Pharmacokinetics of Intravenous Dantrolene in Children

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To determine the pharmacokinetics of iv dantrolene and its metabolites in children, ten children 2–7 yr of age scheduled for minor elective surgery, were studied. After induction of anesthesia and tracheal intubation, dantrolene (2.4 mg/kg) was administered iv over 10.2 ± 0.83 min. Venous blood samples (3 ml) were obtained 1, 5, 10, 20, and 30 min and 1, 2, 4, 8, 12, and 20 h after the dantrolene infusion. Whole blood concentrations of dantrolene, 5-hydroxydantrolene, and nitroreduced acetylated dantrolene were measured by high-performance liquid chromatography. The whole blood concentration of dantrolene decreased rapidly from a mean (±SD) of 6.03 ± 0.69 µg/ml 1 min after the end of the dantrolene infusion to 3.56 ± 0.49 µg/ml at 1 h. Between 1 and 4 h, the concentration of dantrolene either remained constant or increased slightly. Then, after the concentration of dantrolene decreased slowly with an elimination half-life (mean ± SD) of 10.0 ± 2.6 h. The mean (±SD) time for the concentration of dantrolene to decrease to 3.0 µg/ml was 6.55 ± 2.88 h. The whole blood concentration of 5-hydroxydantrolene reached a maximum of 0.60 ± 0.18 µg/ml approximately 7 h after the dantrolene and decreased thereafter with an elimination half-life of 9.0 ± 2.5 h. The concentration of nitroreduced acetylated dantrolene was below the limit for detection at all times. All children recovered without complications. Intravenous dantrolene, 2.4 mg/kg, produces safe and predictable blood concentrations in children similar to those reported in adults. (Key words: Anesthesia; pediatrics. Hyperthermia: malignant. Neuromuscular relaxants dantrolene. Pharmacokinetics dantrolene, 5-hydroxydantrolene.)

INTRAVENOUS DANTROLENE sodium (Dantrium®) has been recommended for prophylaxis in malignant hyperthermia susceptible (MHS) patients as well as for treatment of malignant hyperthermia during anesthesia.1–4 Flewelen and Nelson investigated the pharmacokinetic profile of dantrolene in six MHS adults.5 In their study, dantrolene (2.4 mg/kg) was administered iv over a 10–30 min period. Flewelen and Nelson found that the whole blood concentration of dantrolene 5 min after the infusion was 5.36 ± 0.9 µg/ml, that the blood concentration exceeded 2.0 µg/ml for approximately 6 h, and that the elimination half-life was 12 ± 6.8 h.6 Although the dose of iv dantrolene recommended for adults and children is similar,2,6 the pharmacokinetic profile for iv dantrolene in children has not been determined. Lietman et al. previously reported the pharmacokinetic profile for dantrolene and its major metabolite, 5-hydroxydantrolene (5-OH dantrolene), after oral administration in children.6 They found a lower peak whole blood concentration of dantrolene (1.5 ± 3.0 µg/ml) and a shorter mean elimination half-life (7.3 h) in children than was measured in adults after iv dantrolene.1,5,6 To determine the pharmacokinetic profiles for dantrolene and its metabolites after a single iv dose in children, we studied ten children undergoing elective surgery.

Methods

With approval from the Human Subjects Review Committee and informed written consent from the parents, ten children 2–7 yr of age were studied. All children were ASA physical status 2, fasting, and unpremedicated.

In all children the ECO, blood pressure, heart sounds, rectal and axillary temperature, end-tidal PCO₂, and hemoglobin oxygen saturation were monitored. After administration of iv atrovent, anesthesia was induced with thiopental and tracheal intubation was facilitated with atracurium. Anesthesia was maintained with nitrous oxide in oxygen and iv fentanyl and diazepam.

Lyophilized dantrolene powder was reconstituted with sterile water to yield a solution with a dantrolene concentration of 0.35 mg/ml. Dantrolene 2.4 mg/kg was then administered as a continuous iv infusion over 10.2 ± 0.83 min during maintenance anesthesia. Venous blood samples (5 ml volume) were obtained from the opposite limb at 1, 5, 10, 20, and 30 min and 1, 2, 4, 8, 12, and 20 h after completion of the infusion. The blood was stored in heparinized vactuators at −20°C until analysis. Whole blood concentrations of dantrolene, 5-OH dantrolene, and nitroreduced acetylated dantrolene were measured by high-performance liquid chromatography (HPLC).7,8 All three calibration curves were linear throughout the ranges of concentrations studied. The coefficients of variation for the dantrolene and 5-OH dantrolene analyses were 2.9% and 4.7%, respectively, between concentrations of 0.05 µg/ml and 10.0 µg/ml. The reliable limit of detection for dantrolene, 5-OH dantrolene, and nitroreduced acetylated dantrolene was 0.1 µg/ml.

At the completion of surgery, neuromuscular blockade was reversed. Postoperatively, all children were observed in the recovery room for 24 h. Axillary or rectal temperature and respirations were monitored continuously. Heart rate and systolic arterial pressure were measured hourly until discharge from the recovery room.

Age, weight, MH history, and surgical procedures were recorded. Pharmacokinetic variables including the volume

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of distribution at steady state (Vdss)\textsuperscript{9} were determined using standard noncompartmental methods.\textsuperscript{10} The elimination half-life (t1/2β) was determined using linear regression analysis of the natural logarithm of the whole blood concentration versus time. For dantrolene the t1/2β was calculated from the terminal three or four concentration–time data periods, whereas the t1/2β for 5-OH dantrolene was calculated from the terminal three data points (in two children only the terminal two points were used). The area under the curve (AUC) was calculated using the trapezoidal method from time 0 to the last blood sample (C). The AUC\textsubscript{t→∞} was calculated using the ratio C\textsubscript{t}/β, where β is the elimination rate constant. The individual pharmacokinetic variables for both dantrolene and 5-OH dantrolene for the ten children studied are presented in table 2.

In two children a reliable elimination rate constant for 5-OH dantrolene could not be calculated. In these children the AUC\textsubscript{0→∞} 5-OH dantrolene was estimated by measuring the AUC\textsubscript{0→2.5h} and estimating the AUC\textsubscript{2.5h→∞} using the terminal rate constant for dantrolene. The total body clearance (CL) of dantrolene was calculated using the equation CL = dose/AUC\textsubscript{0→∞}.

All data are presented as means ± SD. Statistical significance (P < 0.05) was determined using Student's t test.

Results

The demographic data for the ten children are listed in table 1. The mean (±SD) age was 3.6 ± 1.3 yr. MH susceptibility was based on a family history of either an MH reaction or positive muscle biopsy except in patient 5. This patient developed masseter spasm at induction of anesthesia during a previous anesthetic.

Typical whole blood dantrolene and 5-OH dantrolene concentration–time profiles for one patient are shown in figure 1. This figure demonstrates the parallel terminal elimination phases for dantrolene and 5-OH dantrolene. Because the slopes of the terminal elimination phases for dantrolene and 5-OH dantrolene did not differ significantly, we used the elimination rate constant for dantrolene to estimate AUC\textsubscript{0→∞} in the children in whom a reliable elimination rate constant for 5-OH dantrolene could not be calculated.

The individual pharmacokinetic variables for both dantrolene and 5-OH dantrolene for the ten children studied are presented in table 2.

We found that the mean (±SD) whole blood concentration of dantrolene decreased from 6.03 ± 0.93 μg/ml at 1 min after the administration of dantrolene to 3.56 ± 0.49 μg/ml at 1 h (fig. 2, table 3). Between 1 and 4 h after the administration of dantrolene, the concentration of dantrolene either remained constant or increased slightly. Thereafter, the concentration decreased slowly with a mean (±SD) elimination half-life of 10.0 ± 2.6 h (r² > 0.98). The mean (±SD) time for the whole blood concentration of dantrolene to decrease to 3.0 μg/ml was 6.55 ± 2.88 h. The concentration of dantrolene exceeded 2.0 μg/ml in all ten children for at least 6 h after administration of the dantrolene.

The concentration–time profile for 5-OH dantrolene reached a mean (±SD) peak whole blood concentration of 0.60 ± 0.18 μg/ml at approximately 7 h and then
decreased following first-order kinetics (fig. 3, table 3). The $t_{1/2}$ for 5-OH dantrolene was $9.0 \pm 2.5$ h in eight of the ten children ($r^2 > 0.98$). The AUC ratio was $0.205 \pm 0.070$ (range, 0.11–0.50). The clearance of dantrolene correlated significantly with the AUC ratio ($r^2 = 0.82, P < 0.01$).

The whole blood concentrations of nitroreduced acetylated dantrolene were below 0.10 $\mu$g/ml at all times.

None of the children developed MH crises in the perioperative period. There were no cardiorespiratory changes associated with the administration of iv dantrolene (2.4 mg/kg) during anesthesia or for the subsequent 20 h.

### Discussion

Of the ten children in this study, nine had a family history of MH and one had developed masseter muscle rigidity during a previous anesthetic. Because none of these children had a muscle biopsy for MH, none were confirmed MHS. Nonetheless, we determined the pharmacokinetic profiles for dantrolene and its metabolites in these ten children with the expectation that the profiles in MHS children who are biopsy-positive should be similar to those in children who are either biopsy-negative or non-MHS. This is based on two studies by Flewellen and Nelson in which they reported similar pharmacokinetic profiles for dantrolene in both biopsy-positive MHS adults and non-MH adult volunteers.\(^1,8\)

Studies in MHS swine have demonstrated that the blood concentration of dantrolene that maximally depresses the twitch response also prevents MH crises.\(^1,8\) Flewellen and Nelson demonstrated that when the whole blood concentration of dantrolene in humans exceeds 2.5–3.0 $\mu$g/ml, the twitch response is maximally depressed.\(^1,8\) Their conclusion that 2.4 mg/kg iv dantrolene should provide adequate blood concentrations of dantrolene to prevent MH crises in humans is supported clinically by a multicenter study, which found the same dose of dantrolene to be effective in reversing acute MH crises.\(^12\) The results of our study indicate that a single iv dose of 2.4 mg/kg dantrolene produces blood concentrations of dantrolene that exceed 5.0 $\mu$g/ml for approximately 6.5 h in children (fig. 2, table 3). If continued prophylaxis is necessary (i.e., whole blood concentrations $>5.0 \mu$g/ml), then we recommend that a second dose of one-half of the original dose of dantrolene or 1.2 mg/kg be given approximately 6 h after the initial dose. We base this recommendation on a simulation of the pharmacokinetic profile of dantrolene when two doses of dantrolene (2.4 and 1.2 mg/kg) are given 6 h apart. For this simulation

### Table 2. Individual Pharmacokinetic Variables

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<tr>
<th>Patient Number</th>
<th>Weight (kg)</th>
<th>Dose (mg)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g·ml$^{-1}$·h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g·ml$^{-1}$·h)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g·ml$^{-1}$·h)</th>
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### Fig. 2. Whole blood concentration of dantrolene versus time for 10 children who received 2.4 mg/kg dantrolene. The concentration of dantrolene is shown on a logarithmic scale. Data are mean ± SD.
we assumed the pharmacokinetics of dantrolene are not dose-dependent. The simulation predicted an additional 10 h of prophylaxis.

The concentration–time profiles for dantrolene were similar among the ten children studied. The concentrations of dantrolene decreased rapidly for the first hour, then remained constant or increased slightly during the next 3 h, and finally decreased slowly with an elimination half-life of approximately 10 h. We speculate the constant or increasing concentrations during the 1–4 h after dantrolene may be attributed to either the distribution kinetics of dantrolene or an enterohepatic cycling process. Nonetheless, the constant or increasing concentrations during this 1–4 h interval serves to maintain the whole blood concentration of dantrolene >3.0 μg/ml for approximately 6.5 h in most children.

The pharmacokinetic profile for iv dantrolene in children is similar to that reported previously in adults (fig. 2, table 3). Although the mean elimination half-life of dantrolene in children was 20% less than that reported in adults, this difference did not reach statistical significance because of the large standard deviations in both studies. The Vd, for children in this study was 20% less than the Vd (dantrolene) estimated by Larach et al. The explanation for this small difference in Vd is unclear. In view of the lipophilic nature of dantrolene, we would speculate that differences in tissue disposition (and binding) of dantrolene are more likely to account for this difference in Vd than differences in plasma protein binding. Further studies are required to determine the extent of plasma protein binding of dantrolene in children and adults.

The pharmacokinetics of 5-OH dantrolene are clinically relevant because this metabolite of dantrolene is 30–50% as effective as dantrolene in depressing the twitch response. The concentration–time profile for the metabolite 5-OH dantrolene in this study (fig. 3, table 3) differs significantly from that after oral dantrolene. The salient differences in the concentration–time profiles between these two studies include a higher peak blood concentration, an earlier peak blood concentration, and a more rapid elimination half-life for 5-OH dantrolene after oral dantrolene than were measured after iv dantrolene. These differences may be attributed, in part, to extensive first pass hepatic metabolism of dantrolene after oral administration.

Because the elimination half-life of 5-OH dantrolene was calculated from only two or three terminal values on the concentration–time profile, our estimate of the half-life may be subject to error. However, despite this potential error, the individual terminal phases of the concentration–time profiles for 5-OH dantrolene reflected those of dantrolene, the parent compound (fig. 1). Indeed, the elimination half-lives for 5-OH dantrolene and dantrolene did not differ significantly (table 3). We speculated that the similarity in the elimination half-lives of 5-OH dantrolene and dantrolene in this study may be attributed to the limiting step in the apparent elimination rate of 5-OH dantrolene being the rate of its formation from dantrolene (i.e., its elimination rate is formation rate-limited).

We found a threefold variation in the AUC ratio in the ten children studied. This large variation in the AUC ratio indicates that there is significant interindividual variability in the extent of formation of the metabolite 5-OH dantrolene in children. Furthermore, because the

<table>
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<th>Number of Patients</th>
<th>Drug or Metabolite</th>
<th>Cmax (μg/ml)</th>
<th>Cmin (μg/ml)</th>
<th>tmax (h)</th>
<th>AUCmin (μg·ml⁻¹·h)</th>
<th>Clearance (mL·min⁻¹·kg⁻¹)</th>
<th>Vd, (L/kg)</th>
<th>Time to 1.5% Cmax (h)</th>
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<td>Children</td>
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<td>6.05 ± 0.93*</td>
<td>3.57 ± 0.88</td>
<td>10.0 ± 2.6</td>
<td>67.2 ± 19.2</td>
<td>0.640 ± 0.175</td>
<td>0.54 ± 0.08</td>
<td>6.55 ± 2.88</td>
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<tr>
<td>Adults</td>
<td>10 5-OH dantrolene</td>
<td>0.60 ± 0.18</td>
<td>—</td>
<td>9.0 ± 2.5</td>
<td>12.9 ± 5.25</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Adults</td>
<td>6 Dantrolene</td>
<td>3.56 ± 0.9</td>
<td>3.56 ± 0.9</td>
<td>12.0 ± 6.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

Values are given as mean ± SD.

* One minute after dantrolene.

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**Table 3. Pharmacokinetic Data for Dantrolene and 5-OH Dantrolene**

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**Fig. 3.** Whole blood concentration of 5-OH dantrolene increased to a maximum concentration (0.60 μg/ml) by 7 h and then decreased with an elimination half-life of 9.0 ± 2.5 h. The concentration of 5-OH dantrolene is shown on a logarithmic scale. Data are mean ± SD.
clearance of dantrolene correlated significantly with this AUC ratio, the metabolism of dantrolene to 5-OH dantrolene is likely an important clearance mechanism for dantrolene.

Continuous infusions of iv dantrolene have been used for several hours in MHS patients. However, these infusions were complicated by acute thrombophlebitis that required anticoagulation. We do not recommend the use of continuous iv infusions of dantrolene for two reasons: 1) alkaline solutions (lyophilized dantrolene [pH 9.6]) may cause acute inflammation of the vascular endothelium; and 2) the pharmacokinetic profile of iv dantrolene in this study indicates that whole blood concentrations of dantrolene exceed 3.0 µg/ml for approximately 6.5 h after a single iv dose of a 2.4 mg/kg dantrolene. Because the concentration of dantrolene decreases thereafter with an elimination half-life of approximately 10 h, a second dose of dantrolene should be given after 6 h to maintain prophylactic blood concentrations.

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References