Propofol pharmacokinetics in children with biliary atresia

A. A. Raoof, L. J. van Obbergh and R. K. Verbeeck

Summary
We studied the pharmacokinetics of an i.v. bolus dose of propofol 2.5–3.0 mg kg⁻¹ in eight children (age 4–24 months) with biliary atresia and in six control (ASA I) children (age 11–43 months). Blood samples were obtained for 4 h after administration of propofol. Blood concentrations of propofol were measured by high pressure liquid chromatography. Systemic clearance of propofol (Cl) and volume of distribution at steady state (Vd) showed a highly significant correlation with body weight. Propofol Cl and Vd, normalized for body weight, were similar in children with biliary atresia (mean 37.5 (sd 8.3) ml min⁻¹ kg⁻¹ and 3.5 (1.6) litre kg⁻¹, respectively) compared with control children (38.7 (6.8) ml min⁻¹ kg⁻¹ and 2.4 (0.8) litre⁻¹ kg⁻¹, respectively). We conclude that in children with biliary atresia the pharmacokinetics of propofol are similar to those of healthy children. (Br. J. Anaesth. 1995; 74: 46–49)

Key words

Propofol (2,6-diisopropylphenol) is a short-acting, i.v. anaesthetic agent used in adults and children [1]. Its approval for use as an anaesthetic agent is currently limited to children of 3 yr or older. Propofol is eliminated rapidly, mainly by biotransformation to a glucuronide conjugate [2–4]. In adults, total body clearance of propofol is similar to or higher than liver blood flow, suggesting that extrahepatic metabolism contributes to its overall metabolism [3–5]. Extrahepatic metabolism of propofol in adults has indeed been shown to occur in patients undergoing coronary bypass surgery [6] and in patients during the anhepatic phase of orthotopic liver transplantation [7, 8]. Studies in adult patients showed that the pharmacokinetics of propofol were not markedly affected by uraemia or by uncomplicated cirrhosis [9, 10]. The pharmacokinetics of propofol have also been studied in children [11–15]. The high values for clearance of propofol relative to hepatic blood flow in children and in adults suggest that extrahepatic metabolism of propofol may also be important in this age group. Children with biliary atresia have a serious degree of hepatic dysfunction resulting in end-stage cirrhosis, and impaired hepatic elimination (i.e. metabolism, biliary excretion, or both) of drugs in general is to be expected. We therefore investigated the pharmacokinetics of propofol after i.v. bolus administration in very young children (mean age 12.3 (range 4–24) months) with cirrhosis secondary to biliary atresia and in a “control” group, which was a little older (23.0 (11–43) months).

Patients and methods
The pharmacokinetics of propofol were studied in two groups of children undergoing digestive endoscopies: a control group consisting of six children with normal hepatic and renal function (ASA I, age 11–43 months); and a group of eight children with biliary atresia (age 4–24 months). The study was approved by the local Human Ethics Committee and informed consent was obtained from the parents of the children.

Before induction of anaesthesia, i.v. cannulae (Abbocath 22-G) were inserted into a forearm vein of both arms (for blood sampling and drug administration). Anaesthesia was induced with thiopental (mean 37.5 (sd 8.3) ml min⁻¹ litre⁻¹ kg⁻¹) compared with control (ASA I) children (age 11–43 months). We conclude that in children with biliary atresia the pharmacokinetics of propofol are similar to those of healthy children. (Br. J. Anaesth. 1995; 74: 46–49)

Table 1 Pharmacokinetic variables in children with normal liver function (controls) and those with biliary atresia (mean (sd) [range])

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 6)</th>
<th>Biliary atresia (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>23.0 (11–43)</td>
<td>12.3 (4–24)</td>
<td>0.053</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.6 (2.1)</td>
<td>7.3 (1.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>T½ (min)</td>
<td>100 (31)</td>
<td>141 (76)</td>
<td>ns</td>
</tr>
<tr>
<td>Cl (ml min⁻¹)</td>
<td>418 (141)</td>
<td>268 (113)</td>
<td>0.046</td>
</tr>
<tr>
<td>Vd拙 (litre)</td>
<td>60.5 (29.1)</td>
<td>53.5 (30.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Vd拙 (litre)</td>
<td>25.9 (13.6)</td>
<td>27.5 (17.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Cl (ml min⁻¹ kg⁻¹)</td>
<td>38.7 (6.8)</td>
<td>37.5 (8.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Vd拙 (litre)</td>
<td>5.9 (1.7)</td>
<td>7.1 (3.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Vd拙 (litre)</td>
<td>2.4 (0.8)</td>
<td>3.5 (1.6)</td>
<td>ns</td>
</tr>
</tbody>
</table>

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Propofol blood concentration-time profiles for both body weight (table 1). Figure 1 shows that the mean and volumes of distribution were normalized for Because of this weight difference between the two weight observed in the control group (table 1). The difference in age explains the significantly higher body not statistically significant (P = 0.053). The difference in age explains the significantly higher body weight of individual patients was examined essentially to obtain objective values for the concentration of propofol at time 0, and for the “terminal” slope of the semi-logarithmic propofol blood concentration-time curve (λz). Subsequently, so-called model-independent variables such as the terminal half-life of propofol in blood (T½), systemic (blood) clearance (Cl) and volumes of distribution (Vd(α) and Vd(β)) were calculated as follows: T½ = 0.693/λz, Cl = Do/AUC, Vd(α) = Do/AUC, λz and Vd(β) = Do/AUMC/AUCβ, where Do = propofol dose administered i.v., AUC = area under the propofol blood concentration-time profile, and AUMC = area under the moment curve. AUC and AUMC were obtained from the best-fit coefficients and exponents as follows (19): AUC = Σ(Ci/λi) and AUMC = Σ(Ci/λi2).

Data are presented as mean (SD). Group means were compared using unpaired Student’s t test. The dependence of pharmacokinetic variables on age or body weight of individual patients was examined using linear regression. P < 0.05 was considered significant.

Results

The control children were older than the children with biliary atresia (mean 23.0 months vs 12.3 months, respectively), although this difference was not statistically significant (P = 0.053). The difference in age explains the significantly higher body weight observed in the control group (table 1). Because of this weight difference between the two study groups, pharmacokinetic variables such as Cl and volumes of distribution were normalized for body weight (table 1). Figure 1 shows that the mean propofol blood concentration-time profiles for both study groups were very similar. The terminal half-life of propofol in blood was 99.6 (30.8) min in the control group and 141.3 (75.9) min in the children with biliary atresia. Systemic Cl of propofol not normalized for body weight was significantly smaller in the children with biliary atresia (268 (113) ml min⁻¹) compared with the control children (418 (141) ml min⁻¹). Weight-normalized systemic Cl, however, did not differ significantly between the study groups. Vd(α) and Vd(β) did not differ between the control children and the children with biliary atresia, regardless of whether the values were normalized or not for body weight. Cl (r = 0.94, P < 0.0001), Vd(α) (r = 0.59, P = 0.027) and Vd(β) (r = 0.60, P = 0.023) were significantly correlated with body weight.

Discussion

Pharmacokinetic studies in adult patients have shown that the systemic clearance of propofol exceeds liver blood flow [3-5]. This implies that extrahepatic metabolism contributes to the overall metabolism of this i.v. anaesthetic, which has also been demonstrated experimentally [6-8]. The contribution of extrahepatic sites, such as gut wall, kidney and lung, to the overall metabolism of a drug may increase in patients with severe liver disease [20, 21]. Studies in children aged 3–12 yr indicated a systemic clearance of approximately 30–40 ml min⁻¹ kg⁻¹ [11-15], and these values also approximate to or exceed normal liver blood flow in this age group [22]. Because the systemic clearance of propofol both in adult patients and children approaches or exceeds liver blood flow, the hepatic extraction ratio of propofol is probably very high [23]. This implies that the systemic clearance of propofol is probably influenced primarily by liver blood flow and less by changes in plasma protein binding and metabolic capacity [23]. In the present study the pharmacokinetics of propofol were studied in two groups of very young children: their ages ranged from 4 to 43 months. Blood sampling was limited to 4 h after administra-
tion of propofol because of ethical limitations on the total volume of blood that may be obtained from these young children. While this restricted blood sampling scheme may not reveal the "true" terminal elimination phase of the drug from blood, it allows a reasonably good estimate of variables such as systemic clearance and steady state distribution volume. In table 2, weight-normalized Cl and Vd of propofol, and terminal blood (plasma) half-life, as reported in the literature for control children, are compared with values obtained in the present study. Although the children who participated in the present study were, on average, younger than those studied elsewhere, weight-normalized clearance and steady state distribution volume were within the range of the average values reported previously. The terminal half-life of propofol in the present study was shorter than the values reported in the literature. This is almost certainly explained by the shorter sampling time used in the present study (4 h) compared with others (24 h). However, recent work suggests that the true terminal half-life of propofol may be several days because of its extremely high solubility in fat tissue [24]. Estimation of such a long terminal half-life would therefore require several days of blood sampling after single-dose administration of the anesthetic.

The following conclusions may be drawn from the results of our study: (1) systemic clearance of propofol and volume of distribution at steady state in very young children (4–43 months) seem to be similar to values reported in the literature for older children (3–12 years); (2) a wide inter-subject variability in both variables was observed in these very young children; (3) differences in body weight may account for an important part of this inter-subject variability, especially for systemic clearance of propofol; and (4) biliary atresia does not appear to significantly affect the pharmacokinetics of propofol. Body weight was also identified recently by Kataria and colleagues [15] as the most significant covariate of the pharmacokinetics of propofol in children. The fact that biliary atresia does not affect the systemic clearance of propofol suggests that this serious hepatic dysfunction does not alter the factor(s) (possibly liver blood flow) controlling the elimination of this anesthetic. On the other hand, it is also possible that extrahepatic metabolism of propofol, less likely to be affected by biliary atresia, is a major determinant of its overall elimination rate.

Table 2 Propofol pharmacokinetic variables in "healthy" children: comparison between the current study and those reported previously. *Chinese children. †Median

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (yr) (mean (range))</th>
<th>Cl (ml min⁻¹ kg⁻¹)</th>
<th>Vd (litre kg⁻¹)</th>
<th>T1/2h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saint-Maurice and colleagues [13]</td>
<td>10</td>
<td>5.5 (4–7)</td>
<td>30.6</td>
<td>10.9</td>
<td>735</td>
</tr>
<tr>
<td>Valtonen and colleagues [14]</td>
<td>8</td>
<td>6.5 (3–10)</td>
<td>32.0</td>
<td>2.2</td>
<td>215</td>
</tr>
<tr>
<td>Jones, Chan and Andrew [11]*</td>
<td>12</td>
<td>7.9 (4–12)</td>
<td>40.4</td>
<td>5.0</td>
<td>209</td>
</tr>
<tr>
<td>Kataria and colleagues [15]</td>
<td>53</td>
<td>7.0† (3–11)</td>
<td>34.0</td>
<td>9.7</td>
<td>329</td>
</tr>
<tr>
<td>Present study</td>
<td>6</td>
<td>1.9 (1–4)</td>
<td>38.7</td>
<td>2.4</td>
<td>100</td>
</tr>
</tbody>
</table>

References
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