Pharmacokinetics and Safety of Gadobenate Dimeglumine in Patients from 2 to 5 Years of Age

G. Pirovano[1], M. Pasowicz[2], M. A. Kirchin[3], N. Shen[4], J. R. Parker[5], and A. Spinazzi[1]
[1]Medical Affairs, Bracco Diagnostics Inc., Princeton, New Jersey, United States, [2]Radiology, John Paul II Hospital, Kracow, Poland, [3]Medical Communications, Bracco Imaging, Milan, Italy, [4]Biometrics, Bracco Diagnostics Inc., Princeton, New Jersey, United States, [5]Medical Communications, Bracco Diagnostics Inc., Princeton, NJ, United States

Purpose: To assess blood pharmacokinetics and safety of gadobenate dimeglumine in 2- to 5-year–old patients.

Materials and Methods: 15 subjects (7 males, 8 females; mean age: 3.53 years [range 2 to 5.1 years]; mean weight 16.6 kg [range 11 to 22 kg]) were enrolled in a single-center, open-label pharmacokinetic study and received 0.1 mmol/kg bw gadobenate dimeglumine. Blood samples were drawn within 1 h predose, and at 5 min, 10 min (pre-MRI), 30 min, 1 h, 2 h, and 6 h postdose (post-MRI). Urine was collected from the time of contrast administration up to 24 hours postdose. Blood and urine samples were analyzed for gadolinium (Gd) using ICP-AES. Adverse events (AEs) were monitored from the time informed consent was given through 72 h postdose. Physical examinations were performed predose and 24 h postdose. Vital signs and ECGs were acquired within 1 hour predose and then at 1, 2, and 24 h postdose. The pharmacokinetic parameters were calculated from the blood Gd concentration-time data using compartmental and noncompartmental techniques. Pharmacokinetic parameters were summarized using descriptive statistics (mean ± SD, geometric mean, coefficient of variation [%CV], median, minimum, and maximum). Data were summarized for the whole population as well as for subgroups by age (2–3 years, 3–4 years, 4–5 years) and sex.

Results: The peak Gd concentration (range: 50.6–91.1 μg/mL) was observed immediately after completion of contrast injection. After reaching peak concentrations, Gd blood levels dropped rapidly during the next 30-60 minutes, followed by a slower rate of decline. At 6 hours after gadobenate dimeglumine administration, all subjects' residual Gd in blood was close to 1.0 μg/mL, indicating that Gd was successfully cleared from the blood by 6 hours postdose. The mean estimated elimination or terminal half-life was 1.2 hours. The pharmacokinetic parameters were consistent whether determined by noncompartmental or compartmental analyses (Tables 1,2). Some subjects had incomplete urine collection because of diaper usage or difficulty with very young patients' compliance during the urine collection period; nonetheless, approximately 81% of the dose of Gd was recovered from urine within 24 hours. Four adverse events were reported for 2 subjects. All events were mild in intensity and unrelated to gadobenate dimeglumine administration. No clinically meaningful differences were observed at any time point between predose and postdose changes for any vital signs, ECG parameters, or laboratory tests.

Conclusions: Administration of gadobenate dimeglumine was well tolerated in pediatric subjects undergoing MRI procedures. No differences in whole blood or urinary pharmacokinetic parameters were observed between pediatric subjects 2 to 5 years when compared to adult subjects studied in previously. Adjustment of gadobenate dimeglumine dosage for pharmacokinetic or safety reasons does not appear to be necessary for pediatric subjects.

Table 1: Whole Blood Pharmacokinetic Parameters of Gd: Non-compartmental Analysis

Parameter	n=15 Mean ± SD
Tmax (hr)	0.08 ± 0.00
Cmax (μg/mL)	65.70 ± 12.24
t½,λz (hr)	1.23 ± 0.16
AUC_{0-t} (μg·hr/mL)	75.76 ± 9.96
AUC_{0-inf} (μg·hr/mL)	78.42 ± 10.86
V (L/kg)	0.36 ± 0.05
CL (mL/min/kg)	0.20 ± 0.03
Vss (L/kg)	0.32 ± 0.03

Table 2: Whole Blood Pharmacokinetic Parameters of Gd: Compartmental Analysis

Parameter	n=15 Mean ± SD
CL (mL/min/kg)	0.21 ± 0.03
Vc (L/kg)	0.20 ± 0.05
t½,α (hr)	0.13 ± 0.08
t½,β (hr)	1.22 ± 0.24
Vss (L/kg)	0.32 ± 0.04

Abbreviations: AUC_{0-t}=area under the blood concentration-time curve from time zero to the last quantifiable blood concentration; AUC_{0-inf}=area under the blood concentration-time curve from time zero to infinity; CL=blood clearance; Cmax=peak Gd blood concentration; SD=standard deviation; t½,α = distribution half-life; t½,β = elimination half-life; t½,λz=terminal phase half-life; Tmax=time at which maximum blood concentration of Gd was observed; V=apparent relative volume of distribution; Vc=central volume of distribution; Vss=steady-state volume of distribution.