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S. Hanquinet
C. Christophe
D. De Greef
P. Gordon
N. Perlmutter

Clinical evaluation of gadodiamide injection in paediatric MR imaging

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S. Hanquinet (✉)
Department of Radiology,
Hôpital Universitaire Cantonal de
Pédiatrie, Rue Willy Donzé, 6
CH-1211 Genève 14, Switzerland

S. Hanquinet · C. Christophe · N. Perlmutter
Children's University Hospital Reine
Fabiola, Brussels, Belgium

D. De Greef
Nycomed SA/NV, Brussels, Belgium

P. Gordon
Nycomed Imaging AS, Oslo, Norway

Abstract The safety and efficacy of intravenous gadodiamide injection, 0.1 mmol/kg body weight, have been evaluated in an open label, non-comparative as to drug, phase III clinical trial in 50 children from 6 months to 13 years of age, referred for MRI requiring the injection of a contrast medium. The central nervous system and other body areas were examined with T1 sequences before and after intravenous injection of the contrast medium. Overall safety was very good and no clinically relevant changes were evident as regards heart rate and venous blood oxygen saturation after injection. No adverse event or discomfort was experienced by conscious patients that could with certainty be related to the contrast medium, but slight movements were observed in two sedated patients that could be related to the injection. Comparing pre- and post-injection images, additional diagnostic information could be obtained from the latter in 41 patients (82 %). In these images, the number of lesions detected increased and they were generally better delineated and their size more easily estimated. The results of this trial indicate that gadodiamide injection is safe and effective for MRI examinations in children.

Introduction

Magnetic resonance imaging (MRI) is a modality that is increasingly used in the evaluation of neurological, musculoskeletal, abdominal, mediastinal and cardiovascular lesions or pathology in the paediatric population. Although the technique has high sensitivity as regards the detection of pathological changes, the need for paramagnetic MRI contrast agents has become widely recognised, also in neonates and young children [1–4]. The potential gains, however, must be balanced against the effects of administering a drug during an otherwise uninvasive examination procedure, including potential toxicity. In a paediatric population, safety and patient tolerance are especially important considerations, thus, the use of safer, non-ionic contrast media might be considered of benefit, also for MRI [5].

Gadodiamide injection (Gd DTPA-BMA; OMNISCAN, Nycomed Imaging AS, Oslo, Norway) is a non-ionic chelate of gadolinium. It has been shown to be safe and effective at all doses and for all indications investigated in adults [6–8]. As part of the paediatric programme of gadodiamide injection, we performed an open phase III clinical evaluation of its safety and efficacy in children referred for MRI examination of the central nervous system (CNS) and other body areas.

Materials and methods

Fifty children (25 girls and 25 boys) were enrolled in the study. They were referred for MRI involving the injection of contrast medium for the evaluation of suspected benign or malignant tumours or lesions, or for evaluation after surgery. The study was approved by the hospital's medical ethics committee, and parental informed consent was obtained in each case before inclusion of the child in the trial.

The patients were between 6 months and 13 years old. Nine patients were less than 2 years of age, and the mean age was 6.2 years. The region of interest was the CNS in 18 patients, the abdomen in

Table 1 Clinical indication for the MRI examination and number of cases where the injection of contrast medium was absolutely necessary to provide the diagnosis or exclude the suspected pathology

Clinical indication	No. of patients referred	No. of cases with absolute need for contrast medium injection
Central nervous system		
Infection	3	1
Epilepsy	3	2
Suspected mass	12	2
Head and neck		
Mass	7	1
Thorax to abdomen		
Mass	11	4
Elbow		
Infection	1	1
Knee		
Infection	5	2
Mass	2	1
Trauma	1	–
Suspected aseptic necrosis	1	1
Tibia		
Mass	2	1
Foot		
Infection	1	–
Mass	1	–
Total	50	16

11, the head and neck in 7 and various areas of the limbs in 14 (Table 1). Twenty-five patients received premedication: 1 patient received diazepam (Valium); 6 patients younger than 1 year or weighing less than 12 kg were sedated with chloral hydrate (80 mg/kg via a nasogastric tube); 15 patients older than 1 year were sedated with sodium pentobarbital (Nembutal; 5–7 mg/kg rectally) and droperidol + fentanyl (Thalamonal; 1 ml/40 kg intramuscularly); 3 patients were examined under general anaesthesia.

Gadodiamide injection was administered intravenously through a connecting tube at a dose of 0.1 mmol/kg body weight (b.w.; 0.2 ml/kg). The volume injected was not to exceed 20 ml (mean 4.75 ml, range 1.5–14.0 ml) and the injection was completed within 1 min (mean 32 s). Saline flush was always performed. No injection problems were encountered. Safety was evaluated by recording injection-associated discomfort/distress and adverse events, and by monitoring heart rate and venous blood oxygen saturation. Injection-associated discomfort was defined as a transient sensation of warmth or coolness anywhere in the body and pressure or pain at the site of injection occurring during the administration of the contrast medium. Only patients who were not sedated were observed for such discomfort. In sedated patients, distress was defined as any sign of feeling unwell observed by the staff that was considered to be related to the injection. Heart rate and venous blood oxygen saturation were recorded before the first imaging sequence, immediately before, immediately after and 2 min after the injection of contrast medium, and after the last post-contrast sequence was completed. The patients were closely followed for up to 24 h after the MRI examination, and any adverse events that occurred were recorded.

Imaging was performed on a 0.5-T system. T1-weighted images were obtained before and immediately after the administration of gadodiamide injection in at least one plane. The main parameter used for the statistical analysis was the change in heart rate induced by the gadodiamide injection, i.e. to establish whether injection of gadodiamide influenced heart rate in children. The factors of sedation, age and baseline heart rate were evaluated to establish whether they had any statistically significant impact on the change. The analysis revealed an interaction between sedation and change in heart rate over time. The mean change and associated 95 % confidence intervals were therefore calculated separately for the sedated and non-sedated patient groups.

Results

Clinical safety evaluation

No serious adverse events were reported following the administration of gadodiamide injection at a dose of 0.1 mmol/kg. Slight movements were observed in two sedated patients in connection with the injection and were recorded as distress. Two patients experienced one adverse event each that was considered of uncertain relationship to the contrast medium: one patient aged 11 years had mild headache that started about 4 h after the injection, lasted for 14 h and needed analgesic medication; another patient aged 6 months presented cutaneous flush of moderate intensity 30 min after injection that lasted for 10 min and regressed without medication.

No individual changes in heart rate were considered by the investigator as clinically relevant. The statistical analysis performed on heart rate data obtained from the entire trial population revealed no overall variation over time ($P = 0.63$). Thus, there was no significant effect of the administration of gadodiamide injection on heart rate. However, the interaction between sedation status and change in heart rate over time was statistically significant ($P = 0.008$), indicating statistically different patterns for the changes in the sedated and non-sedated groups. A slight increase of the mean heart rate was observed from immediately before to 2 min after injection in the sedated group, while an equivalent decrease was observed in the non-sedated group. The difference is of no clinical concern. It is indeed very small (3 to 4 beats per minute) and concerns mean values for patients with a wide range of ages. The changes in venous blood oxygen saturation were small and none was considered clinically relevant.

Image evaluation

Abnormal structures, tumours or lesions were identified before and after injection of contrast medium in 40 patients and either before or after injection in 42 patients. In 18 cases there was a tumour and 24 cases had a non-

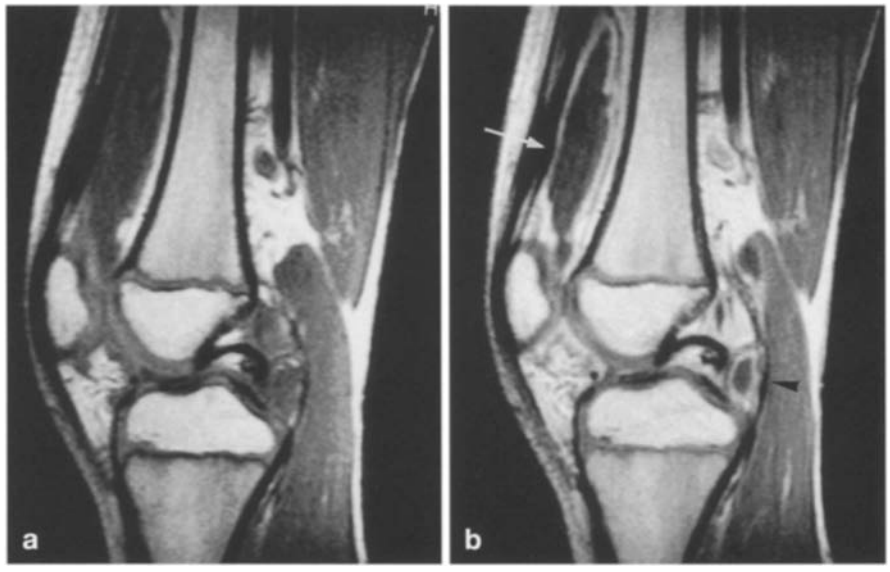

Fig. 1a, b Patient aged 11 years with swelling of the knee without trauma. The post-injection diagnosis was of juvenile rheumatoid arthritis. **a** T1-weighted images without contrast enhancement showing suprapatellar synovial effusion. **b** After contrast medium injection, there is high contrast enhancement of the synovial hypertrophy *(white arrow)* with suprapatellar synovial effusion and formation of synovial cysts *(black arrow)*

tumorous lesion. Contrast enhancement was seen in the region of interest in 35 of 50 patients. More diagnostic information was acquired in 41 patients following injection of contrast medium, and the additional information was considered to be of marginal, moderate and significant help in 11, 9 and 21 cases, respectively. Representative examples of how the use of contrast enhancement provided significant help in diagnosis are presented in Fig. 1 and 2. The use of gadodiamide injection assisted in the evaluation of tumour/lesion size in 21 patients. In eight cases (16 %), lesions were seen after but not before contrast medium injection. Four lesions were partly or wholly obscured after injection because they were located near bone marrow or fat; one such case is presented in Fig. 3 for example. New information that affected management was gained in 16 patients (32 %) and the clinical diagnosis was modified following injection in 13 patients (26 %). With the clinical indications encountered in this trial, and balancing all the diagnostic information obtained, the use of contrast medium was retrospectively found absolutely necessary to provide the diagnosis or exclude the suspected pathology in 16 patients (32 %; Table 1). A diagnosis by surgery, biopsy or other techniques was subsequently available in only eight patients. The post-injection diagnosis was confirmed in seven cases. In the eighth case, a patient who presented a mass in the tongue, the post-injection images suggested a dermoid cyst but surgery revealed an ectopic salivary gland.

Discussion

Gadodiamide injection is, like other extracellular MRI contrast media, freely distributed to the extracellular space and is excreted through the kidneys at a rate dependant on the glomerular filtration rate (GFR) [9, 10]. In children about 6 months of age and older, both GFR and the relative volume of the extracellular space are comparable to those in adults and the elimination of injected gadodiamide is assumed to be as in adults. On T1-weighted images, the contrast enhancement is mainly due to redistribution from the vascular compartment into the extracellular space by perfusion in the tissues. In the CNS, enhancement is possible in areas of breakdown of the blood-brain barrier and in lesions with abnormal vascularity.

The imaging characteristics of gadodiamide injection used in these 50 children at a dose of 0.1 mmol/kg b. w. appear to be similar to those of the other gadolinium-based paramagnetic contrast media. The usefulness of the product for MRI of the body, including CNS, was demonstrated in that additional information helpful in making the diagnosis was obtained in 41 patients (82 %). In these patients lesion conspicuity, evaluation of lesion size and margins and identification of tumour recurrence were improved following the injection of contrast medium. The number of detected lesions was also increased. On the images with contrast enhancement the vascular or inflammatory nature of the lesions appeared clearly and the abscesses were better identified through a typical annular signal enhancement. Injection of contrast medium allows precise pre-operative anatomic evaluation of a mass and also provides information on the vascularity of the lesion and possible invasion of adjacent structures or vessels. Injection of a contrast medium appears to be absolutely necessary in the follow-up of operated tumours, even though differentiation between inflammatory reaction and tumour recurrence may be difficult on contrast-enhanced im-

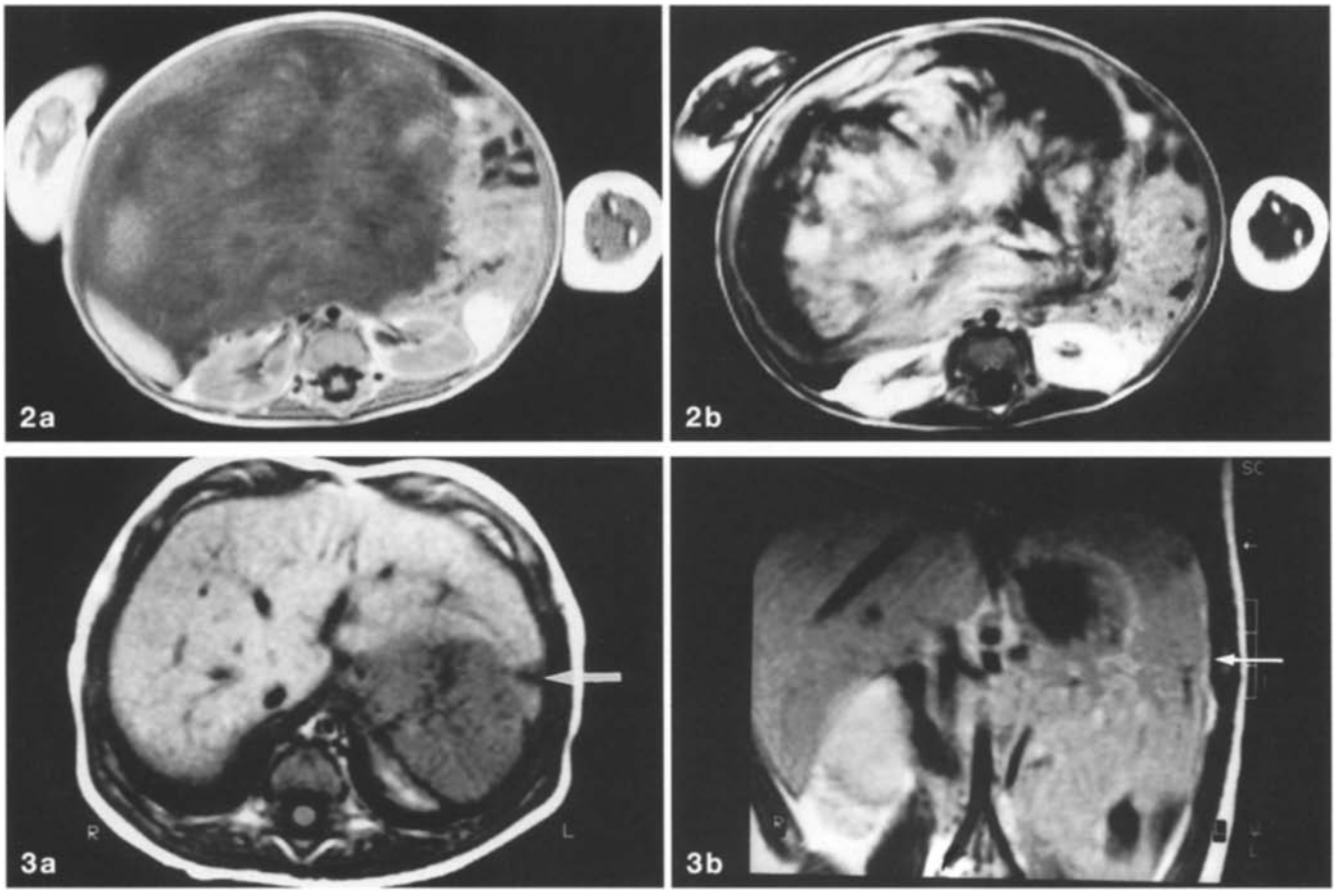

Fig. 2 a, b Patient aged 6 months with abdominal distension and constipation. The diagnosis of rhabdomyosarcoma was provided by anatomic pathology. **a** T1-weighted image without contrast enhancement showing a voluminous mass of low signal intensity. **b** After contrast medium injection there is better delineation and heterogeneous contrast enhancement showing diffuse vascularisation of the lesion and the presence of necrotic areas

Fig. 3 a, b Follow-up of a patient aged 9 months treated by chemotherapy and surgery for an abdominal rhabdoid tumour. **a** Axial T1-weighted image without contrast enhancement showing the presence of a metastasis with hyposignal *(white arrow)* in the left lobe of the liver. **b** After contrast medium injection (coronal plane), the metastasis *(white arrow)* becomes isointense with the normal liver parenychyma and is no longer visible

ages in the early post-operative stage. Dynamic imaging or follow-up examinations are required.

In one-third of our patients injection of contrast medium was retrospectively found absolutely necessary to assure certain diagnosis. The safety of the product, as evaluated by recording adverse events and changes in heart rate and venous blood oxygen saturation, was very good. These results are similar to those obtained with gadodiamide injection in adults and in a first experience in children [11].

In conclusion, our findings emphasise the need for contrast medium injection in the evaluation of known or suspected tumours or lesions in children. The results of this phase III clinical trial show that gadodiamide injection is both effective and safe in children and adolescents for MRI examinations of the CNS or other body areas.

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