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Pregled
Review

GADOLINIUM-BASED CONTRAST AGENTS IN PAEDIATRIC POPULATION: A REVIEW

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With the advancement of technology and development of magnetic resonance imaging, a major turning point in the field of radiology occurred in the twentieth century. Visualization of all parts of the human body was greatly facilitated while maintaining excellent spatial resolution without the use of ionizing radiation. In the pediatric population, this method is especially useful in the evaluation of the brain, thorax, abdomen, pelvis, and extremities. This is one of the first methods of choice for younger patients due to the non-use of ionizing radiation. Magnetic resonance contrast agents are used to increase the contrast of the obtained image and better resolution. The most used contrast agents include Gadolinium-Based Contrast Agents, whose first application took place in 1983. According to their molecular structure, they are divided into linear and macrocyclic, and in addition, they can be divided into ionic and nonionic. Macrocyclic compounds are generally considered safer due to the lower rate of dissociation of the free gadolinium ion, which is toxic in this form. Gadolinium-Based Contrast Agents have long been believed to be completely safe, but their association with nephrogenic systemic fibrosis was observed in the 2000s, after which the focus was on the use of macrocyclic compounds in pediatric patients for proven safety. In addition to the mentioned side effects, the development of acute allergic reactions is also possible, and more recently, findings on the deposition of gadolinium in tissues have been discovered. Despite the very low rate of all these side effects in pediatric patients, their long-term safety and use in the neonatal age has not yet been established. Precisely because of this, they should be applied with caution, with an emphasis on the application of the lowest possible doses, the use of macrocyclic chelates and a good risk assessment. This review paper collects and analyses so far published research on Gadolinium-Based Contrast Agents in the pediatric population.

Keywords: CONTRAST AGENTS, GADOLINIUM, MAGNETIC RESONANCE IMAGING, PAEDIATRIC PATIENTS

INTRODUCTION

With the advancement of technology and development of magnetic resonance imaging (MRI), a major turning point in the field of radiology occurred in the twentieth century. Visualization of all parts of the human body was greatly facilitated while maintaining excellent spatial resolution while not using ionizing radiation. Magnetic resonance imaging in the pediatric population is a useful method in the evaluation of numerous conditions in pediatric patients, such as congenital abnormalities, chronic diseases of the central nervous system, inflammatory bowel disease, joint infections, tumors and many more. This is one of the first methods of choice for younger patients due to the non-use of ionizing radiation. However, before performing the examination itself, it is necessary to consider information about the child's health problems, used medications, recent operations, if the patient has embedded medical or electronic devices and the existence of allergies (1).

MRI is associated with possible complications, which can be classified into several categories: biological effect of non-ionizing electromagnetic fields, risk for hearing due to loud noises during the examination, injuries due to ferromagnetic devices, risk of sedation or general anesthesia - the main short-term risks are insufficient or excessive. Other side effects include possible pulmonary complications, and currently not enough is known about all possible long-term effects, length of examination and finally the risk of Gadolinium-Based Contrast Agents (GBCA) (2).

GBCAs are the most commonly used contrast agents in magnetic resonance imaging due to gadolinium's high magnetic moment and the fact that its compounds are the most stable ions with unpaired electrons. The signal intensity of individual tissues in MRI depends on the relaxation of water protons and is reflected in the values of T1, T2 and T2*. GBCAs shorten T1 and T2 relaxation times (due to acceleration of proton relaxation in the body), creating a higher signal and better contrast between tissues of similar magnetic characteristics. The result is increased intensity on T1 (hyperintensity) and decreased intensity on T2 images (hypointensity), with the fact that their effect is more pronounced on T1 temporal relaxation while using diagnostic doses. Consequently, their effect is visible only on T1 images. Gadolinium, as a contrast, is retained extracellularly and does not enter the cells (preferably due to the toxic properties of gadolinium, especially in the case of chelates with low molecular stability). Its characteristic is rapid passage through vascular spaces and going into the extracellular or interstitial space. Gadolinium compounds are almost completely excreted by the kidney (through glomerular filtration >80% in the first three hours, and >94% in 24 hours), and those that bind to plasma proteins and enter hepatocytes partly also via bile. Application of these compounds is done intravenously or enterally, less often locally (3, 4). According to their molecular structure, they are divided into linear and macrocyclic, and in addition, they can be divided into ionic and nonionic (shown in Table 1). Macrocyclic compounds are generally considered safer due to the lower rate of dissociation of the free gadolinium ion, which is toxic in this form. GBCAs have long been believed to be completely safe, but their association with nephrogenic systemic fibrosis (NSF) was observed in the 2000s, after which the focus was on the use of macrocyclic compounds in pediatric patients for proven safety and stability.

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The aims of this work were to show the incidence of acute and late reactions of GBCA in pediatric patients, including the deposition of gadolinium in the brain tissue of children, to demonstrate the safety of currently approved extracellular macrocyclic gadolinium compounds and to describe the specifics and safety of linear gadolinium for liver imaging of children.

METHODS

The review article included the latest relevant studies on the safety of GBCAs. The database that was predominantly searched was PubMed/Medline, and along with it, other Internet platforms were used if useful material was found. The reference list within each article was checked in order to find additional articles.

The searched literature was chosen based on the criterion that it includes the pediatric population, but occasionally it was compared with the adults if significant findings were present. Selected sources with the latest knowledge and guidelines were divided into four categories that included acute and late side effects, gadolinium accumulation in the brain, safety of currently approved macrocyclic compounds and gadolinium for liver imaging, and were presented in tables.

RESULTS

Several studies have been conducted on a large number of pediatric patients on the incidence and type of side effects after the use of GBCA in children. Forbes-Amrhein et al conducted a study on large population with the aim of determining the frequency and severity of acute allergic reactions; incidence of adverse events was 0.06%, with no significant differences regarding the frequency of occurrence and the type of contrast agent used (5). Most of reactions were mild (47.6%), such as urticaria/pruritus and skin edema, itching/scratching in the throat, nasal obstruction, sneezing, conjunctivitis, and rhinorrhea. Moderate reactions (47.6%) included diffuse urticaria/pruritus, diffuse erythema, facial edema without dyspnea, throat tightness or hoarseness also without dyspnea, and bronchospasm with mild or no hypoxia. Severe reactions (4.8%) included: diffuse edema or facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing or bronchospasm, significant hypoxia and anaphylactic shock. No death was reported related. In conclusion, the most of the reactions (95%) in this study refer to those of mild or moderate severity, and the only chelate that caused a severe reaction was gadoterate, Table 2.

In the study by Dillman et al. mild acute reactions accounted for 74%, 10% were moderate reactions, and 7% were severe reactions, which included convulsions, arrhythmias and cardiopulmonary arrest (6). As in the previous study, no deaths were recorded. Acute allergic reactions were more common in adult patients (0.07%) than in pediatric 0.04%. Also, it was observed that 63% of female patients in the adult and 83% in the pediatric population experienced acute reactions, while the figure for men was significantly lower (35% as the sum of adult and pediatric patients); the reason for this gender difference is still not revealed, Table 2.

A retrospective study by McDonald et al. reported 17 allergy-like reactions (0.10%), of which 13 were mild (rash, throat discomfort, and nasal or eye symptoms), and 4 were moderate (difficulty breathing), and 23 physiological reactions (0.14%), all were of mild severity such as nausea, vomiting, vasovagal symptoms, flushing or chills (7). As in

Table 1.
List of Gadolinium-Based Contrast Agents

Trade (chemical) name	Structure (use)
Dotarem (gadoterate meglumine)	Macrocyclic ionic (intravenous, intra-articular)
ProHance (gadoteridol)	Macrocyclic non-ionic (intravenous)
Gadovist (gadobutrol)	Macrocyclic non-ionic (intravenous)
Magnevist (gadopentate dimeglumine)	Linear ionic (intravenous, intra-articular)
MultiHance (gadobenate dimeglumin)	Linear ionic (intravenous)
Omniscan (gadodiamide)	Linear non-ionic (intravenous)
OptiMark (gadoversetamide)	Linear non-ionic (intravenous)
Primovist (gadoxetate)	Linear ionic (intravenous)

previous investigations, no deaths were recorded. The incidence of acute allergic reactions was significantly higher after gadobenate compared to gadodiamide (0.49% vs. 0.04%) and slightly higher after gadobutrol compared to gadodiamide (0.14% vs. 0.04%), but in physiological reactions no significant difference was found. The higher the age of the subject, the greater the risk for allergic reactions (0.14% → 12-17 years compared to 0.07% → 2-12 years), and significantly more for physiological reactions (0.26% → 12-17 years compared to 0.03% → 2-12 years) was observed. As mentioned in the previous study, a higher incidence of reactions was observed in female patients compared to the male population (0.12% vs. 0.08%), Table 2.

In the last decade, gadolinum deposits in the brain tissue were confirmed by several independent researces. In the study by Stanescu et al. the highest levels of gadolinium deposition were found in patients who were repeatedly exposed to gadolinium linear ionic contrast agents (gadopentetate dimeglumine) and macrocyclic nonionic compounds (gadobutrol and gadoteridol) (8). In those patients who received <5 doses during their lifetime, significantly less deposition was observed in contrast to those who exceeded this number. Study by Ryu et al. found greater change in the pons with gadodiamide compared to gadopentetate dimeglumine, while no significant difference in the change in the thalamus was observed (9). This indicates an increased risk with linear nonionic compounds compared to linear ionic ones. In the study by Roberts et al. presented a case of 13-year-old girl who underwent routine MR imaging every 12 months using only gadopentetate dimeglumine (10). On the initial MR imaging of the brain, the cerebellum and globus pallidus had a normal appearance, but, after 6 doses of contrast agent hyperintensity was observed bilaterally in the nucleus dentatus and globus pallidus. Study by Towbin et al. indicated that there was a notable increase in the T1 signal with a greater number of contrast applications (11). The effect of gadoterate, a macrocyclic compound was studied by Topcuoglu et al., who showed that three applications of this macrocyclic compound were required to produce a measurable level of gadolinium retention in the brain (12). In an animal study, it was shown that gadoterate meglumine accumulates not only in the cerebrum, but also in the femur and kidneys. On the other hand, Tibussek et al. studied the accumulation of gadolinium after the application of gadoterate and gadoteridol, even after multiple intravenous applications did not observe the association of these GBCA with hyperintensity in T1 sequences (13). A study by Bhargava et al. found no correlation of a macrocyclic compound, in this case gadobutrol, with the side effect of its accumulation in the brain tissue of pediatric patients (14). Among 46 children who received five or more

Table 2.
List of studies that investigated acute and late side effects

First author, year	Number of respondents	Age	Sex	Contrast agents	Main results
Forbes-Amrhein MM, 2018 (5)	32365 applications of GBCA	0-17 y mean age → 11,4 ± 3,8	M → 17.156 (53%) F → 15.209 (47%)	- gadofosveset trisodium (Ablavar) - gadoxetate (Eovist) - gadoterate (Dotarem) - gadopentetate dimeglumine (Magnevist)	- 21 acute allergic-like reactions (without differences in type of contrast agent used) - Most reactions (95%) refered to mild or moderate, and only gadoterate caused a severe reaction - The overall incidence of acute allergic reactions was 0.06% - Reactions → M > F - No deaths
Dillman JR, 2007 (6)	78353 applications of GBCA, of which 13344 were related to children	Pediatric (<19 years) and adult patients)	M → 46% F → 54 %	- gadopentetate dimeglumine (Magnevist) - gadobenate dimeglumine (MultiHance) - gadodiamide (Omniscan)	- Mild acute reactions were the most common (74%) - Acute allergic reactions were more common in adult patients - Reactions → F > M - No deaths
McDonald JS, 2021 (7)	10190 patients that underwent a total of 16237 GBCA applications	< 18 y mean age → 12	M → 2.208 (51%) F → 7.982 (49%)	- gadodiamide (Omniscan) - gadobutrol (Gadovist) - gadobenate dimeglumine (MultiHance)	- 0.10% acute allergic reactions and 0.14% physiological reactions - Higher incidence with the application of gadobutrol and gadobenate compared to gadodiamide - Older patients were at a higher risk - Reactions → F > M - No deaths

Table 3.
List of studies investigating GBCA accumulation in the brain

First author, year	Number of respondents	Age	Sex	Contrast agents	Main results
Stanescu AL, 2020 (8)	10	1-13 y mean age → 7	M → 7 F → 3	- gadopentetate dimeglumine (Magnevist) - gadoteridol (ProHance) - gadobutrol (Gadovist) - gadofosveset trisodium (Ablavar) - gadoterate (Dotarem)	- The highest levels of deposition in patients who were repeatedly exposed to linear ionic GBCA (gadopentetate dimeglumine) and macrocyclic nonionic compounds (gadobutrol and gadoteridol) - The highest level of deposition was in the globus pallidus - In patients who received <5 doses, significantly less deposition was observed in contrast to >5 doses
Ryu YJ, 2018 (9)	92	1 month to 14 y mean age → 6.4 ± 4.6	M → 59 F → 33	- gadodiamide (Omniscan) - gadopentetate dimeglumine (Magnevist) - gadoterate (Dotarem)	- When using gadodiamide, a significantly greater change in the pons was observed compared to gadopentetate dimeglumine, while no significant difference in the change of thalamus was observed - Increased risk with linear nonionic compounds compared to linear ionic ones - Macrocyclics did not cause increased gadolinium accumulation
Roberts DR, 2016 (10)	1	13 y	1 F	- gadopentetate dimeglumine (Magnevist)	- After 4 doses of GBCA → subtle hyperintensity of the dentate nucleus on the T1 image - By the fifth dose → hyperintensity was clearly present within the nucleus dentatus - By the sixth dose → hyperintensity was observed bilaterally in the nucleus dentatus and globus pallidus
Towbin AJ, 2021 (11)	50	< 18 y mean age → 6.4	M → 25 F → 25	- gadopentetate dimeglumine (Magnevist)	- Significant increase in T1 signal with a greater number of contrast applications - Sex, age and strength of the MRI field are not related to the change in signal intensity ratio, however the type of MRI sequence as well as the brand of the device showed differences
Topcuoglu ED, 2020 (12)	45	5-17 y mean age → 13.7 ± 3.4	M → 23 F → 22	- gadoterate (Dotarem)	- To reach a detectable level of gadolinium retention in the brain, this macrocyclic compound had to be applied three times
Tibussek D, 2017 (13)	24	5-18 y mean age → 12.71	M → 9 F → 15	- gadoteridol (ProHance) - gadoterate (Dotarem)	- Even after multiple intravenous administrations, association of GBCA with hyperintensity in T1 sequences was not observed
Bhargava R, 2018 (14)	91	0-17 y mean age → 5.4	F and M	- Gadobutrol (Gadovist)	- No correlation of gadobutrol with the side effect of its accumulation in the brain tissue of pediatric patients was found
Young JR, 2018 (15)	10 (gadoteridol) - 9 (gadodiamide)	<10 y mean age: → 5.6 (gadoteridol) - → 9.6 (gadodiamide)	M → 7 F → 3 (gadoteridol) - M → 5 F → 4 (gadodiamide)	- gadoteridol (ProHance) - gadodiamide (Omniscan)	- The mean signal intensity ratio in the gadoteridol group did not significantly alter, whereas the mean signal intensity in the gadodiamide group significantly increased

doses of gadobutrol, no change in signal intensity ratio of the globus pallidus or nucleus dentatus was observed, nor among six children who underwent more than 14 doses of gadobutrol. The effect of gadoteridol was described in the study by Young et al. and a comparison of its safety in terms of gadolinium retention compared to the linear gadodiamide was performed (15). The mean signal intensity ratio did not significantly alter in the group that received gadoteridol, whereas the mean signal intensity of the specified area significantly increased in the group that received gadodiamide.

Table 4.
List of studies investigating safety of currently approved macrocyclic compounds

First author, year	Number of respondents	Age	Sex	Contrast agent	Main results
Chang D-H, 2019 (16)	1631	< 18 y mean age → 10.2 ± 4.9	M → 872 (53,5%) F → 759 (46,5%)	- gadoterate (Dotarem)	- Only one reaction after gadoterate application (vomiting of mild intensity) - The most frequently reported side effects → vomiting and nausea, followed by urticaria and itching - No NSF
Balassy C, 2015 (17)	3810	<18 y	M and F	- gadoterate (Dotarem)	- In children aged 2 to 6 years → itching, headache and dizziness - In children aged 6 to 12 years → hematuria and vomiting - In children aged 12 to 17 years → asthenia, urticaria and nausea
Scala M, 2018 (18)	45	<2 y mean age → 9.9 ± 7.4 months	M → 22 (48.9%) F → 23 (51.1%)	- gadoterate (Dotarem)	- The most commonly reported side effects → pyrexia, leukopenia, while the rest were related to gastrointestinal disorders - The majority of adverse effects (61.5%) were of mild intensity, 38.5% of them were moderate, and none of the more severe form was recorded - Regarding hematology and biochemical parameters → slight decrease in the mean values of erythrocytes, hemoglobin, leukocytes, lymphocytes, platelets, aspartate transaminase, alanine transaminase, alkaline phosphatase and lactate dehydrogenase was observed, however, it is not considered clinically significant
Farmakis SG, 2020 (19)	150	<2 y mean age → 12.1 months	M → 84 (56%) F → 66 (44%)	- gadoterate (Dotarem)	- Vomiting (8.7%), transient flushing or warmth (5.3%) and nausea (4.7%) - Other physiological reactions → dizziness (0.7%) and altered taste (0.7%) - Two allergy-like reactions were recorded in 2 patients (sneezing and non-specific sounds when breathing) - None of these reactions could be attributed solely to gadoterate meglumine due to previously used sedative agents - The majority of reported side effects were of mild intensity and physiological in nature, consistent with the most commonly reported adverse events in previous studies, however the overall adverse event rate including both immediate and late reactions was 15.3% and it is higher than those previously recorded in the literature
Emond S, 2011 (20)	104	< 18 months mean age → 8.1 months	M → 58 (55.8%) F → 45 (43.3%)	- gadoterate (Dotarem)	- No cases of acute adverse reactions, as well as the occurrence of NSF, were recorded
Glutig K, 2016 (21)	1142	< 18 y	M → 604 F → 538	- gadobutrol (Gadovist)	- Individual adverse events included vomiting, nausea, urticaria, dyspnea, and eyelid edema; no serious side effects were reported - No skin reactions were recorded in any case, which would indicate NSF - The severity of all side effects reported in this study ranged from mild to moderate.
Glutig K, 2019 (22)	3710 patients (404 children)	All ages	M → 1664 F → 2008	- gadobutrol (Gadovist)	- Regarding pediatric patients in the group (younger than seven years) → no adverse effects of gadobutrol were recorded - The only recorded side effect was in a 14-year-old patient with a suspected brain tumor → burning sensation along the forearm immediately after applying GBCA and a headache lasting 5 minutes

First author, year	Number of respondents	Age	Sex	Contrast agent	Main results
Kunze C, 2016 (23)	44	< 2 y mean age → 8.8 months	M → 26 F → 18	- gadobutrol (Gadovist)	- Most side effects after administration → mild symptoms that include cough, pyrexia, nasopharyngitis, rhinitis and vomiting - One subject had vomiting of mild intensity - No clinically significant changes in laboratory parameters were observed, as well as changes in vital signs and heart rhythm
Shah CC, 2021 (24)	125	<2 y mean age → 8.1 months	M → 70 F → 55	- gadoteridol (ProHance)	- Six of them (4.8%) experienced 11 side effects during the 48-hour follow-up period after the application itself - Almost all side effects were related to laboratory values → elevated platelet levels, mildly decreased hemoglobin, mildly decreased hemoglobin and erythrocyte counts, moderately decreased platelet levels and mildly elevated blood chloride - All events are not directly correlated with gadoteridol, but there is a possibility that they are caused by the general poor condition of the patient or the pathology from which he suffers
Maximova N, 2016 (25)	21	2-17 y mean age → 10	M → 15 F → 6	- gadoterate (Dotarem)	- The amount of gadolinium in the liver and the total dose of GBCA that was administered correlated positively in each of the 21 cases - The amount of gadolinium and iron in the liver were also found to be positively correlated - Gadolinium levels in the liver were reduced in deferoxamine-treated patients → additional research is required to determine the safety in patients with iron excess and severe siderosis
Jurkiewicz E, 2022 (26)	80	2-17 y mean age → 9.3 y	M → 41 (51.3 %) F → 39 (48.8%)	- gadopiclenol	- Two patients (2.5%) experienced nonserious adverse events considered related to gadopiclenol: a mild QT interval prolongation and a moderate maculopapular rash - The profile of gadopiclenol in children → similar to that observed in adults - No indication for age-based dose adaptation - Gadopiclenol at 0.05 mmol/kg seems to have a good safety profile and could improve lesion detection and visualization, therefore providing better diagnostic confidence
Heshmatzadeh Behzadi A, 2022 (27)	766	All ages, mean age → 53.1 y	M → 332 F → 434	- gadoterate (Dotarem) - gadoteridol (ProHance) - gadobutrol (Gadovist)	- No side effects, including those from gadoterate, were documented in this cohort - This data shows that GBCA used in MRIs of the central nervous system have a great safety and effectiveness profile

There are several studies investigating safety of currently approved macrocyclic compounds. The large international (SECURE) study reported only one case of reaction after the application of gadoterate in children and it was vomiting of mild intensity, the cause is most likely related to intracranial pressure due to a brain tumor from which he suffers, however, it cannot be ruled out with certainty that it is not the result of an interaction with the contrast agent (16). Indeed, the most frequently reported side effects after applying gadoterate are precisely vomiting and nausea, followed by urticaria and itching. No suspicion of NSF has been documented. In the study by Balassy et al. the safety of using gadoterate was investigated in clinical trials in the pediatric population (17). Reported reactions were generally mild, such as itching, headache, dizziness, hematuria, vomiting, asthenia, urticaria and nausea. The study by Scala et al. included pediatric patients <2 years old, who had gadoterate intravenously administered once (18). The most commonly reported side effects included pyrexia (13.3%) and leukopenia (4.4%), while the rest were related to gastrointestinal disturbances. The majority of adverse consequences (61.5%) were of mild intensity, 38.5% of them were moderate, and none of the more severe form was recorded. Only one patient developed a rash of moderate intensity. In the research by Farmakis et al. adverse reactions included vomiting (8.7%), transient flushing or warmth (5.3%), nausea (4.7%), dizziness (0.7%) and altered taste (0.7%) (19). Two allergy-like reactions were recorded in 2 patients (sneezing and non-specific sounds when breathing). None of these reactions could be attributed solely to gadoterate meglumine due to previously used sedative agents. The majority of reported immediate adverse events (1.3%) in this study were of mild intensity and physi-

ological in nature, consistent with the most commonly reported adverse events in previous studies, however the overall adverse event rate including both immediate and late reactions was 15.3% and it is higher than those previously recorded in the literature. The study by Emond et al. showed no case of acute adverse reactions after the use of gadoterate, as well as the occurrence of nephrogenic systemic fibrosis (20). The GARDIAN study was created to assess the tolerance and safety of gadobutrol (21). Individual adverse events included vomiting (n=3, 0.26%), nausea (n=2, 0.18%), and injection site reaction, urticaria, dyspnea, and eyelid edema (n=1 each, 0.09%). No serious side effects were reported. No skin reactions were recorded in any case, which would indicate NSF. Gadobutrol is a very well-tolerated contrast agent that produces outstanding imaging quality, according to the findings of this significant pediatric subanalysis. The study by Glutig et al. was conducted on both adult and pediatric populations (22). Regarding pediatric patients in the group of those younger than seven years, no adverse effects of gadobutrol were recorded. The only recorded side effect was in a 14-year-old patient with a burning sensation along the forearm immediately after applying GBCA and a headache lasting 5 minutes. In the study by Kunze et al. similar conclusions were reached, as in the previous two studies (23). Most side effects after gadobutrol administration in children were of mild symptoms. Once again, the favorable safety profile of this compound was demonstrated. In the study Shah et al. out of 125 children who received gadoteridol, six of them (4.8%) experienced 11 side effects during the 48-hour follow-up period after the application itself (24). Almost all side effects were related to laboratory values, such as elevated platelet levels, mildly decreased hemoglobin, mildly decreased hemoglobin and erythrocyte counts, moderately decreased platelet levels, and mildly elevated blood chloride. All events could not be directly correlated to gadoteridol.

The aim of the study by Maximova et al. was to determine whether gadolinium deposition in the liver occurs in pediatric patients with iron accumulation, but normal liver and kidney functions, to whom gadoterate meglumine was administered. Finally, a positive association was found between the total dose of GBCA administered and the level of gadolinium in the liver. Additionally, a positive corelation between the concentration of iron and gadolinium in the liver was found. Gadolinium levels in the liver were reduced in deferoxamine-treated patients. Therefore, further studies on the safety of GBCA in severe siderosis are needed, and in patients with iron overload and a history of exposure to these compounds, chelation should be considered (25).

In the study Jurkiewicz E et al. evaluated safety, pharmacokinetic and efficacy of gadopiclenol, a new high-relaxivity gadolinium-based contrast agent (26). Two patients (2.5%) experienced nonserious adverse events considered related to gadopiclenol: a mild QT interval prolongation and a moderate maculopapular rash. Gadopiclenol's safety profile in children aged 2 to 17 years was good and consistent with that seen in adults. Finally, the study of Heshmatzadeh Behzadi A et al. confirmed the effectiveness and safety of gadoterate meglumine (27).

DISCUSSION

The review revealed the most common side effects observed through noumerous studies refered to symptoms with mild acute manifestations, such as urticaria and rashes, while more serious acute reactions were rare and often difficult to attribute with certainty to contrast agents. Regarding the late reactions, the most significant of them is nephrogenic systemic fibrosis, the occurrence of which in pediatric patients has been shown as an extremely rare phenomenon, and was recorded exclusively in patients with existing severe kidney damage after aplication of withdrawn linear compounds (5-7).

Recently discovered gadolinium brain tissue deposition was investigated in several studies, of which almost all confimed higher levels of gadolinium deposition in patients who were repeatedly exposed to gadolinium linear contrast agents. The results also showed that unlike linear compounds, repeated applications of macrocyclic ones did not cause increased accumulation of gadolinium in the majority of research (8, 9, 13).

There are also numerous studies investigating adverse effects of the currently approved macrocyclic contrast agents. Almost all studies showed the majority of reactions were acute and of mild intensity with low incidence (16, 18, 20, 21). It seems the incidence of the reactions is increasing with age of children, but it remains lower compred to adults. Severe reactions, such as NSF, or death were almost no reported. Looking at complete safety of gadolinium contrast agents, the rate of side effects is much lower than when using iodine contrasts for computed tomography.

All data in this paper are part of the results of the undergraduate thesis "Safe use of gadolinium contrast agents" written at the University Department of Health Studies, University of Split (28).

CONCLUSION

In conclusion, despite the generally low side effect rate and occurrence of general mild reactions in pediatric patients, their long-term safety of use, especially in the neonatal age, has not yet been established. The use of this compounds should be reasonable and clinically justified in the pediatric population.

Abbreviations:

MRI - magnetic resonance imaging
GBCA - gadolinium-based contrast agents
NSF - nephrogenic systemic fibrosis

NOVČANA POTPORA/*FUNDING*
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ETIČKO ODOBRENJE/*ETHICAL APPROVAL*
Nije potrebno/*None*

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Sažetak

KONTRASTNA SREDSTVA NA BAZI GADOLINIJA U PEDIJATRIJSKOJ POPULACIJI: PREGLEDNI RAD

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Unaprjeđenjem tehnologije te samim razvitkom magnetske rezonance dogodio se glavni preokret u domeni radiologije u dvadesetom stoljeću. Uvelike je olakšana vizualizacija svih dijelova ljudskog tijela uz održavanje odlične prostorne rezolucije bez upotrebe ionizirajućeg zračenja. U pedijatrijskoj populaciji pregled magnetskom rezonancom korisna je metoda u evaluaciji mozga, toraksa, abdomena, zdjelice te ekstremiteta. Upravo je ovo jedna od prvih metoda izbora za mlađe pacijente zbog nekorištenja ionizirajućeg zračenja. S ciljem povećanja kontrastnosti i rezolucije dobivene slike koriste se kontrastna sredstva magnetske rezonancije. Među najčešće korištena kontrastna sredstva spadaju kontrastna sredstva na bazi gadolinija. Prema molekularnoj strukturi dijele se na linearne i makrocikličke, a uz to postoji još i podjela na ionske i neionske. Makrociklički spojevi općenito se smatraju sigurnijima zbog niže stope disocijacije slobodnog iona gadolinija, koji je u tom obliku toksičan. Za gadolinijska kontrastna sredstva dugo se vjerovalo da su u potpunosti sigurna, ali njihova povezanost s nefrogenom sistemskom fibrozom primijećena je 2000-ih, nakon čega se usmjerilo ka korištenju makrocikličkih spojeva u pedijatrijskih bolesnika zbog dokazano veće sigurnosti. Osim navedene nuspojave, moguć je razvoj i akutnih alergijskih reakcija, a u novije vrijeme otkrivene su i spoznaje o taloženju gadolinija u tkivima. Unatoč vrlo niskoj stopi navedenih nuspojava u pedijatrijskih pacijenata, njihova dugoročna sigurnost i primjena u neonatalnoj dobi još nije utvrđena. Upravo zbog toga, važno ih je oprezno koristiti uz naglasak na apliciranje najmanjih mogućih doza, korištenje makrocikličkih spojeva te dobru procjenu rizika. Ovaj pregledni rad prikuplja i analizira do sada objavljena istraživanja o kontrastnim sredstvima na bazi gadolinija u pedijatrijskoj populaciji.

Ključne riječi: GADOLINIJ, KONTRASTNA SREDSTVA, MAGNETSKA REZONANCA, PEDIJATRIJSKI PACIJENTI

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