Fluoride excretion in children after sevoflurane anaesthesia

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Background. Defluorination of sevoflurane is catalysed by the hepatic enzyme cytochrome P450 2E1 (CYP2E1). Data about the ontogenesis (developmental variations in activity) of this enzyme suggest a low metabolism of sevoflurane during the first months of life.

Methods. To test this hypothesis, 45 children less than 48 months of age undergoing sevoflurane anaesthesia were enrolled in a prospective open clinical trial. The 24 h urine fluoride excretion was measured in five groups of children (A, <4 months; B, 4 to <8 months; C, 8–12 months; D, >12–24 months; and E, >24–48 months old). An index of sevoflurane metabolism (ISM) was calculated as the ratio of fluoride excretion, cumulative expiratory sevoflurane concentrations measured every minute during anaesthesia, and body surface area. ISM values were median (IQ 25–75%).

Results. ISM was lower in group A (n=9, 18.9 (11.2–29.5) than group C (n=11, 44.2 (37.5–53.5), P<0.05), group D (n=7, 52.6 (45.8–68.4), P<0.01) and group E (n=9, 53.6 (50.7–85), P<0.001). Median ISM expressed as a function of median age, exponentially increased with a rapid increase during the first months of life, followed by a slower increase after 10 months of age.

Conclusion. These results suggest that, in children less than 48 months, sevoflurane metabolism parallels postnatal development of CYP2E1.

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dextrose 1% isotonic sodium chloride was infused peroperatively at 25 ml kg⁻¹ during the first hour, then 83 ml h⁻¹ m⁻². The airway was managed with a laryngeal mask or tracheal tube as indicated by the surgery. No neuromuscular blocking agent was administered. Sevoflurane administration was adjusted as clinically indicated. Immediately after induction of anaesthesia, i.v. acetaminophen 30 mg kg⁻¹ was administered and followed by 15 mg kg⁻¹ orally every 6 h. Intra-operative analgesia was given intravenously or by regional anaesthesia performed before the surgical incision. For postoperative analgesia, intermittent i.v. nalbuphine 0.2 mg kg⁻¹ or continuous i.v. morphine 20–40 μg kg⁻¹ h⁻¹ was used. Dextrose 5% infusion (83 ml h⁻¹ m⁻²) with electrolytes was used postoperatively until the patient was able to eat normally.

The bladder was emptied after induction of anaesthesia by manual abdominal pressure. If a urinary catheter was not required, a bag was stuck on the skin for urinary collection during the first 24 h after the beginning of sevoflurane anaesthesia. The child was only included in the study at the time of the urine collection if no urine leakage was observed during this period. It was necessary to screen 70 children before definitively including 45 patients in the study because of urine leakage during the 24-h urine collection.

After mixing and measuring the 24-h urine collection, a sample was frozen at −20°C until measurement of fluoride concentration. The fluoride urine concentrations were determined with an ion-selective electrode. Its performance was checked by an Interlaboratory Control program, managed by the Canadian toxicologic centre in Quebec (CHUQ, Sainte-Foy). The intra-assay coefficient of variation was 1.24, 0.21 and 0.48% for fluoride concentrations of 13, 53, and 133 μmol litre⁻¹, respectively. The inter-assay coefficient of variation was 4 and 4.2% for fluoride concentrations of 64 and 223 μmol litre⁻¹, respectively.

The ISM was calculated using the urinary fluoride excretion during the first 24 h, the exposure to sevoflurane, and the body surface area, as follows:

\[ \text{ISM} = \frac{100 \times (F \times U)}{E \times S} \]

with \( F \) being urine fluoride concentration (μmol litre⁻¹), \( U \) being 24-h urine volume (litre), \( E \) being exposure to sevoflurane (% min), and \( S \) being body surface area (m²) [calculated using \( 4W+7(W+90) \), where \( W \) is weight (kg)].

The exposure to sevoflurane (E) was estimated by the sum of the inspiratory sevoflurane concentrations that were measured every minute during sevoflurane administration. Measurements were made using an infra-red based, multi-gas module (SAM module, Marquette electronics™, Milwaukee, USA) and sidestream sampling with a flow rate of 250 ml min⁻¹. Rise time (delay before automatic return to zero) to avoid contamination of measurement by

### Table 1 Physical characteristics of the patients. Results are medians (interquartile range 25–75%). BSA, body surface area. Exposure corresponds to the sum of expiratory sevoflurane concentrations measured every minute during anaesthesia. ISM was calculated as indicated in the data analysis section. Comparison between groups by Kruskal–Wallis analysis: compared with group A: *P<0.05, **P<0.01, ***P<0.001; compared with group E: *P<0.05

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>A (9)</th>
<th>B (9)</th>
<th>C (11)</th>
<th>D (7)</th>
<th>E (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>2.4 (2–3.2)</td>
<td>5.1 (4–7.5)</td>
<td>9 (8.2–9.5)</td>
<td>18.3 (16–21.5)</td>
<td>28.7 (28–38)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.9 (4.2–5.7)</td>
<td>6.7 (6.5–7.5)</td>
<td>9 (8.7–9.9)</td>
<td>12 (10.5–12.2)</td>
<td>13.5 (13–15)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>0.28 (0.25–0.31)</td>
<td>0.35 (0.34–0.38)</td>
<td>0.43 (0.42–0.47)</td>
<td>0.54 (0.49–0.55)</td>
<td>0.59 (0.57–0.65)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2/9</td>
<td>1/8</td>
<td>1/10</td>
<td>3/4</td>
<td>3/6</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>96 (68–190)</td>
<td>166 (100–215)</td>
<td>163 (147–204)</td>
<td>130 (91–160)</td>
<td>123 (117–157)</td>
</tr>
<tr>
<td>Exposure (MAChours)</td>
<td>1.19 (1.07–1.88)</td>
<td>1.79 (1.46–2.55)</td>
<td>2.41 (1.99–2.94)</td>
<td>1.88 (1.13–2.55)</td>
<td>2.17 (1.6–2.29)</td>
</tr>
<tr>
<td>Urinary fluoride concentration (μmol litre⁻¹)</td>
<td>35.5 (30.4–42)</td>
<td>105 (79–155)</td>
<td>116 (91.9–145)*</td>
<td>156 (108–166.3)**</td>
<td>121 (104–174.6)***</td>
</tr>
</tbody>
</table>
| ISM (% μmol %⁻¹ min⁻¹ m⁻²) | 18.9 (11.2–29.5) | 26.9 (21.4–48.1) d | 44.2 (37.5–53.5)* | 52.6 (45.8–68.4)** | 53.6 (50.7–85)**

Fig 1 Individual points (n=45) for the ISM; groups A (<4 months), B (4 to <8 months), C (8–12 months), D (>12–24 months), and E (>24 months).
previous sampling) was less than 600 ms and the accuracy equal to 5% of the reading.

Data are expressed as medians (interquartile range 25–75%). The ISM were compared in five groups of children (A, <4 months of age; B, 4 to <8 months; C, 8–12 months; D, >12–24 months; and E, >24 months) using Kruskal–Wallis analysis of variance. \( P < 0.05 \) was considered statistically significant. If \( P \) was significant, Kruskal–Wallis analysis was followed by a Dunn’s multiple comparison test.

Statistical analysis was performed on the Statview® 4.5 software (Abacus Concepts Inc., Berkeley, CA, USA). A relation between the median values of ISM and the age of each group was searched for by non-linear regression analysis using Prism, version 3.02 (Graph Pad software Inc.).

Results

The physical characteristics of the patients are given in Table 1. No significant differences between groups in exposure to sevoflurane (duration of anaesthesia, real cumulative exposure, or MAC-hour exposure) were found (Table 1). Median expiratory concentration was 2.3 (1.9–2.7)%.

Fluoride urine 24 h concentrations and ISM varied in the five groups: the younger the children, the lower the ISM values. Individual data for ISM are shown in Figure 1. The relationship between age and ISM was best predicted by non-linear manipulation. The plot of median ISM as a function of the median age for each group showed an exponential increase in ISM with age, with a curve linearity suggesting an allometric model (i.e. a linear relation between ISM and age after double logarithmic transformation) (Fig. 2). To confirm this hypothesis, median and individual values of age and ISM were normalized by double logarithmic transformation. Thereafter, median values of ISM and age were highly correlated by linear regression analysis (\( R^2 = 0.98 \)). The plot of individual data of ISM and age after allometric transformation (Fig. 3) also showed a linear relationship, despite a lower correlation coefficient, that was explained by the interindividual variability.

Discussion

The natural log relationship of fluoride urinary excretion to age after sevoflurane anaesthesia in small children, suggests an allometric evolution of the metabolism of sevoflurane during the three first years of life, characterized by a low sevoflurane metabolism during the first 3 months, followed by an increase in the rate of defluorination until 10 months of age. Allometry is used to describe the change in relative size of two physiological variables during growth or evolution.\(^8\) It is frequently observed in the evolution of an organism’s morphology and means that the variations during development of physiological variables are linearly related only after double logarithmic transformation. Such a relationship between ISM and age suggests that sevoflurane metabolism parallels postnatal development of CYP2E1.

Data concerning the metabolism of sevoflurane in children are limited to two previous studies.\(^3\,9\) Those findings were correlated with our study: they have, respectively, shown smaller plasma fluoride peaks between 1 and 6 months,\(^3\) and a lower area under the curve of plasma fluoride in children aged from 1 to 12 yr,\(^3\) than in adults.

Fluoride production is related both to the administered dose of sevoflurane and to the CYP2E1 level activity.\(^10\) Fluoride urinary excretion probably reflects more accurately the fluoride production than plasma concentrations, and has been used to demonstrate the role of CYP2E1 in the hepatic biotransformation of sevoflurane.\(^11\) However, the use of urinary excretion standardized to sevoflurane exposure and
body surface area in this study is original and has not been validated previously. The concept was guided by the need to take into account both variable exposures to sevoflurane, and physiological variables that are better indexed to body surface area than to body weight.

A limitation of our conclusion is the existence of extrahepatic metabolism of sevoflurane,\(^1\) explained by the expression of CYP2E1 in the lung, small intestine, and brain, albeit to a lesser extent than in the liver.\(^2\) In human hepatic microsomes, the rate of defluorination of sevoflurane has been shown to be well-correlated with liver CYP2E1 activity and selective inhibition.\(^4\)

One of the clinical implications of the present study is that sevoflurane is the first substrate of CYP2E1 that could be used as an \textit{in vivo} probe of its activity in children. Until now, chlorzoxazone, a centrally acting neuromuscular blocking agent, remained the only \textit{in vivo} probe for CYP2E1 phenotyping in adults.\(^13\) Because of the absence of pharmacological data, its safety in childhood has not been established. Several factors regulate CYP2E1 activity. Developmental expression is one of the keys factors. CYP2E1 is absent or barely detectable in the fetal liver, developing post-natally. Ontogenesis relates to the developmental variation in enzyme activity during growth. Knowledge of the ontogenesis of CYP2E1 resulted from \textit{in vitro} studies using post-mortem liver samples from children of varying postnatal age.\(^6\) Further implications of the immature metabolism of sevoflurane in infants and small children relate to nephrotoxicity from fluoride production.

More than 100 specific exogenous substrates of CYP2E1 have been identified, in addition to a number of endogenous ones.\(^5\)\(^14\) Low CYP2E1 activity could be protection against the toxicity of drugs or compounds that undergo activation by CYP2E1 to produce metabolites that are cytotoxic or genotoxic, such as halothane and acetaminophen. Oxidative hepatic metabolism of halothane by CYP2E1 mediates an immune-based fulminant hepatic necrosis, because of the production of a reactive trifluoroacetyl halide.\(^15\) The lower incidence of this rare but fatal side-effect in children,\(^16\) rather than in adults, could be explained by a lower CYP2E1 activity. The toxicity of acetaminophen is related to its transformation by CYP2E1 in presence of overdose or hepatic glutathion depletion, to a toxic metabolite identified as N-acetyl-p-benzoquinone imine.\(^17\) In mice, this toxicity is delayed, if expression of the CYP2E1 is lacking.\(^18\) Pretreatment by propylene glycol, that inhibits CYP2E1, also prevents hepatic necrosis.\(^17\) It is generally accepted that children are less susceptible than adults to acetaminophen toxicity because of developmental differences in its metabolism.\(^19\) One of these differences could be a lower CYP2E1 activity.

In conclusion, the allometric variation of fluoride excretion after sevoflurane anaesthesia during the first years of life, confirms previous \textit{in vitro} data about CYP2E1 ontogenesis.

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References
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