in the older children. When comparing the two agents, the decrease in heart rate after propofol was greater than after thiopentone. This suggests that propofol causes more baroreflex depression than thiopentone, in
agreement with previous studies in adult patients [36, 37].

Paediatric patients are thought to have a limited ability to increase myocardial contractility and heart rate is an important factor in determining cardiac output [38]. However, the toddlers in this study had an increase rather than a decrease in stroke volume index associated with the reduction in heart rate. This suggests that the myocardium is capable of increasing stroke volume in this age group. Ventricular diastolic filling time and stroke volume are inversely proportional to baroreceptor reflex-mediated changes in heart rate. The net effect of these haemodynamic responses was to produce a non-significant difference in the reduction of cardiac index in all four groups. Like thiopentone, there was no compensatory increase in systemic vascular resistance after propofol.

Diazepam premedication was necessary to reduce anxiety and allow baseline haemodynamic measurements. We used a dose of 0.4 mg kg⁻¹ because, with smaller doses, excitement may occur from a lack of inhibition [39]. Its use as premedication is not associated with significant cardiovascular depression [40]. Any incidental haemodynamic effects caused by the premedication should be considered as relevant to the use of these induction agents in the clinical setting.

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REFERENCES