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ORIGINAL ARTICLE

The safety and efficacy of neuroimaging with gadoversetamide injection in pediatric patients

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ABSTRACT

Objective: The safety and efficacy of gadoversetamide injection (OptiMARK*) was examined in pediatric patients referred for magnetic resonance imaging (MRI) of the central nervous system (CNS).

Research and design methods: This was an open-label, multicenter study in patients aged between 2 and 18 years scheduled for a contrast-enhanced MRI study. Patients received a single injection of gadoversetamide (0.1 mmol/kg). Safety of gadoversetamide was evaluated by physical examinations and monitoring of adverse events, laboratory values, vital signs, and electrocardiogram readings before and after drug administration. Efficacy was assessed by three independent, blinded readers for confidence in diagnosis and level of conspicuity for lesion visualization on precontrast and postcontrast images. The diagnostic accuracy, sensitivity, and specificity of lesion detection were determined for the precontrast images, the postcontrast images, and the precontrast and postcontrast images read together.

Results: No drug-related moderate or serious adverse events were observed in this study, according to site investigators. A total of four adverse events in four of 100 patients (4%) were deemed likely related to gadoversetamide injection by the site investigators. All were mild in severity and not clinically significant. The most common adverse events, regardless of relationship to study drug, were injection-site reactions and a small prolongation of the QT interval. The administration of gadoversetamide significantly increased the level of lesion conspicuity and diagnostic confidence ($p < 0.05$). Compared with the nonenhanced image, gadoversetamide significantly increased the accuracy and sensitivity of lesion detection ($p < 0.05$). Limitations of the study included a lack of physiological measurements after sedation and prior to contrast administration, a single dose of gadoversetamide administered (0.1 mmol/kg) and patients younger than 2 years of age were excluded.

Conclusion: The administration of gadoversetamide injection (0.1 mmol/kg) was safe, well tolerated and produced clinically appropriate contrast enhancement for MRI of the CNS in the pediatric population.

Introduction

The efficacy of paramagnetic metal ions such as gadolinium at shortening T1 relaxation time and increasing signal intensity of magnetic resonance (MR) images is well established. In the past, the toxicity of these ionized metal ions limited their use. However, the formulation of gadolinium–organic molecule chelates in the 1980s greatly improved the safety of gadolinium, and since then the use of gadolinium-

* OptiMARK is a registered trademark of Tyco Healthcare/Mallinckrodt, St. Louis, MO, USA

based contrast agents has gained wide acceptance. Today, gadolinium-based magnetic resonance imaging (MRI) contrast agents are widely regarded as very safe in the general population. Major adverse effects occur rarely with gadolinium-based agents, and minor effects, including nausea, headache, urticaria and taste perversion, also are infrequent[1,2].

Gadoversetamide injection (OptiMARK*) is a nonionic gadolinium chelate currently approved for use as an intravenous contrast agent in adults undergoing MRI of the liver or structures within the central nervous system (CNS). During the original clinical development of gadoversetamide, its diagnostic utility and safety were demonstrated in adults suspected of a CNS abnormality. In these studies, the most common adverse events were similar to those reported for other gadolinium contrast agents and included taste perversion, nausea, and headache[3–5].

The continued clinical development of gadoversetamide included an evaluation of safety and pharmacokinetics in a single cohort of healthy pediatric subjects. This preliminary study found no adverse events or toxicity following a single 0.1 mmol/kg dose of gadoversetamide[6].

The established safety and tolerability profile of gadoversetamide demonstrated in adults and children[6,7], coupled with its proven utility for lesion enhancement in MRI, suggests a potential diagnostic benefit for gadoversetamide in pediatric patients with suspected CNS lesions. Since other gadolinium chelates have shown clinical utility and safety in pediatric patients[8–12], it is reasonable to investigate the clinical utility of gadoversetamide in pediatric patients requiring MRI of the CNS. This study was designed and conducted by Tyco Healthcare/Mallinckrodt as part of the continued clinical development of gadoversetamide in a pediatric patient population. The data presented below describes the safety and efficacy of gadoversetamide (0.1 mmol/kg) in a cohort of pediatric patients suspected of having a CNS abnormality.

Patients and methods

Study population

The study population included patients 2–18 years of age with a body weight of at least 11 kg who were referred for a contrast-enhanced MR examination of the CNS. Patients were excluded from enrollment if they had known or suspected abnormal renal function (for the patient's age). The protocol was approved by the Institutional Review Boards of the ten participating clinical sites. All patients were recruited via informed consent (parental permission) and, for those > 7 years of age who were capable, by informed assent.

Study protocol

Prior to the injection of gadoversetamide, precontrast images, including T1-weighted (sagittal and axial planes) and T2-weighted (axial plane) and proton density and/or inversion recovery (axial or coronal) MR images of the CNS, were collected. Each patient received a single intravenous injection of gadoversetamide at a dose of 0.1 mmol/kg administered at a rate of 1–2 mL/s, followed by a normal saline flush (5–10 mL). Postcontrast T1-weighted (axial, coronal, and/or sagittal planes) images were collected for each patient beginning immediately after injection of gadoversetamide.

Safety assessments

The safety of gadoversetamide was evaluated by physical examinations, adverse events, and changes from baseline in laboratory findings, vital signs, and electrocardiograms (ECGs). Medical and surgical histories of enrolled patients were taken within 24 h prior to gadoversetamide administration, and physical examinations were performed within 24 h pre- and post-administration of gadoversetamide. Adverse events were monitored continuously from the time of signing the informed consent (no more than 24 h before administration of the study drug), during, and for 24 h after the administration of gadoversetamide. Laboratory values (hematology, clinical chemistry, and urinalysis) were obtained prior to and 2 and 24 h postadministration of gadoversetamide. Baseline vital signs (radial pulse, systolic and diastolic blood pressure, respiratory rate, and body temperature) were recorded within 24 h prior to administration of gadoversetamide. Monitoring for changes in vital signs took place immediately postimaging and at 1, 2, and 24 h after contrast administration. A standard 12-lead ECG was performed within 24 h prior to, and immediately postimaging, and 2 and 24 h after administration of gadoversetamide. A core ECG laboratory evaluated the ECGs. Assessments included measurement of the heart rate, PR interval, QRS complex, QT interval (both uncorrected and corrected for changes in heart rate using the Bazett's correction method [QTcb]), and the ST segment and provided an overall impression of the clinical cardiac status.

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Efficacy assessments

All MR images were read by investigators at the study sites and independently by three blinded readers who were board-certified radiologists unaffiliated with the study sponsor or investigation sites. The blinded readers had no knowledge of the study protocol, patient identity, clinical history, presenting conditions, or drug administration.

The primary efficacy endpoint evaluated the difference between precontrast (T1- and T2-weighted images) and postcontrast T1-weighted images and for the difference between the precontrast images and the combined evaluation of the precontrast and postcontrast images together for the degree of confidence in diagnosis (CD) and level of conspicuity (LC) for lesion visualization. Images were scored for CD using a scale of 0 to 10, with zero indicating no confidence in the ability to make a diagnosis and 10 indicating 100% confidence in the diagnosis being made. Lesion conspicuity was also scored on a scale of 0 to 10, with zero being not visible (0% visibility) and 10 being highly obvious (100% visibility). Additionally, the diagnostic accuracy, sensitivity, and specificity of lesion detection were determined for the precontrast images, the postcontrast images, and the precontrast and postcontrast images read together. For this evaluation, the final diagnosis made at the clinical site served as the clinical truth.

Statistical methods

Safety

Adverse events were summarized by body system and by age, race, and gender. The number and percent of patients experiencing an adverse event were also evaluated by frequency, severity, and possible relationship to gadoversetamide. At each time point and for each parameter, laboratory values were classified as low, normal, or high relative to normal age-adjusted ranges. Vital signs and ECG data were analyzed using a mixed-model with repeated measures analysis of variance [SAS PROC MIXED with the REPEATED option, version 8.02 (SAS Institute, Cary, NC, USA)]. All comparisons were two-tailed unless otherwise specified, and the significance limit for all analyses was $\alpha = 0.05$.

Efficacy

The efficacy population included all patients who met the protocol-specified inclusion and exclusion criteria, received a dose of gadoversetamide, and completed all required postcontrast MRI sequences. The blinded readers evaluated the MR images under three different circumstances: precontrast images evaluated alone, postcontrast image evaluated alone, and precontrast and postcontrast images evaluated together. The differences in precontrast and postcontrast CD and LC scores constituted the primary basis for gadoversetamide efficacy. Descriptive statistics were calculated for the change in LC endpoints and change in CD. Each image was evaluated by three blinded readers comprising a repeated-measures cluster of size 3. A hypothesis test for mean change of zero was carried out using a mixed-model analysis of variance (SAS PROC MIXED with the REPEATED option, SAS version 8.02). Based on a paired *t*-test, a sample of $n = 30$ patients would give approximately 80% power to detect a 0.50 difference in the pre- to postcontrast mean score, and approximately 90% power to detect a 0.60 difference. A sample size of 70 patients would provide approximately 80% power to detect a 0.35 difference in the pre- and postcontrast mean scores; at approximately 90% power, to detect a 0.40 difference.

The site investigators determined the clinical diagnosis and their degree of CD and LC for each evaluated lesion. If more than one lesion was observed in a single patient, the individual lesion scores for CD or LC were averaged for the patient. When a pathology report was available within 2 weeks after gadoversetamide administration, the pathologic finding was considered the final clinical diagnosis.

The investigator's final clinical diagnosis of presence or absence of a lesion served as the gold standard for sensitivity, specificity, and accuracy of the diagnosis. For the blinded readers, four outcomes were possible relative to the investigators' assessments: true positive, false positive, true negative, and false negative. A GEE model with the binomial distribution and logit link (SAS PROC GENMOD) was used to estimate accuracy, sensitivity and specificity. The model main effects were image sets (pre-T1, pre-T2, post-T1, and combined pre and post). The ESTIMATE option was used to test selected comparisons among image sets. For each image set, least squares means with their associated standard errors and confidence intervals, and differences between dose groups were obtained using the LSMEANS option. Logit Least squares mean estimates were transformed to probability estimates using the inverse logistic transformation.

Results

Study population

A total of 105 patients were enrolled in the study at ten investigative sites. Five of these patients were discontinued from the study prior to receiving

gadoversetamide; two did not require contrast-enhanced MRI, one was unable to be sedated because of an upper respiratory infection, one did not meet protocol diagnostic criteria, and peripheral access was unobtainable for one patient.

The remaining 100 patients received a dose of gadoversetamide and were included in the safety analyses. Two of the 100 patients were not included in postcontrast evaluations; one patient was lost to follow-up, and the other was enrolled twice. This patient was enrolled, withdrew, and then re-enrolled. Thus, the efficacy population consisted of 98 evaluable patients.

Seventy patients were aged between 2 and 11 years (6.4 ± 2.7 years, mean ± SD) and 30 patients were aged between the ages of 12 and 18 years (14.1 ± 1.9 years) (Table 1). A substantial number of these patients had extensive past medical histories, many of which included previous surgeries or known lesions, especially among the older patients. Of the 100 patients who received gadoversetamide, 85 received a concomitant medication. The most frequently administered concomitant medications were for sedation during MRI.

Safety

Safety of the drug was evaluated in 100 patients. For the purposes of the study, an adverse event was defined as any untoward medical occurrence in a subject or clinical investigation, whether or not considered related to the study drug. All of the following observations were determined by site investigators. A total of 44 adverse events were reported, 13 of which occurred in one patient; four (9%) of the 44 adverse events recorded were ruled probably related to gadoversetamide by the investigators; eight (18%) of the 44 were considered possibly related to gadoversetamide; and most adverse events (28/44 or 64%) were ruled unrelated to gadoversetamide by the investigators.

Almost all adverse events (41/44 or 93%) were considered mild by the investigators; the remaining 3/44 (7%) were judged by the investigators to be moderate in intensity. The relationship of gadoversetamide to four adverse events (prolonged QT interval, hypocalcaemia, elevated urinary zinc, and decreased hemoglobin) could not be determined by the site investigators.

One serious adverse event occurred during the study, but according to the site investigator, it was unrelated to gadoversetamide. The patient, who had a history of epigastric pain associated with nausea, vomiting, and irritability, was hospitalized for abdominal pain 11 h after receiving gadoversetamide. The event was considered by the on-site investigator to be moderate in severity and unrelated to gadoversetamide. This patient accounted for 13 of the 44 adverse events observed in this study.

The most common adverse events experienced by the 100 patients in this study, regardless of relationship to gadoversetamide, included injection site reactions and the presence of a prolonged QT interval (>450 ms; Table 2). A prolonged QT interval occurred in three of 100 patients; however, one event occurred prior to the administration of gadoversetamide. There were no deaths, and no patients were discontinued from the study because of an adverse event.

Only four of the 44 adverse events (9%) were considered likely related to the administration of gadoversetamide. Two were mild injection site reactions. One of these patients experienced extravasation of gadoversetamide during injection. The injection was immediately terminated and no further sequelae occurred. A second injection was successfully completed 10 min later, and the patient was able to continue with the study. The other two adverse events

Table 1. *Summary of demographic characteristics for all dosed patients*

Parameter	2–11-year age group $n = 70$	12–18-year age group $n = 30$
Age (years)		
Mean (SD)	6.4 (2.7)	14.4 (1.9)
Range	2–11	12–18
Sex N (%)		
Male	42 (60.0)	18 (60.0)
Female	28 (40.0)	12 (40.0)
Height (cm)		
Mean (SD)	117.1 (22.1)	157.4 (14.4)
Range	45.5–160	126–179
Weight (kg)		
Mean (SD)	26.3 (10.3)	67.4 (28.3)
Range	11.2–57.2	27.3–128.2

Table 2. *Summary of adverse events before and after the administration of gadoversetamide**

WHOART term	Patients $N = 100$ n (%)	Severity			Relationship to drug		
		Mild	Moderate	Unrelated	Unlikely	Likely	Unassessable
Injection site reaction	3 (3)	3		1		2	
Cold sensation	1 (1)		1		1		
ECG abnormal	1 (1)	1		1			
Headache	1 (1)	1		1			
Involuntary muscle contraction	1 (1)	1		1			
Abdominal pain	1 (1)		1	1			
Diarrhea	1 (1)	1		1			
Nausea	2 (2)	2		1	1		
Vomiting	2 (2)	2			2		
Ear disorders NOS	1 (1)	1		1			
QT interval prolonged	3 (3)	3				2	1
Elevated urinary Zn*	2 (2)	1	1	1			1
Hyperglycemia†	1 (1)	1		1			
Hyperphosphatemia*	1 (1)	1		1			
Hyperuricemia	1 (1)	1			1		
Hypocalcemia*	2 (2)	2		1			1
Hypomagnesemia*	1 (1)	1		1			
Hypoproteinemia*	1 (1)	1		1			
Low urine cooper*	1 (1)	1		1			
Low urine Mg*	1 (1)	1		1			
Serum Fe decreased*	1 (1)	1		1			
Serum Zn decreased*	1 (1)	1		1			
Hemorrhage NOS	1 (1)	1		1			
Anemia*	1 (1)	1		1			
Hematocrit decreased*	1 (1)	1		1			
Hemoglobin decreased*	2 (2)	2		1			1
Rhinitis	1 (1)	1					
Rash erythematous	1 (1)	1			1		
Skin reaction localized	1 (1)	1		1			
Cystitis	1 (1)	1		1			
Hematuria	1 (1)	1		1			
Serum creatinine increased	1 (1)	1			1		
Eosinophilia*	1 (1)	1		1			
Lymphadenopathy	1 (1)	1		1			

WHOART = World Health Organization adverse reaction term; NOS = not otherwise specified
*Adverse event occurred in a single patient
†Hyperglycemia occurred in one patient at two measurements during the study: at 2 h and 24 h post-administration of gadoversetamide

involved clinically insignificant increased QT interval. Although identified as prolonged by the investigator, the QT interval did not exceed 410 ms for either patient. Corrected for heart rate, the QTcb increased by 31 ms to 460 ms in one patient and by 15 ms to 430 ms in the second. All four events were considered mild in severity, and none required medical intervention.

Statistical analysis detected significant decreases 2 h after the administration of gadoversetamide but not after 24 h in hematocrit (–1.0 ± 2.4%; $p = 0.0014$ for 2–11-year age group, –1.5 ± 2.1%; $p = 0.0021$ for 12–18-year age group), hemoglobin (–0.4 ± 0.8 g/dL; $p = 0.0008$ for 2–11-year age group, –0.5 ± 0.7 g/dL; $p = 0.0027$ for 12–18-year age group), red blood cells (–0.1 ± 0.3

$\times 10^6/\mu L$; $p = 0.0009$ for 2–11-year age group, $-0.2 \pm 0.2 \times 10^6/\mu L$; $p = 0.0007$ for 12–18-year age group), and monocytes ($-1.5 \pm 1.7/\mu L$; $p < 0.0001$ for 2–11-year age group). Significant decreases in platelets were only observed for the 2–11-year age group ($-13.8 \pm 43.6/\mu L$; $p = 0.0173$) at 2 h after administration. Eosinophils decreased ($-0.3 \pm 1.2/\mu L$; $p = 0.0345$) in the 2–11-year age group 2 h after administration of gadoversetamide. Although these group changes were statistically different from baseline, they were small and not clinically significant. On an individual basis, 21 patients had one or more hematologic parameters outside the normal range. The site investigators determined that all the abnormal values were clinically insignificant, with one exception. One patient experienced a decrease in the hematocrit, hemoglobin, and red blood cell count that were reported as clinically significant events; however, the on-site investigator documented no need to intervene with specific medical treatment or continued laboratory monitoring.

Transient, clinically insignificant changes in laboratory values were observed after the administration of gadoversetamide. Compared with baseline values, serum glucose concentrations increased significantly 2 h (23.9 ± 42.8 mg/dL; $p < 0.0001$ for 2–11-year age group and 21.6 ± 37.7 mg/dL; $p = 0.0045$ for 12–18-year age group), and 24 h (6.4 ± 15.7 mg/dL; $p = 0.0027$ for 2–11-year age group and 16.0 ± 34.4 mg/dL; $p = 0.0163$ for 12–18-year age group) after the administration of gadoversetamide. As patients were not required to fast, the increased serum glucose levels may have resulted from patients eating after the MR procedure. Decreases in the serum calcium concentration occurred 2 h (-0.2 ± 0.5 mg/dL; $p = 0.0004$ for 2–11-year age group) and 24 h (-0.2 ± 0.3 mg/dL; $p = 0.0130$ for 12–18-year age group) after the administration of gadoversetamide. Although these changes were statistically significant, the values remained within the normal range for the patients' ages. At the same time, two patients in the 2–11-year-old group showed an increase in urine calcium (41.5 ± 101.8 mg/dL). Small changes in serum and urinary concentrations of zinc were also observed. Zinc serum concentrations transiently decreased after the administration of gadoversetamide (Figure 1), which corresponded with an apparent increase in the amount of zinc excreted in the urine (Table 3). The small amount of zinc excreted within the 24 h after gadoversetamide administration (mean of 3.8 mg for patients 2–11 years old and 9.2 mg for patients 12–18 years old) represents only a small fraction of the average total body zinc pool (≈40 mg/kg). Other changes in serum chemistries were statistically significant, but none were clinically relevant. No abnormal laboratory values were considered related to gadoversetamide; however, the relationship to the study drug could not be determined by the site investigator for three events (hypocalcaemia, elevated urinary zinc, and decreased hemoglobin).

Statistically significant changes in vital signs were observed, but all were transient and small in magnitude (Table 4). Changes in radial pulse and blood pressure of >20 beats/min or >20 mmHg, respectively, were observed, but in most cases these changes were isolated to measurements taken immediately after MRI. Alterations in heart rate and blood pressure are possibly explained by the fact that most of these changes occurred in the 53 patients who were sedated after baseline readings but prior to imaging.

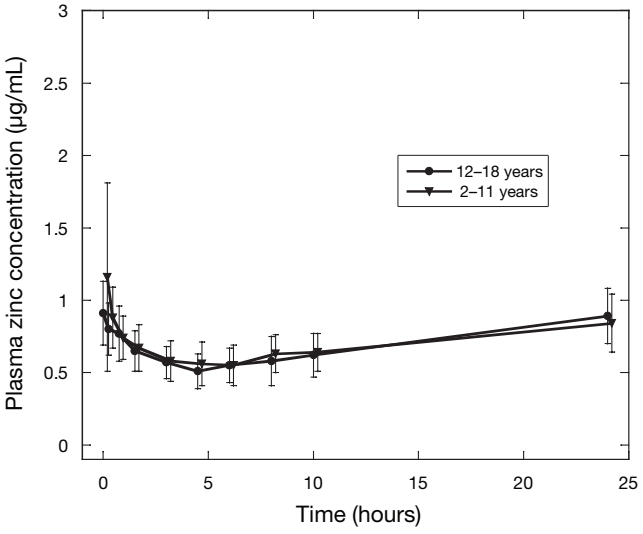

Figure 1. *Plasma zinc concentrations after the administration of gadoversetamide in pediatric patients. No significant ($p < 0.05$) differences occurred between the two age groups*

Table 3. *Cumulative urinary zinc recovery (mg) after the administration of gadoversetamide**

Urine collection periods	2–11-year age group Zinc (mg)	12–18-year age group Zinc (mg)
0–4 h	2.61 (1.07)	6.24 (3.39)
0–8 h	3.27 (1.26)	7.94 (4.11)
0–12 h	3.68 (1.31)	8.80 (3.92)
0–24 h	3.85 (1.36)	9.25 (4.09)

*Values represent the mean (SD)

After the administration of gadoversetamide, the QT interval showed a small, statistically significant increase in duration (Table 5) without the appearance of dysrhythmia or any change in the clinical cardiac status of the patient. During this time, a corresponding and significant decrease in heart rate relative to baseline values occurred. When corrected for heart rate, QTcb showed no significant increase in duration compared to baseline. In addition, the QTcb intervals did not increase more than 60 ms above baseline values for any patient, and the small number of increases between 31 and 60 ms (19 of 275 observations) were not considered clinically significant.

Fifteen minutes after injection of gadoversetamide, the PR interval increased significantly ($p = 0.0124$) compared to baseline (4.3 ± 13.4 ms), in the 2–11 year age group. Although the increase was statistically significant, the change was small and not clinically significant. Four patients experienced a PR interval greater than the age-adjusted normal range, and one patient had a heart rate above the upper limit of normal; neither finding was considered to be of clinical significance. Furthermore, no significant changes in the T wave were observed and no U waves appeared.

Efficacy

The number of lesions and patients with lesions detected by the principle investigator at the study site served as clinical truth. During post-T1 imaging, 84 lesions were detected in 52 patients. A cross section of lesion types were diagnosed by the principle investigators with the top four including astrocytomas, metastases, benign gliomas and post-surgical changes.

Administration of gadoversetamide produced a statistically significant increase in the level of lesion

Table 4. *Change from baseline* statistics for vital signs at times relative to injection†*

Parameter	Baseline	Immediately postimaging	1 h postcontrast	2 h postcontrast	24 h postcontrast
Systolic (mmHg)	108.4 (12.2)	–3.5 (12.2)‡	–2.0 (12.3)	0.5 (13.3)	2.4 (12.5)
Diastolic (mmHg)	62.8 (8.4)	–3.2 (13.0)‡	–0.9 (11.4)	0.2 (10.2)	0.1 (9.4)
Pulse (beats/min)	89.7 (16.3)	–6.1 (14.0)‡	–4.5 (16.3)‡	–0.2 (16.2)	2.5 (16.2)
Respiration (breaths/min)	20.7 (3.2)	–0.2 (4.2)	0.1 (3.5)	0.9 (7.7)	–0.1 (3.2)
Temperature (°C)	36.4 (0.5)	–0.3 (0.6)‡	–0.1 (0.6)‡	–0.1 (0.6)	–0.1 (0.6)

*Change from baseline = postdosing value minus baseline
†Values represent the mean (SD)
‡Statistically significant ($p < 0.05$) change from baseline

Table 5. *Summary of baseline and change from baseline values for ECG parameters*

Parameter	*n*	Mean (SD)	Median	Range	*p*-value*
QT (ms)					
Baseline	99	350.7 (33.1)	354.0	268–462	
15 min postimaging	95	16.9 (27.2)	18.0	–48–88	< 0.0001
2 h postcontrast	99	–1.5 (27.9)	–2.0	–62–86	0.5904
24 h postcontrast	97	–10.4 (24.0)	–12.0	–100–70	< 0.0001
QTcb† (ms)					
Baseline	99	417.2 (17.5)	416	386–509	
15 min postimaging	95	2.1 (17.1)	–1.0	–33–53	0.2303
2 h postcontrast	99	–1.8 (18.5)	–3.0	–62–47	0.3316
24 h postcontrast	97	–3.1 (17.0)	–2.0	–92–41	0.0801
PR (ms)					
Baseline	98	132.0 (18.2)	130.0	98–192	
15 min postimaging	94	2.7 (13.1)	2.0	–34–40	0.0498
2 h postcontrast	98	0.6 (12.2)	2.0	–32–26	0.6134
24 h postcontrast	96	–1.6 (9.6)	–2.0	–30–18	0.1100

**p*-values reflect comparison with baseline
†Corrected QT interval according to Bazett's correction; QTcb = $QT/(RR)^{1/2}$

conspicuity and diagnostic confidence (Table 6). However, the mere presence of contrast alone did not produce an increase in the level of lesion conspicuity or diagnostic confidence. The change in lesion conspicuity and diagnostic confidence occurred only when the precontrast images were evaluated in conjunction with the postcontrast images.

The administration of gadoversetamide significantly increased the accuracy and sensitivity of the blinded readers' ability to determine the presence or absence of a lesion in the pediatric CNS (Table 7). Compared with the precontrast T1-weighted images, gadoversetamide significantly ($p < 0.05$) increased the diagnostic accuracy (73 vs. 82%) and sensitivity (81 vs. 92%) of blinded readers in detecting the presence of a lesion. Improvement in specificity also occurred after gadoversetamide administration (63 vs. 70%), but the changes were small and not statistically significant. Agreement of accuracy scores among the three blinded readers based on the kappa assessment were 0.39 for the pre-T1 images, 0.39 for the post-T1 images and 0.49 when the pre-T and post-T1 images were evaluated at the same time.

Discussion

The results of this study demonstrate that gadoversetamide at a dose of 0.1 mmol/kg is safe and well tolerated in a pediatric patient population 2–18 years of age referred for contrast-enhanced MRI. No serious drug-related or unexpected adverse events or clinically relevant changes in physical examination findings or laboratory values occurred after administration of gadoversetamide. In addition, no clinically significant changes in vital signs or ECG assessments occurred after administration of gadoversetamide.

Gadoversetamide possesses a safety profile in the pediatric population comparable to that in adults. In a meta-analysis of safety data gathered from the clinical development of gadoversetamide in adults, 99/959 (10.3%) of the adverse events were considered related to the study drug or procedure[13].

In this study, only 4/44 adverse events (9%) were related to the study drug. With the exception of a prolonged QT interval, the drug-related adverse events reported in this study were similar in nature and incidence to those reported in studies of other gadolinium-based contrast agents administered to pediatric patients[8–12]. However, extensive analysis of the QT interval was not performed in these studies. Furthermore, the clinical conditions and health status of the pediatric patients in this study could have led to some of the safety outcomes unrelated to the study drug that were reported in this trial. When the safety of gadoversetamide 0.1 mmol/kg was evaluated in healthy pediatric volunteers, there were no adverse events and no clinically significant changes in laboratory values or vital signs[6].

Table 6. *Change in conspicuity level and confidence in diagnosis based on precontrast and postcontrast images*

Comparison	*n**	Mean	Standard deviation	Minimum	Maximum	*p*-value
Conspicuity level						
Post-T1 vs. pre-T1	229	0.41	3.94	–10	10	0.1127
Combined vs. pre-T1	229	0.60	3.76	–9	10	0.0161
Confidence in diagnosis						
Post-T1 vs. pre-T1	135	0.39	2.51	–9	9	0.0713
Combined vs. pre-T1	135	0.66	2.32	–3	9	0.0011

*Three blinded readers analyzed each image set for a total 294 images sets reviewed by the blinded readers. Of those 294 image sets, lesions were found in either the pre- or the postcontrast images for 229 of the image sets. If lesions were not detected a conspicuity score of zero was assigned to the image. Of the 294 image sets read by the blinded readers, lesions were found in both the pre- and postcontrast images for 135 of the image sets. Since images with no lesions were not scored for confidence in diagnosis, comparisons between pre- and postcontrast images could not be made for image sets where a lesion was only detected in either the pre- or postcontrast images

Table 7. *Accuracy, sensitivity, and specificity of lesion detection in the presence and absence of gadoversetamide*

Image set	Accuracy (%)	Sensitivity (%)	Specificity (%)
Pre-T1	72.6	81.3	63.0
Pre-T2	73.5	90.0	54.6
Post-T1	81.8*	92.1*	70.2
Combined image set	80.0	92.3*	66.2

*Significant difference ($p < 0.05$) compared with precontrast T1-weighted images

A prolonged QT interval was identified as an adverse event in three patients by the site investigators. One patient was identified prior to the administration of gadoversetamide. The other two patients had maximum QT intervals of 408 ms and 410 ms, respectively and maximal QTcb increases of 15 ms and 31 ms, respectively at 15 min after injection of gadoversetamide. Actual measurement of the QT interval showed a small but statistically significantly increase in duration for both age groups after the administration of gadoversetamide. During this time, heart rate decreased significantly compared with baseline. Physiologically, the duration of the QT interval varies with changes in heart rate. As heart rate decreases, the duration of the QT interval generally will increase under normal physiological conditions. Upon correction for heart rate variations using the Bazett's method, the QTcb interval did not increase significantly after the administration of gadoversetamide. Studies in adults with different underlying pathologies also showed no significant increase in the QTcb interval after the administration of gadoversetamide at doses up to and including 0.5 mmol/kg (Tyco Healthcare/Mallinckrodt Inc unpublished internal data). In total these data indicate that administration of gadoversetamide does not cause an increase in the duration of ventricular repolarization as measured by the QTcb interval.

As in studies with other gadolinium chelates, gadoversetamide produced minor, clinically insignificant changes in blood and urine levels for zinc and calcium[14,15]. Because the thermodynamic stability constant of zinc for the versetamide ligand is higher ($\log\beta_{101}$ = 11.9) than that of calcium ($\log\beta_{101}$ = 7.73), serum zinc appears to displace calcium associated with the versetamide ligand (Tyco Healthcare/Mallinckrodt Inc unpublished internal data). Thus, the monocalcium monosodium salt of versetamide in the gadoversetamide formulation likely accounts for the observed increases in urinary zinc.

The administration of gadoversetamide, as well as another gadolinium-based agent (gadodiamide), has been shown to cause colorimetric interference with the determination of serum calcium, causing a transient, spurious measurement of hypocalcemia[16-18]. However, the current study utilized an inductively coupled plasma-mass spectrometry method to measure serum and urinary calcium concentrations. The presence of gadoversetamide does not cause an artificial decrease in the measurement of calcium concentration using this analytical method[19].

This study also demonstrated that gadoversetamide increases the ability to diagnose CNS lesions in pediatric patients. The administration of gadoversetamide significantly increased the level of lesion conspicuity. Some lesions not observed on the precontrast T1-weighted images became more conspicuous after administration of gadoversetamide, while some lesions that were easily observed at baseline became less conspicuous with contrast. In both situations, the administration of gadoversetamide played a role in changing the level of lesion conspicuity. Although the mean changes in lesion conspicuity were small, these changes significantly impacted the sensitivity and accuracy of detecting the presence or absence of a lesion.

The administration of gadoversetamide significantly increased confidence in diagnosis. Evaluations by the blinded readers and an analysis of the study site data demonstrated a small but statistically significant increase in diagnostic confidence after administration of gadoversetamide. The principal investigators at the study sites also found significant improvements in diagnostic confidence level that were larger, on average, than those observed by the blinded readers. These data suggest that under normal clinical conditions, where the physician knows patient history and presenting conditions, contrast plays a role in confirming a diagnosis and provides greater confidence in making that diagnosis.

Several limitations occurred during the conduct of the study. Baseline measurements of clinical chemistries, vital signs and ECG took place prior to the sedation. The absence of values collected after sedation and prior to contrast administration make it difficult to differentiate effects produced by sedation and those possibly caused by the presence of gadoversetamide. This study used only a single dose of gadoversetamide (0.1 mmol/kg). In adults higher doses of gadolinium contrast agents have proven beneficial in detecting small lesions in the CNS[20]. Higher doses of gadoversetamide may have increased the efficacy of detecting CNS lesions in the pediatric population. Finally, patients younger than 2 years of age were not included in the patient population.

Conclusion

This study demonstrated gadoversetamide to be safe and well-tolerated in this population (age 2–18 years) at a dose of 0.1 mmol/kg. Gadoversetamide produced no serious or unexpected adverse events, or changes in laboratory parameters. No unexpected adverse events, changes in physical exams or detrimental changes in vital signs or ECG parameters occurred after the administration of gadoversetamide.

The data from this study indicate that gadoversetamide provides clinical utility when used in a pediatric patient population of 2–18 years of age. The level of lesion conspicuity and confidence in diagnosis increased significantly after the injection

of gadoversetamide. In addition, the administration of gadoversetamide significantly increased accuracy and sensitivity of MR image diagnosis of a CNS lesion.

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