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Pharmacokinetics, Safety, and Efficacy of Gadopiclenol in Pediatric Patients Aged 2 to 17 Years

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Objectives: The aim of this study was to evaluate the pharmacokinetic (PK) profile, safety, and efficacy of gadopiclenol, a new high-relaxivity gadolinium-based contrast agent, in children aged 2 to 17 years.

Materials and Methods: Children scheduled to undergo contrast-enhanced magnetic resonance imaging of the central nervous system (CNS cohort) or other organs (body cohort) were included sequentially into 3 age groups (12–17, 7–11, and 2–6 years). Gadopiclenol was administered at the dose of 0.05 mmol/kg. A sparse sampling approach was applied, with 4 blood samples per child collected up to 8 hours postinjection. Population PK modeling was used for the analysis, including the CNS cohort and adult subjects from a previous study. Adverse events were recorded, and efficacy was assessed for all children.

Results: Eighty children were included, 60 in the CNS cohort and 20 in the body cohort. The 2-compartment model with linear elimination from the central compartment developed in adults was also suitable for children. Pharmacokinetic parameters were very similar between adults and children. Terminal elimination half-life was 1.82 hours for adults and 1.77 to 1.29 hours for age groups 12–17 to 2–6 years. The median clearance ranged from 0.08 L/h/kg in adults and 12–17 years to 0.12 L/h/kg in 2–6 years. The median central and peripheral volumes of distribution were 0.11 to 0.12 L/kg and 0.06 L/kg, respectively, for both adults and children. Simulations of plasma concentrations showed minor differences, and median area under the curve was 590 mg·h/L for adults and 582 to 403 mg·h/L for children. Two patients (2.5%) experienced nonserious adverse events considered related to gadopiclenol: a mild QT interval prolongation and a moderate maculopapular rash. Despite the limited number of patients, this study showed that gadopiclenol improved lesion detection, visualization, and diagnostic confidence.

Conclusions: The PK profile of gadopiclenol in children aged 2 to 17 years was similar to that observed in adults. Thus, there is no indication for age-based dose adaptation, and comparable plasma gadopiclenol concentrations are predicted to be achieved with body weight–based dosing in this population. Gadopiclenol at 0.05 mmol/kg seems to have a good safety profile in these patients and could improve lesion detection and visualization, therefore providing better diagnostic confidence.

Key Words: gadopiclenol, GBCA, MRI, pharmacokinetics, safety, pediatric patients

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Magnetic resonance imaging (MRI) is a routine noninvasive diagnostic technique providing crucial anatomical and pathogenic information in a wide variety of medical conditions without radiation to patients. Magnetic resonance imaging diagnostic value is further improved when a gadolinium (Gd)-based contrast agent (GBCA) is administered, as they often provide additional, clinically relevant information (such as location, type, and stage of lesions for diagnosis and treatment planning) compared with unenhanced MRI.[1]

With the emergence of safety concerns related to the use of GBCAs, such as nephrogenic systemic fibrosis (NSF) and Gd deposition in brain and other tissues, it is important to use the lowest GBCA dose providing sufficient enhancement for diagnosis in routine practice,[2] especially in patients with renal impairment, patients susceptible to receive multiple doses, and pediatric patients.[3] In this regard, a deep learning–based technology that could reduce the GBCA dose while maintaining image quality and contrast information of full-dose contrast images has been proposed.[4] Furthermore, developing new GBCAs allowing the reduction of injected Gd dose while keeping the same efficacy provided by the current GBCAs and/or improving the rate of lesion detection and characterization with the same usual dose is of paramount importance.[5]

Gadopiclenol (Guerbet, Aulnay-sous-Bois, France) is a nonionic macrocyclic GBCA currently under development, having a high thermodynamic and kinetic stabilities and the highest r1 relaxivity among currently available GBCAs (r1 = 12.8 $mM^{-1}{\cdot}s^{-1}$ at 1.41 T and 11.6 $mM^{-1}{\cdot}s^{-1}$ at 3 T in biological medium at 37°C).[6] In adults, gadopiclenol is mainly excreted in urine in an unchanged form (98% excreted within 48 hours) and has a terminal plasma elimination half-life ($t_{1/2}$) of 1.5 to 2 hours (depending on the administered dose).[7] In patients with mild (estimated glomerular filtration rate [eGFR], 60–89 mL/min/1.73 m^2) to severe (eGFR, 15–29 mL/min/1.73 m^2) renal impairment, urinary excretion of gadopiclenol was delayed and ranged between 96% and 85% ($t_{1/2}$ between 3.3 hours for mild and 11.7 hours for severe renal impairment).[8]

Results from 4 published clinical trials, including a total of 392 adult subjects (healthy volunteers, patients with brain lesions, and patients with renal impairment), showed that gadopiclenol presents a good biological and clinical safety profile.[7–10]

The aim of this trial was to investigate the pharmacokinetic (PK) profile of gadopiclenol at 0.05 mmol/kg after a single intravenous injection and to evaluate its safety and efficacy in pediatric patients aged 2 to 17 years.

MATERIALS AND METHODS

Study Design and Population

This phase II open-label, uncontrolled, multicenter, international pediatric study was conducted between November 2018 and August 2020. The study was approved by independent ethics committees and authorized by national regulatory authorities. Patients' parents or legal guardian gave their informed consent to involve their child in the study. The study was registered on ClinicalTrials.gov (NCT03749252).

Male or female pediatric patients aged 2 to 17 years, with known or suspected lesions, scheduled to undergo routine contrast-enhanced MRI of central nervous system (CNS cohort) or of other organs (body cohort) such as head and neck, thorax, abdomen, pelvis, or musculoskeletal system were included in the study. Patients were recruited sequentially into 3 predefined age groups: adolescents (12–17 years), then preadolescents (7–11 years), and finally young children (2–6 years). The decision to start the next age group was taken by a trial safety review board, based on safety assessment of at least 15 patients included in previous age group.

Patients were not included if presenting with acute or chronic renal insufficiency (eGFR out of age-adjusted reference ranges), known cardiac disease, severe liver disease, planning to receive any other contrast agent 1 week prior or after gadopiclenol administration, or undergoing treatment or procedure before or after gadopiclenol administration that would alter gadopiclenol PK parameters.

Included patients underwent unenhanced and contrast-enhanced MRI and were confined for up to 1 day. Follow-up visits were scheduled 1 week and 3 months after inclusion for urine sampling and safety assessment. If, due to the COVID-19 pandemic, these follow-up visits were remotely performed, other on-site visits could also be scheduled at maximum 30 and 120 days, respectively.

Gadopiclenol at 0.05 mmol/kg (0.1 mL/kg) was administered as a single intravenous bolus injection at rate of 1 to 2 mL/s followed by a saline flush. Pharmacokinetic parameters were only investigated in the CNS cohort, whereas the safety, urinary excretion, and efficacy of gadopiclenol were evaluated in both the CNS and body cohorts.

Pharmacokinetic Assessments

A population pharmacokinetics (popPK) approach was used, as it allows sparse blood sampling in children. In each patient, 4 blood samples were collected postinjection of gadopiclenol for PK analyses. An optimized flexible design with 4 sampling windows covering the first 8 hours was used (1–20 minutes, 30–45 minutes, 2–3 hours, and 7–8 hours).

As a popPK model for gadopiclenol was already developed in adult subjects, this model was used as starting point for the pediatric population with the objective to enrich and update the existing model if possible. Preliminary checks were performed to assess whether the existing model was predictive of data collected in pediatric patients, and if so, pediatric data were added to adult data to update the existing model. The same population of the adult model was used (ie, 35 healthy volunteers and 11 CNS patients administered doses of gadopiclenol ranging from 0.025 to 0.3 mmol/kg).[7]

The popPK modeling was performed with NONMEM (Nonlinear Mixed Effect Modeling) software, v.7.4 (Icon plc, Dublin, Ireland). The analysis was performed on the per protocol set defined as all patients of the CNS cohort without major deviations likely to impact the popPK model. Predictability and stability of the selected model were assessed using prediction-corrected visual predictive checks.

The following PK parameters were determined from the final popPK model: total clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2), and $t_{1/2}$. Based on the final popPK model, gadopiclenol concentrations at 10, 20, and 30 minutes after injection and the area under the curve (AUC_{inf}) were simulated after the generation of 1000 replicates of the final data set.

When possible, urine was collected over 8 hours following gadopiclenol injection in patients able to control daytime urination, to evaluate gadopiclenol urinary excretion. Long-term gadopiclenol urinary excretion was assessed using spot urine samples collected at the 1 week and 3 months follow-up visits (or up to 30 and 120 days, respectively).

Gadopiclenol concentration was determined using a validated liquid chromatography coupled with tandem mass spectrometry method with a limit of quantification (LOQ) of 5 μg/mL.

Efficacy Evaluation

Efficacy assessments were performed on site for both the CNS and body cohorts. The technical adequacy of images was assessed using a 4-point scale (nondiagnostic, poor, fair, and good). Percentage of lesion enhancement and lesion-to-background ratio were assessed for up to 3 of the most representative lesions as follow:

$$\text{Percentage of lesion enhancement} = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \times 100$$

$$LBR = \frac{SI_{post}}{SI_b}$$

where SI_{post} = Lesion signal intensity (SI) on postinjection images,
SI_{pre} = Lesion SI on preinjection images, and
SI_b = Background tissue SI on postinjection images.

In addition, lesion border delineation, internal morphology, and contrast enhancement were assessed using a 4-point scale (none or poor, moderate, good, and excellent). Investigator's diagnostic confidence was assessed whether it improved, remained unchanged, or got worse after gadopiclenol administration.

Safety Evaluation

Safety evaluation was performed for all patients who had received gadopiclenol. Adverse events (AEs) were monitored from signature of informed consent to the last follow-up visit. Additional blood samples were collected before and 1 day after gadopiclenol administration to measure several hematology and biochemistry parameters. Vital signs and electrocardiography (ECG) measurements were performed before, 30 to 90 minutes and 1 day after gadopiclenol administration. Tolerance at injection site was assessed 30 to 90 minutes and 1 day after gadopiclenol administration. Any symptoms evocative of NSF were recorded, and a deep skin biopsy was to be performed if NSF was suspected.

Statistical Methods

The results were reported using descriptive statistics obtained using SAS (Version 9.4; SAS Institute Inc, Cary, NC). Summary statistics (number [n], mean, standard deviation [SD], median, minimum, maximum, and the number of missing values) were calculated for quantitative variables, whereas the number of patients and percentages were presented for categorical variables.

RESULTS

A total of 80 pediatric patients were enrolled in 14 centers from 5 countries: Poland (46.3%), Slovakia (20.0%), Bulgaria (15.0%), Ukraine (10.0%), and Hungary (8.8%). All patients received gadopiclenol: 60 patients in the CNS cohort (20 in each age group) and 20 patients in the body cohort. All included patients completed the study. Only 1 major protocol deviation (PK blood samples assessed out of stability period) was reported in a patient from the CNS cohort. Demographic characteristics of patients are presented in Table 1. Overall, 26 patients were between 2 and 6 years (mean of 4 years), 23 between 7 and 11 years (mean of 9 years), and 31 between 12 and 17 years (mean of 14 years). Patients were equally distributed between males and females.

Pharmacokinetic Results

A total of 59 pediatric patients of the CNS cohort were considered for the popPK analysis. The adult data set consisted of 46 subjects. Of the 236 planned plasma samples, 218 were used in the model (14 were below LOQ, 3 were not reportable and considered as missing, and 1 was not collected). The individual and median plasma gadopiclenol concentrations over time per age group are presented in Figure 1.

Eleven plasmatic profiles were considered as potential outliers (Fig. 1). During preliminary checks, the overall pattern of concentrations

TABLE 1. Demographic Characteristics of Patients

	CNS and Body					
	12–17 y (N = 31)	7–11 y (N = 23)	2–6 y (N = 26)	CNS Cohort (N = 60)	Body Cohort (N = 20)	Total (N = 80)
Age, y*	14.3 (1.6)	8.8 (1.2)	3.8 (1.3)	9.1 (4.6)	10.0 (5.0)	9.3 (4.7)
Sex, n (%)						
Male	12 (38.7%)	10 (43.5%)	19 (73.1%)	32 (53.3%)	9 (45.0%)	41 (51.3%)
Female	19 (61.3%)	13 (56.5%)	7 (26.9%)	28 (46.7%)	11 (55.0%)	39 (48.8%)
Height, cm*	165.9 (9.0)	136.2 (10.1)	105.8 (11.1)	136.7 (26.6)	141.3 (29.6)	137.8 (27.3)
Weight, kg*	60.72 (12.53)	34.76 (11.89)	18.74 (7.50)	38.93 (21.05)	41.67 (21.33)	39.61 (21.02)

*Data presented as mean (standard deviation).

CNS, central nervous system.

measured in the pediatric population over time was found to be consistent, but slightly higher than what was simulated from the adult model. The elimination phase observed for children was parallel with that simulated from adult model but started earlier than adults. More variability was also observed in the data of the pediatric patients compared with adults, in particular because of some very high values. After the preliminary checks, the 2-compartment model developed in adults was considered suitable for pediatric patients, and the 2 populations were combined.

The base model was obtained on the whole population, combining the children and adult data sets. The model considered was a 2-compartment model with linear elimination from the central compartment. The model was parameterized in terms of CL, V1, V2, and intercompartment clearance (Q).

To account for the heterogeneity of variability, the interindividual variability and residual error were described separately for adults and children. Exponential models were used to describe the interindividual variability on CL, V1, and V2 for adults and on CL, V1, and Q for children. A proportional model was considered as the best model for error for the 2 populations. After univariate and multivariate analyses, the effect of eGFR on CL and age on V1 were identified as significant covariates. No adult or pediatric subject was considered a priori as outliers for the analysis. However, to measure the impact of the 11 plasmatic profiles considered as potential outliers, sensitivity analyses were performed. The sensitivity analysis showed that the fixed effect parameters were not altered by the removal of these patients, who contributed significantly to the wide variability.

Despite a slight under prediction of limited impact between 1 and 3 hours after injection, the model obtained after the sensitivity analysis, excluding physiologically unrealistic data, was considered to best reflect the PK characteristics of gadopiclenol and as a tool suitable for prediction and simulations of gadopiclenol exposure in the pediatric population.

The derived PK parameters were equivalent for adults and children, with median CL ranging from 0.08 L/h/kg (adult and 12–17 years old group) to 0.12 L/h/kg for youngest children, median V1 ranging between 0.11 and 0.12 L/kg, median V2 of 0.06 L/kg for both adults and children, and median $t_{1/2}$ ranging from 1.82 hours for adults to 1.29 hours for youngest children (Table 2).

Based on the simulated AUC_{inf} values, the 12–17, 7–11, and 2–6 years patients were 1% (582 mg·h/L), 19% (478 mg·h/L), and 32% (403 mg·h/L) less exposed than adults (590 mg·h/L) for body weight–based dosing, respectively (Fig. 2). The median gadopiclenol concentrations at 10, 20, and 30 minutes after injection showed differences less

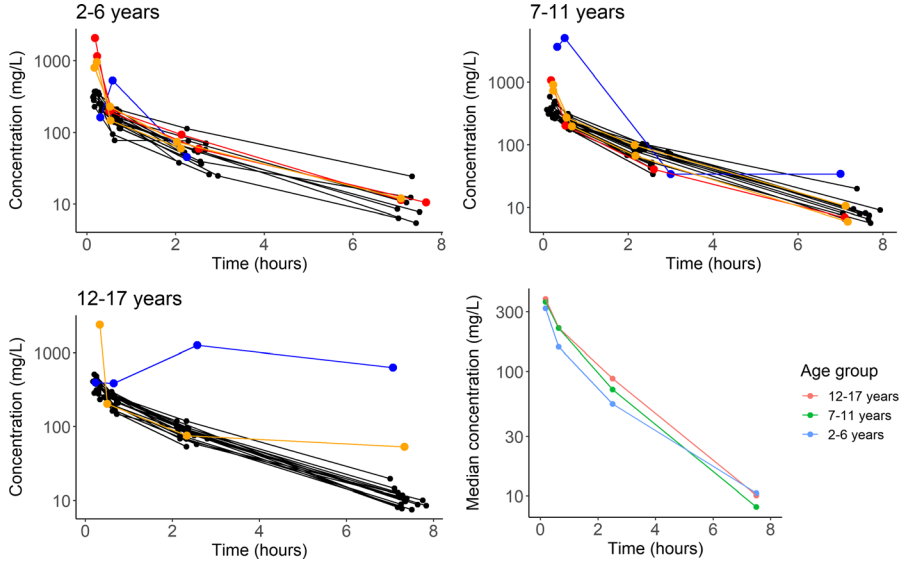

FIGURE 1. Individual and median gadopiclenol plasma concentrations over time by age group. Individual gadopiclenol plasma concentrations indicated in blue are profiles incompatible with an intravenous administration, and in orange and red are profiles with very high initial gadopiclenol plasma concentration incompatible with the administered dose divided by the theoretical blood (orange) and plasma volume (red).

TABLE 2. Derived PK Parameters Based on Final Population PK Model Without Outliers

Age Group	Clearance, L/h/kg	Central Volume of Distribution, L/kg	Peripheral Volume of Distribution, L/kg	Terminal Half-Life, h
2–6 y	0.12 (0.05–0.28)	0.12 (0.06–0.26)	0.06 (0.06–0.06)	1.29 (0.69–3.38)
7–11 y	0.10 (0.04–0.24)	0.12 (0.06–0.24)	0.06 (0.06–0.06)	1.48 (0.83–3.20)
12–17 y	0.08 (0.04–0.20)	0.11 (0.05–0.24)	0.06 (0.06–0.06)	1.77 (1.00–3.57)
>18 y	0.08 (0.05–0.14)	0.11 (0.04–0.28)	0.06 (0.03–0.14)	1.82 (0.93–3.68)

Data presented as median (min-max).

PK, pharmacokinetic.

than 16%, 20%, and 23%, respectively, between each patients' population (12–17, 7–11, 2–6, and >18 years) (Fig. 2).

Despite these minor differences, there is no indication for dose adaptation based on age in addition to body weight–based dosing.

Results of gadopiclenol urinary excretion over 8 hours were difficult to interpret due to a high intersubject variability likely due to incomplete (nonquantitative) sample collection. The mean (SD) gadopiclenol dose recovered in urine over 8 hours after administration was highly variable: 80.60% (45.31), 103.53% (43.87), and 67.09% (36.11) for the 2–6, 7–11, and 12–17 years groups, respectively. Gadopiclenol concentration in urine at day 8 was below LOQ (<5 µg/mL) in 70 samples, whereas slightly above LOQ in 10 samples (including 1 sample analyzed beyond validated stability period). At day 90, gadopiclenol concentration in urine was below LOQ in all but 1 sample (with implausible result).

Efficacy Results

Among the 60 patients of the CNS cohort, the technical adequacy was mainly rated as good for both precontrast (unenhanced) (95.0%) and paired (unenhanced and contrast-enhanced) images (98.3%). Among the 20 patients of the body cohort, the technical adequacy was good in 80% of precontrast images and 90% of paired images (Table 3). All images were assessable.

In the CNS cohort, the number of detected lesions per patient ranged from 0 to 25 in the 12 to 17 years group, 0 to 13 in the 7 to 11 years group, and 0 to 2 in the 2 to 6 years group. Overall, lesions were identified in 32 patients (53.3%) with precontrast images and 34 patients (56.7%) with paired images. When considering up to 3 most representative lesions per patient, 61 lesions were identified on precontrast images and 63 on paired images. In the body cohort, 0 to 2 lesions were detected per patient. Overall, 12 lesions were detected in 11 patients (55.0%) both with precontrast and paired images.

Regarding contrast quality, the mean (SD) percentage of enhancement was 11.9% (43.5) in the CNS cohort and 101.1% (65.6) in the body cohort. The mean (SD) lesion-to-background ratio was 0.9 (0.5) in the CNS cohort and 1.7 (2.3) in the body cohort (Table 4). In the CNS cohort, no enhancement was observed in 44 lesions (69.8%). For the remaining lesions, enhancement was graded moderate in 5 lesions (7.9%), good in 5 (7.9%), and excellent in 9 (14.3%). All lesions in the body cohort showed enhancement: moderate in 1 lesion (8.3%), good in 5 lesions (41.7%), and excellent in 6 lesions (50%).

In the CNS cohort, lesion border delineation was similar on precontrast and paired images for 53 lesions, including 42 graded good or excellent. Paired images improved the score for 6 lesions, whereas it was downgraded for 4 lesions. Lesion internal morphology was similar with precontrast and paired images for 57 lesions, including 45 graded good or excellent. An improvement with paired images was reported for 6 lesions (Table 5).

In the body cohort, among the 12 detected lesions, lesion border delineation was similar on precontrast and paired images for 6 lesions (including 4 good), improved with paired images for 5 lesions and downgraded for 1 lesion. Lesion internal morphology was similar on

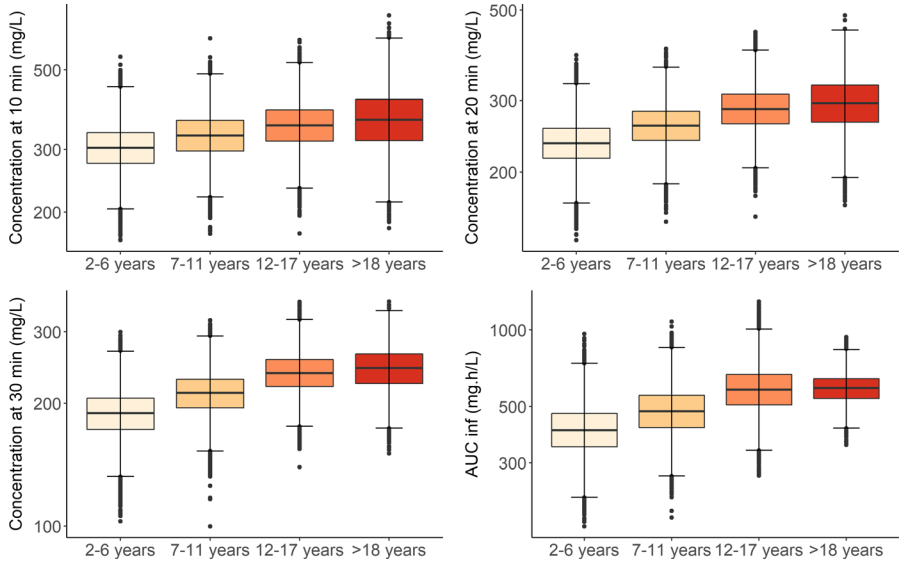

FIGURE 2. Simulated gadopiclenol plasma concentrations and AUC_{inf} by age group. In the box plot, the solid line is the median, the end of the "box" are the first and third quartile. The whiskers show the lowest value still within 1.5 interquartile range (IQR) of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile. Data values that do not fall between the whiskers are plotted as outliers (markers outside of the whiskers).

TABLE 3. Images Adequacy and Number of Lesions Detected

	CNS Cohort (N = 60)		Body Cohort (N = 20)	
	Pre	**Paired**	**Pre**	**Paired**
Technical adequacy for diagnosis				
Nondiagnostic	0	0	0	0
Poor	0	0	1 (5.0%)	0
Fair	3 (5.0%)	1 (1.7%)	3 (15.0%)	2 (10.0%)
Good	57 (95.0%)	59 (98.3%)	16 (80.0%)	18 (90.0%)
No. detected lesions per patient				
No lesion	**28 (46.7%)**	**26 (43.3%)**	9 (45.0%)	9 (45.0%)
1 lesion	**15 (25.0%)**	**17 (28.3%)**	10 (50.0%)	10 (50.0%)
2 lesions	5 (8.3%)	5 (8.3%)	1 (5.0%)	1 (5.0%)
3 lesions	5 (8.3%)	5 (8.3%)	0	0
>3 lesions	7 (11.7%)	7 (11.7%)	0	0

CNS, central nervous system; Pre, unenhanced MRI; Paired, unenhanced + contrast-enhanced MRI.

precontrast and paired images for 4 lesions (graded good), improved on paired images for 5 lesions and downgraded for 3 lesions (Table 5).

The investigator's confidence in diagnosis improved for 25 patients (55.6%) and remained unchanged for 20 patients (44.4%) among the 45 patients with detected lesions. The improvement was more frequent in the body cohort (63.6%) compared with the CNS cohort (52.9%). In the CNS cohort, the main diagnosis made after the MRI examination was most frequently congenital malformation (26.5%) followed by primary tumor (14.7%), inflammatory disease (11.8%), and vascular or neurodegenerative disease (8.8% each). Other various diagnosis included mainly cysts and neurofibromatosis. In the body cohort, vascular diseases and inflammatory diseases were diagnosed in 3 patients each (27.3%) and congenital malformation in 1 patient (9.1%). Other diagnosis included cysts and cryptorchism.

Safety Results

Overall, 31 postinjection AEs were reported in 14 patients (17.5%), most of which were mild or moderate in intensity. Serious AEs (none fatal) were reported in 3 patients (3.8%), but none related to gadopiclenol. Two AEs in 2 patients (2.5%) from the CNS cohort were considered related to gadopiclenol. A 5-year-old patient experienced a QT interval prolongation of mild intensity, not resolved at the end of the study (no follow-up ECG was performed to check if it was resolved or not). Of note, this patient experienced strong anxiety during the ECG before administration of gadopiclenol. A 9-year-old patient experienced a maculopapular rash of moderate intensity, occurring 6 days after gadopiclenol administration and resolved within 7 days.

No major modifications in hematology and biochemistry parameters were observed after gadopiclenol administration. No differences were observed between the CNS and body cohorts and between the 3 age groups. Regarding more particularly serum creatinine, an increase from baseline between 15% and 25% was observed in 8 patients, none of which had eGFR values below the reference range. A decrease in eGFR >25% was observed in 2 patients, whose values remained within reference range and were not considered as clinically significant. However, the variation of eGFR must be cautiously interpreted, as eGFR values >90 mL/min/1.73 m^2 were reported by default as 90 mL/min/1.73 m^2.

Regarding ECG, changes in QT interval were reported as AEs for 2 patients, including 1 reported as related to gadopiclenol as described previously and another being long QT syndrome with late diagnosis (not related to gadopiclenol). No other events related to ECG were reported.

Vital signs were within reference range in most of patients (only 4 patients had systolic blood pressure values <90 mm Hg), and median values of change from baseline were close to zero.

Regarding tolerance at injection site, only 1 patient from the CNS cohort reported redness near the injection site 1 day after injection. Physical examination did not highlight any symptoms that could be related to NSF.

DISCUSSION

This study was primarily performed to investigate the plasma PK of gadopiclenol in pediatric patients aged 2 to 17 years, using a popPK approach, which allows sparse blood sampling and minimizes the clinical burden in children.[11] The study was conducted in accordance with US Food and Drug Administration and European Medicines Agency recommendations.[12,13]

The popPK consisted of a 2-compartment model with a linear elimination from central compartment, which appropriately described the PK of gadopiclenol in adults. Such model has been used to assess the PK profile of other GBCAs in pediatric patients.[14,15]

From this popPK model, the median CL increased slightly from 0.08 L/h/kg in adults and 12 to 17 years old group to 0.12 L/h/kg for the 2 to 6 years old children, and therefore, $t_{1/2}$ decreased from 1.82 hours for adults to 1.29 hours for youngest children. A similar approach was used in another study where pediatric patients aged 2 to 17 years were administered with gadobutrol at 0.1 mmol/kg.[14] In this study, a relatively comparable CL (0.10 L/h/kg) and $t_{1/2}$ (1.69 hours) were reported for these pediatric patients. Furthermore, the relative increase in the median AUC between the 3 age groups was comparable between gadobutrol and gadopiclenol (ie, 19% for 7–11 years and 44% for 12–17 years vs 2–6 years).[14] This was consistent with previous reports showing that GFR normalized to weight is the highest around 2 years of age and decreases afterward to reach adult levels.[16]

Findings from this study showed that adults were slightly more exposed than children with body weight–based dosing. Nevertheless, there is no indication for dose adaptation based on age in addition to body weight–based dosing. Therefore, the efficacy of gadopiclenol in pediatric patients aged 2 to 17 years is expected to be similar to that in adults.

The mean fraction of gadopiclenol dose recovered in urine over 8 hours after administration was 81%, 104%, and 67% for the 2–6, 7–11, and 12–17 years groups, respectively. However, a high intersubject variability was observed, which could be explained by a default in urine collection in some patients (not whole urine collected during the period, bad homogenization), in addition to the accepted variability due to bioanalytical measurement and actually injected dose. Therefore, the

TABLE 4. Assessment of Contrast Quality

	CNS Cohort (N = 60)	Body Cohort (N = 20)	Total (N = 80)
Percentage of enhancement			
Total no. lesions	61*	12	73
Mean (SD)	11.9 (43.5)	101.1 (65.6)	26.6 (57.8)
Lesion-to-background ratio			
Total no. lesions	63	12	75
Mean (SD)	0.90 (0.46)	1.68 (2.25)	1.03 (1.01)

*Percentage of enhancement not calculated for lesions not seen with unenhanced images.

CNS, central nervous system; SD, standard deviation.

TABLE 5. Lesion Border Delineation and Internal Morphology

	Contrast-Enhanced MRI				
Unenhanced MRI	**None/Poor**	**Moderate**	**Good**	**Excellent**	**Total**
Lesion border delineation					
Not seen	—	—	**1 (1.3%)**	**1 (1.3%)**	2 (2.7%)
None	1 (1.3%)	**1 (1.3%)**	—	**1 (1.3%)**	3 (4.0%)
Moderate	**2 (2.7%)**	11 (14.7%)	**3 (4.0%)**	**3 (4.0%)**	19 (25.3%)
Good	—	**3 (4.0%)**	30 (40.0%)	**1 (1.3%)**	34 (45.3%)
Excellent	—	—	—	17 (22.7%)	17 (22.7%)
Total	3	15	34	23	75
Lesion internal morphology					
Not seen	—	—	**2 (2.7%)**	—	2 (2.7%)
Poor	5 (6.7%)	**2 (2.7%)**	**2 (2.7%)**	—	9 (12.0%)
Moderate	**1 (1.3%)**	7 (9.3%)	**2 (2.7%)**	**1 (1.3%)**	11 (14.7%)
Good	—	**1 (1.3%)**	30 (40.0%)	**2 (2.7%)**	33 (44.0%)
Excellent	—	—	**1 (1.3%)**	19 (25.3%)	20 (26.7%)
Total	6	10	37	22	75

Data in boldface are lesions with different assessment between unenhanced and contrast-enhanced MRI.
MRI, magnetic resonance imaging.

mean gadopiclenol urinary excretion measured in this study should be considered with caution. It is known that urinary excretion is the main route of elimination for gadopiclenol. In healthy adult volunteers, depending on study, 79.1% (±23.7) of the dose is eliminated via urine over 6 hours after injection[8] and 85.2% (±25.7) of the dose is eliminated within 48 hours.[7]

Efficacy results from this study showed that gadopiclenol-enhanced MRI allowed the detection of 1 additional lesion in 2 patients from the CNS cohort. A relatively low lesion enhancement was observed in lesions of the CNS cohort compared with lesions of the body cohort. This was due to the nature of CNS lesions, such as congenital malformations and neurodegenerative diseases.[17–20] In a previous phase IIb, double-blind, randomized study performed on adults, it has been shown that lesion border delineation, internal morphology, and contrast enhancement of CNS lesions were not significantly different with gadopiclenol used at 0.05 mmol/kg and gadobenate dimeglumine (the approved GBCA at the time of the study with the highest relaxivity) used at 0.1 mmol/kg.[9]

In accordance with previous results from 4 published clinical trials including adult healthy volunteers, patients with brain lesions, and patients with renal impairment,[7–10] this study showed a good safety profile of gadopiclenol when used in pediatric patients aged 2 to 17 years, with only 2 nonserious AEs related to gadopiclenol (a mild QT interval prolongation and a moderate maculopapular rash). In a thorough QT/QTc phase I, randomized, double-blind study performed on 48 adult healthy volunteers, it has been shown that gadopiclenol did not prolong QT interval at clinical (0.1 mmol/kg) and supraclinical (0.3 mmol/kg) doses.[10]

In 2 other studies with subjects exposed to doses up to 0.2 mmol/kg of gadopiclenol, no cases of QT prolongation were reported.[7,9] Earlier studies showed that anxiety was associated with longer QT intervals, hence, increasing the risk of cardiac arrhythmias.[21] Hence, it cannot be excluded that the QT interval prolongation observed in this 5-year-old patient was due or exacerbated by the strong anxiety observed before administration of gadopiclenol.

Nephrogenic systemic fibrosis is a rare but potentially fatal disease whose symptoms may include scaling, hardening, and tightening of the skin, red or dark patches on the skin, and stiffness.[5] In this study, no NSF cases were reported for a follow-up of 3 months. This result is in line with the fact that NSF cases reported in the literature are mostly associated with the use of linear GBCAs and the use of higher than standard dose.[22] Gadopiclenol is a macrocyclic GBCA with a high kinetic stability, suggesting a low risk for NSF induction.

This study comes with some limitations. The findings from this study performed on patients aged 2 to 17 years cannot be extrapolated to newborns and infants younger than 2 years. Future studies will be performed to investigate the PK, safety, and efficacy of gadopiclenol in these patients. Only gadopiclenol was used in this study, as the main purpose was to investigate the PK of gadopiclenol in these patients. Furthermore, a limited number of patients with lesions, especially for the body cohort, and a high number of unenhancing lesions in the CNS cohort were observed. Future studies are warranted to compare in pediatric patients the efficacy of gadopiclenol at 0.05 mmol/kg with the currently available GBCAs used at standard dose (ie, 0.1 mmol/kg). Gadolinium deposition in brain after multiple administrations of GBCAs (mainly linear) has been widely documented,[23,24] and the potential toxicity of free Gd ions on brain parenchyma is rapidly gaining clinical concerns. Recently, one retrospective study showed that signal intensity in different brain regions on unenhanced T1-weighted images from pediatric patients (aged 1 month to 14 years) increased after serial administration (3 to 9 administrations) of linear GBCAs (gadodiamide or gadopentetate dimeglumine), but not with macrocyclic GBCA (gadoteric acid).[25] In this study, we did not investigate the potential Gd deposition in the brain of included pediatric patients. Nevertheless, as with other macrocyclic GBCAs, it could be reasonably expected that similar results would be obtained with gadopiclenol, especially when a lower dose than usual is used (ie, 0.05 mmol/kg).

CONCLUSIONS

A popPK approach appropriately described the PK profile of gadopiclenol in patients aged 2 to 17 years. Gadopiclenol PK in these patients was similar to that observed in adults. Thus, there is no indication for age-based dose adaptation, and comparable plasma gadopiclenol concentrations are predicted to be achieved with body weight–based dosing in children aged 2 to 17 years. Gadopiclenol at 0.05 mmol/kg seems to have a good safety profile in these patients and could improve lesion detection and visualization, therefore providing better diagnostic confidence.

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