Contrast Media Use in Pediatrics: Safety Issues

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Contents

Abstract

Contrast media appear to be just as safe in children as they are in adults. The risk factors are the same and the same precautions should be taken. The main differences relate to differences in technique necessitated by differences in size, differences in relative body compartment size, growth, immature renal function, etc., as well as to limited published evidence on their use and safety. Not all agents are approved for use in children, but most of the nonapproved agents can be used off-label with the informed consent of the parents.

1 Introduction

Throughout childhood the same contrast media are used as in adults. However, in children, a variety of factors specific to size and age must be taken into account:

1. The physiology of children, particularly neonates, differs from adults. In early life, factors such as a relatively higher circulating blood volume, faster heart rate, shorter circulation time, shorter distances, smaller structures, different body composition, and immature renal function all affect the dose and timing of contrast agent administration.
2. There is very limited evidence available about the handling of contrast media by the neonatal kidney in the first weeks of life. Recommendations have therefore to be based on consensus developed using information from older subjects, rather on direct scientific evidence.
3. Children generally have a lower incidence of adverse reactions, particularly severe reactions, to contrast media.
4. In children, the smaller blood vessels necessitate smaller needles, and these reduce the speed of contrast medium injection, increase the effect of contrast medium viscosity, and lead to altered delay times.

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5. In children, there is a greater risk of fluid imbalance between different compartments, which is particularly important for gastrointestinal, oral, and rectal contrast medium administration. This is very important when using hyperosmolar contrast media, especially in premature infants and in young and sick children and infants with labile circulatory systems.
6. Not all contrast media are approved for pediatric use. For some specific applications, such as liver-specific MR contrast media and ultrasound contrast media, no registered agents are available for neonates and children. If such agents are used in neonates, infants or children their use is off-label, which necessitates more detailed informed consent from the parents ("Off-Label Use of Contrast Media: Practical Aspects"). Also, licensing of contrast media and the approval process, as well as legal requirements, vary significantly throughout Europe and the rest of the world, making general statements difficult. The Summary of Product Characteristics must be consulted for the agent in question.

Some other general considerations apply to all contrast agent use in infants and children. First, a higher level justification is needed for invasive investigations, and use of contrast medium is a first step of invasiveness. Second, all imaging using ionizing radiation must be based on a valid indication because neonates, infants and young children are significantly more sensitive to radiation than adults and have a longer expected life span in which to experience possible long-term adverse effects (Hammer et al. 2011; Krille et al. 2012; Pearce et al. 2012). Third, the different physiology and anatomy of children suggest that contrast agent dynamics and long-term effects may be different from those in adults. For example, it has been suggested that gadolinium may accumulate in the bone marrow under certain circumstances, and may be particularly toxic to bone marrow in young children, in whom there is active hemopoiesis occurring in the peripheral red bone marrow (Hocine et al. 1995; Idee et al. 2006). Currently, there is no evidence that this occurs but it has not been fully investigated. It therefore seems prudent to recommend that macrocyclic gadolinium-based contrast media, which are likely to leave the smallest amount of gadolinium in the bone marrow and the body, should be used in children.

Finally, other methods of achieving contrast between the tissues should be used whenever possible to reduce the need for contrast media. Examples are using air to fill the gastrointestinal tract on plain films or at fluoroscopy, using saline or water to fill and distend bowel and body cavities for CT, MRI, or ultrasound, and using cranberry or blueberry juice or similar manganese containing drinks as bowel contrast media in MRI. These methods will not be discussed further in this chapter, the remainder of which focuses on contrast media.

2 Oral/Gastrointestinal Radiopaque Contrast Media

Oral radiopaque contrast media are used to image the gastrointestinal tract, with typical pediatric indications being gastrointestinal and anorectal malformations (e.g., atresia, duplication, fistula, stenosis, Hirschsprung's disease, etc.), and anatomical and functional assessment of persistent gastro-esophageal reflux and neonatal stool transport and passage problems. In general, particularly in older children, the use of radiopaque contrast media is similar to that in adults, although less frequent. However, in the very young, because of the immature mucosal barrier and the greater risk of fluid and electrolyte imbalance, there are some differences in the ways contrast media are used.

Most commonly barium-based contrast media are used because they give good opacification of the gastrointestinal tract and outline the mucosal lining well. However, in large amounts and higher concentrations, barium agents can cause constipation and, to reduce this, emulsifiers have been added in modern formulations. Also, if perforation with barium spill into the peritoneum occurs, it may cause peritoneal granulomata (Eklöf et al. 1983; Williams and Harned 1991; Hernanz-Schulman et al. 2000). Whenever there is the risk of impaired bowel wall integrity or if there is extensive inflammation, barium-based contrast media should be avoided and water soluble low- or iso-osmolar non-ionic iodine-based contrast media should be used (Zerin 1992; Hiorns 2011).

Hyperosmolar ionic iodine-based contrast media, most commonly containing amidotrizoate, have traditionally been used for upper gastrointestinal tract studies as well as for diagnosing and/or treating meconium transport problems in newborns, especially those born preterm (Kao and Franken 1995). With these contrast media, there is a high risk of fluid and electrolyte imbalance and mucositis, with resultant potentially disastrous and even life-threatening consequences (Leonidas et al. 1976). High osmolar iodine-based agents are, therefore, usually contraindicated in neonates and infants and in many departments are banned, with non-ionic low- or iso-osmolar iodine-based contrast media used instead. The only acceptable exception is if high osmolar agents are diluted at least 3:1 and used to treat preterm babies with meconium transport problems under proper monitoring and with appropriate fluid and electrolyte replacement.

Table 1 Suggested choice of intestinal/enteral radiopaque contrast agent in neonates and young infants

Barium suspensions
Indications
Hirschsprung disease. Avoid overfilling. A small amount of barium to fill the recto- sigmoid only is often sufficient, unless there is a very long aganglionic segment. If the barium is not evacuated, rinse with a saline enema to prevent impaction.
Standard assessment after necrotizing enterocolitis or similar conditions, in the follow-up phase, to assess for possible bowel stenosis and for bowel patency
Oesophageal assessment
Contraindications
Risk of leakage or perforation
Severe inflammatory bowel disease
Marked constipation
Hyperosmolar iodine-based contrast media
Indications
Treatment of neonatal meconium plug and transport problems. Use in 1:3 dilution with saline, and monitor fluid and electrolyte balance.
Low-or iso- osmolar iodine-based contrast media
Indications
All other diagnostic problems, particularly the assessment of neonatal bowel obstruction, the assessment of bowel at risk of perforation, or when there is severe bowel inflammation or severe constipation

Table 2 Recommended age-adjusted amount of diluted oral iodine-based contrast medium (2 % solution) for pediatric CT

Age	CM amount (ml)
Under 6 month	100
6 month–1 year	200
1–3 years	300
3–10 years	700
Older than 10 years	1,000

Non-ionic low- and iso-osmolar iodine-based contrast media are the agents of choice, particularly in neonates and infants with possible fistula or at risk of aspiration or perforation, although they provide less good contrast and poorer outlining of the bowel contour. Very rarely, it may be necessary to use other agents where high mucosal detail is required provided there are no specific contraindications (Table 1). In older children, low-osmolar iodine-based agents can be used as an alternative when barium-based suspensions are contraindicated (McAlister and Siegel 1984; Basu et al. 2009).

For oral bowel contrast during pediatric CT, diluted low-osmolar iodine-based contrast media (e.g., iopamidol) in a 2 % solution are usually used, with the volume given based on the patient's age (Table 2) (Sorantin et al. 2002; Sorantin 2013).

For some indications, air may serve as an ideal negative contrast agent, for example, to diagnose and reduce intussusception or to diagnose deep and high bowel obstruction, and this may help to reduce the use of iodine-based contrast media. Air may also be used for double contrast studies to improve radiopaque contrast medium demonstration of the detail of the gastric wall and bowel.

3 Iodine-Based Contrast Media for Other Intraluminal Applications

Iodine-based contrast media are used in children to opacify the bladder for voiding cystourethrography, and also rarely for bronchography, fistulography, arthrography, or sialography, or for interventional procedures which require body cavities to be outlined. These studies, especially filling body cavities to guide intervention, should be done with the same contrast media as are used intravascularly, i.e., low- or iso-osmolar iodine-based agents. Hyperosmolar ionic iodine-based contrast media should only be used in intact systems where there is no risk of extravasation or accidental intravascular administration, for example, for voiding cystourethrography, commonly using a low-iodine concentration such as 100–150 mgI ml^{-1}. The subtle antimicrobial effect of the hyperosmolar agents may be advantageous for cystography (Dawson et al. 1983; Speck 1999).

4 Intravascular Iodine-Based Contrast Media

Iodine-based contrast media are mainly used intravascularly for CT and interventional procedures, and are also used for diagnostic angiography. Occasionally, they are used for intravenous urography, but this is increasingly being

Table 3 Recommended weight- and age-dependent dose and concentration for pediatric intravenous iodine-based contrast agent use when using age adapted KV settings

Age	Iodine concentration (mg/ml)	Dose (ml/kg b.w.)
Less than 1 year	150–200	2.5
Between 1 and 2 years	200–250	2.0
Older than 2 years	250–300	1.5
Older than 6 years	300–350	1–1.5

Note 1. Use a higher iodine concentration for smaller and more peripheral vessels, and with higher KV. 2. Do not administer more than 100 ml of contrast agent
Adapted from Sorantin 2013

replaced by MR-urography or ultrasonography. Beyond infancy, the indications and contraindications for these agents and their renal excretion are similar to those in adults and will not be discussed further as they are considered in other chapters. The risk of acute and delayed reactions after intravascular iodine-based agents was evaluated by Mikkonen et al. (1995).

In neonates and infants, however, there is very little evidence-based data on renal contrast agent excretion. The neonatal kidney is immature and its function is less than 20 % of that in an adult. Also, in neonates, especially those that are premature, and in young infants, fluid volume and osmolar balance are less stable and circulating relative blood volume is larger than in older children and adults. This means that particular care is necessary when contrast-enhanced studies in neonates, infants, and in preterm babies are being considered.

The recognized complications of iodine-based contrast media, such as contrast-induced nephropathy, 'allergic' reactions, and thyrotoxicosis in patients at risk, also occur in children. Appropriate precautions, similar to those in adults, have to be taken, such as checking for renal disease or renal functional impairment, and assuring adequate hydration (Brasch 2008; Riccabona et al. 2010). Serum creatinine levels in children are much lower than in adults because they have less muscle mass, and the appropriate normal range for age must be used (Schwartz et al. 1976). GFR calculation should be done with equations adapted to be suitable for young pediatric patients (Filler et al. 2013, Langlois 2008; Ring et al. 2008, Schwartz and Work 2008; Schwartz et al. 2009).

For premedication before contrast medium and treatment of adverse reactions, different strategies dependent on age are recommended. These are usually developed as a standard in a given institution, in cooperation with the pediatricians and anesthesiologists, and are similar to the recommended measures in adults. There are also some guidelines for more general use. An example is the corticosteroid and antihistamine premedication regimen for children with known allergy to iodine-based contrast media recommended by the American College of Radiologists (ACR) of oral Prednisone 0.5–0.7 mg/kg (up to 50 mg) at 13, 7, and 1 h before contrast medium injection, and Diphenhydramine 1.25 mg/kg (up to 50 mg) 1 h before contrast medium injection (ACR 2012, 2012a, 2012b).

A particular point of discussion is whether low- or iso-osmolar iodine-based contrast media are preferable. It is possible that low-osmolar low-viscosity contrast media may protect the immature kidney in particular, compared to iso-osmolar contrast media, by keeping sufficient fluid within the vascular bed to prevent sluggish flow and secondary complications (Persson 2011). This phenomenon may also affect contrast medium flow through the renal tubules, and low-osmolar agents may prevent stasis there also.

Contrast agent concentration and iodine load have not been studied in infants, so there is insufficient evidence to produce general guidelines on the optimal contrast medium iodine concentration to use. It has been suggested that a concentration of 150–350 mg I ml^{-1} concentration is sufficient in neonates, infants, and young children, with the lower concentration chosen for younger patients, especially, since lower KV settings of 80 or 100 kV are used. However, higher iodine concentrations and higher KV settings may be necessary to assess small peripheral vessels on CT-angiography (Frush 2008; Zoo et al. 2011; Sorantin et al. 2013a, b).

The dose of a contrast agent depends on its concentration and on the iodine load; the higher the iodine load, the lower the dose and the greater the contrast achieved. However, since neonates and infants have a relatively higher circulating blood volume, a higher dose of contrast agent may be necessary. In general, 2 ml kg^{-1} (to a maximum of 3 ml kg^{-1}) is suggested for neonates, 2 ml kg^{-1} for infants, and thereafter 1–1.5 ml kg^{-1} (Pärtan 2013; Sorantin et al. 2002, 2013a, b) (Table 3). Higher doses and higher iodine concentrations have been used for CT-angiography or interventional procedures, particularly cardiography and angiography, but this was associated with an increased incidence of contrast-induced nephropathy (Frush 2008; Kurian et al. 2013; Heran et al. 2010). Higher contrast agent doses therefore must be considered when risk versus benefit is being assessed for a particular patient and should be

discussed with the clinicians involved, including the pediatric nephrologist, as well as with the parents or carers.

5 Gadolinium-Based Contrast Media

There is little safety data available about the use of gadolinium-based agents in children, particularly neonates and infants aged less than 1 year. As in adults, the important factors are gadolinium elimination, the risk of transmetallation, the effect of renal function, acidosis and dehydration, and the possibility of nephrogenic systemic fibrosis (NSF) ("Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media").

There are very few, partially verified reports of NSF in infants and children (Eldevik and Brunberg 1994; Karcaaltincaba et al. 2009; Riccabona et al. 2008a). NSF has been reported in one 6-year-old patient and in older children after administration of the least stable linear agents to children with renal impairment (Dharnidharka et al. 2007; Foss et al. 2009; Jain et al. 2004). Recent research on the prevalence of NSF in children identified 20 pediatric cases, 12 of which had documented gadolinium exposure (K. Darge, Personal communication). To date, no case has been reported after macrocyclic agents or in children with normal renal function. There is insufficient data to know whether NSF is less likely to occur in children than in adults with a similarly degree of renal impairment. In children, the guidelines recommended by the American College of Radiologists, the ESUR Contrast Medium Safety Committee, the ESPR Uroradiology task force and the ESUR Pediatric working group (ACR 2012; Mendichovszky et al. 2008; Riccabona et al. 2009; Thomsen et al. 2013) should be followed ("Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media", "ESUR Guidelines on Contrast Media Version 8.1"). It should be noted, however, that estimated GFR (eGFR) values in premature infants and neonates may be <30 ml min^{-1} 1.73 m^{-2} because of immature renal function, not renal impairment. Age adapted normal creatinine values, which are much lower than in adults because of the smaller muscle mass (Schwartz et al. 1976) and specific pediatric GFR calculations which take the lower GFR values into account should be used (Langlois 2008; Ring et al. 2008; Schwartz and Work 2008; Schwartz et al. 2009). In premature babies and neonates, although an eGFR value <30 ml min^{-1} 1.73 m^{-2} should not be considered to be an absolute contraindication to the most stable agents, caution should still be exercised when administering gadolinium-based contrast media, since the potentially fatal disease of NSF and the long-term effects of gadolinium retention in the body are not yet fully understood.

Problems have also occurred because of poor hydration and temporarily impaired renal function, with increases in serum creatinine after administration of gadolinium-based agents, in school children and adolescents as well as younger children. There is no good data available yet on the handling of gadolinium-based agents by the neonatal kidney, and therefore recommendations are based on extrapolation from adult physiology. In general, administration of gadolinium-based agents should, if possible, be avoided in the first months of life.

Recommendations for using gadolinium-based contrast media in children are given below:

1. Gadolinium-based contrast media should only be used in children when the clinical problem cannot be solved using other imaging methods, such as ultrasonography, or unenhanced MRI techniques, such as MR angiography or perfusion imaging based on Time-of-Flight or arterial spin labeling techniques (Mannelli et al. 2012; Penfield and Reilly 2008).
2. The most stable macrocyclic gadolinium-based agents should be used, and the less stable linear compounds, which are more likely to induce NSF, should be avoided (Penfield and Reilly 2008; Morcos 2007).
3. Assessment of renal function by measuring creatinine and glomerular filtration rate is essential, using normal ranges suitable for age, particularly in those at risk of renal disease or with a recent disease that might have affected renal function. In children with a GFR lower than 30 ml min^{-1} 1.73 m^{-2}, gadolinium-based contrast media should be avoided unless there is a compelling indication and no alternative substitute of less risk in children.
4. If the GFR is between 30 and 60 ml min^{-1} 1.73 m^{-2}, a pediatric nephrologist should be consulted before the gadolinium-based agent is given and there should be appropriate preparation with hydration, correction of acidosis, and similar measures. Also, informed consent should be obtained from the parents and the patient (if legally applicable).
5. Double dose administration should be avoided in children on general principles, although there is no direct evidence that this is harmful. However, the dose may be corrected to allow for the relatively higher circulating blood volume which, in ml kg^{-1} body weight, is effectively about one and a half times higher than in older patients for the first months of life.
6. In general, administration of gadolinium-based contrast media should be avoided in the first months of life, unless for serious indications, and after careful consideration.
7. As repeated administration potentially leads to a higher cumulative systemic dose and is a possible risk factor, repeated investigations should be avoided and single dose techniques are advised. The patient's cumulative dose should be recorded and in the patient's file or in a register. Careful documentation of an individual patient's dose for follow-up, particularly in at-risk

Table 4 Dose suggestions for pediatric ultrasound contrast agent use (SonoVue®, Bracco, Milano, Italy), based on clinical experience

Contrast-enhanced voiding urosonography (ce-VUS)	
0.5–1 % of actual bladder filling volume	
Note For Optison, 0.5 % of bladder volume appears sufficient (Darge et al. 2013)	
Intravenous contrast-enhanced ultrasonography (iv. CEUS)	
Neonates:	0.1–0.25 ml/kg b.w.
Infants:	0.1 ml/kg b.w.
Older children (>20 kg body weight):	0.05 ml/kg b.w.
Adolescents: adult doses	2.4–4.8 ml

No studies of appropriate dose are available, but some dose-finding studies have been done for ce-VUS
NB No ultrasound contrast agent has been approved for use in children; its use is off-label ("Off-Label Use of Medicines: Legal Aspects", "Off-Label Use of Contrast Media: Practical Aspects")

patients, over a longer period of time is important, but it is also important to keep a register of all patients to obtain data for future analysis which will provide evidence for neonatal and pediatric administration of these agents in the future.

In some countries no cyclic gadolinium-based contrast media are registered for use in neonates and in the first years of life. The safety and imaging potential of some agents, however, have been specifically studied for children aged over 1 year (Baker et al. 2004; Hahn et al. 2009; Forsting and Palkowitch 2010). If a contrast-enhanced study is necessary in neonates and young infants, the risk to benefit relation has to be properly considered, particularly taking into account the risk of alternative iodine-based contrast medium and radiation when a contrast-enhanced CT would be the only alternative. The summary of Product Characteristics (the 'insert') should always be checked to find to what extent the contrast agent has been approved for children. If the agent is not approved, provided it is not contraindicated, it can be used with the informed consent of the parents. Lack of approval is usually because phase 3 studies are rarely done in very young children.

6 Ultrasound Contrast Media

Currently, no ultrasound contrast media are approved for pediatric use and the only compound which was registered for use in children has been taken off the market. However, because of the higher radiation sensitivity of children, particularly the very young, there is an increasing demand to use imaging methods not involving ionizing radiation. This has led to an increased number of off-label administrations of some ultrasound contrast media in neonates, infants, and children (Esposito et al. 2012; Piskunowicz et al. 2011; Riccabona 2012; Schreiber-Dietrich and Dietrich 2012).

The same indications and contraindications apply as in adults (Ter Haar 2009; Torzilli 2005). Since ultrasound contrast media are not excreted by the kidney, renal function, and renal immaturity do not affect the use of these agents (Calliada et al. 1998). Possible impairment of the metabolic pathways of the carrier molecule, which may, for example, be a lipid, protein, or sugar, must be considered and may be a contraindication. Thus, galactosemia was a contraindication for the galactose-based ultrasound contrast medium, which has been taken off the market.

There are a few studies and meta-analyses which have evaluated current knowledge about ultrasound contrast media administration during childhood, most of them focusing only on the intra-vesical use (i.e., contrast-enhanced voiding urosonography- ce-VUS) (Mccarville 2011; Piskunowicz et al. 2012; Papadopoulou et al. 2012; Riccabona et al. 2008b; Riccabona 2012; Taylor 2000; Valentini et al. 2002; Zimbaro et al. 2007). Most studies looked at diagnostic reliability and details of the procedure, and safety aspects in children have rarely been addressed (Darge 2010; Ntoulia et al. 2013; Papadopoulou et al. 2012). However, all the available data, even if it is mostly from adults, indicate a good safety profile for ultrasound contrast media. They have an extremely low incidence of side effects, which are usually mild and far less frequent than with iodine-and gadolinium-based contrast media and also less frequent than in adults (Correas et al. 2001; Morel et al. 2000; Nolsoe et al. 2011; Piscaglia and Bolondi 2006). As with all other contrast media, ultrasound contrast media can be used in any body cavity as well as intravascularly, most commonly intravenously in adults, whereas in children the most common application is intravesically.

The indications for and findings on intravenous administration are similar to those in adults. However, in children, the incidence of malignancy is lower so there is less need for malignancy-related liver imaging. Pediatric intravenous use of ultrasound contrast media is most often for trauma imaging, differential diagnosis, and post-transplant assessment.

The dose should be adapted to the child's size. Currently, there are no proper pediatric studies of appropriate dose for all the available ultrasound contrast media, so the dose is usually extrapolated from the adult dose in relation to the child's body weight, and the higher relative circulating blood volume in children should also be taken into account (Table 4).

The most common use of ultrasound contrast media in children, which is specific to children, is intravesical administration for contrast-enhanced voiding urosonography (ce-VUS) for assessment of vesicoureteral reflux. This may be complemented by perineal ultrasonography during voiding for assessment of the urethra. (Ascenti et al. 2004; Berrocal et al. 2001, 2005; Darge and Troeger 2002; Darge 2008; Darge et al. 2013; Duran et al. 2009; Kenda et al. 2000; Riccabona et al. 2008b). To date, no adverse events have been reported with this use of ultrasound contrast media, which in addition has good sensitivity and specificity (Darge 2011; Papadopoulou et al. 2012; Riccabona 2012).

In conclusion, the use of ultrasound contrast media in neonates, infants, and children has been recommended not only by various local groups, but also by the European Federation of Ultrasound in Medicine and Biology, for well-defined clinical indications, in spite the fact that administration is off-label (Claudon et al. 2008; Piscaglia et al. 2012; Nolsoe et al. 2011; Riccabona 2012). The use of ultrasound contrast media should always be considered as an alternative to other studies that use radiation, and parents should be provided with appropriate information to enable them to decide whether to give informed consent.

7 Conclusion

The safety considerations when using contrast media in neonates, infants, and children are similar, but not the same as, in adults. The dose of contrast agent must be adjusted to the individual patient, and age specific normal values of serum creatinine, etc. must be used. In children, for radiography, including CT, non-ionic iodine-based contrast media should be used and, for MRI, macrocyclic gadolinium-based agents should be chosen. The Summary of Product Characteristics should be consulted, particularly since not all contrast media are tested in children in accordance with the rules of the various Medicine Agencies. This does not mean that untested and officially unapproved contrast media may not be used in children, but that informed consent must be obtained from the parents. However, if a contrast agent is absolutely contraindicated, it may not be used, even with informed consent.

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