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Contrast Agents in Pediatric Neuroimaging

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During the last two decades the development of contrast agents for myelography, angiography, computed tomography (CT) and magnetic resonance imaging (MR) has been remarkable. What follows is a review of contrast agents used in neuroradiology—specifically, the ionic and nonionic contrast agents for radiographic/CT procedures, and the paramagnetic contrast agents used in MR studies. Topics covered are the indications for and use of contrast agents, doses and comparisons, complications and cost benefits, and what the future of contrast media might hold.

Iodinated Contrast Agents

The basic structure of iodinated contrast agents is the benzene ring (Fig. 1), with its attached iodine atoms. The remaining components are the acid group and organic substitutes which influence excretion and toxicity. The hydrogen atoms in the acid group can be replaced by a cation, such as sodium (Na) or meglumine, in which case the contrast agent is ionic. If the hydrogen atom in the acid group is replaced instead by amine-carrying hydroxyl groups, then the compound is nonionic (Fig. 2).

When there is only one benzene ring in the compound, the contrast agent is a monomer; when there are two benzene rings in the compound, the contrast agent is a dimer (Fig. 3). The compound with two benzene rings contains twice the amount of iodine in the molecule compared to the monomer. Monomeric and dimeric contrast agents can be ionic or nonionic, depending on which substitutions are made at the acid group. Examples of common contrast agents used in North America are listed in Table 1.

Recent developments have all centered on the nonionic contrast agents, because these are less toxic than the ionics (1); however, the cost of the nonionics is significantly higher than that of the ionics. Despite the debate regarding the cost effectiveness of the nonionics (2–9), we routinely use nonionic contrast agents for all radiologic investigations at the Hospital for Sick Children in Toronto. We do so because of the lower complication rate, although there is no convincing evidence of any decrease in the mortality rate. Nevertheless, when there is extravasation of contrast into the tissue on IV injection, the morbidity is lower.

Elimination of contrast agents is dependent on organic substitutions. If one of the organic substituents is a hydrogen atom, then the compound is excreted by the biliary system. If none of the organic substituents is a hydrogen atom on the benzene ring, then the contrast is excreted by the kidneys.

There is a major difference in osmolality and viscosity between the ionic and nonionic contrast agents and between the monomeric and dimeric contrast agents. Examples of these are listed in Table 2. Osmolality is defined as milliosmoles per kilogram of water; osmolarity is defined as milliosmoles per litre of solution. In water, the osmalility is equivalent to the osmolarity. Because of the dissociation of the cation and the anion in solution, the ionic contrast agent obviously has a much higher osmolarity than does the nonionic contrast agent. Hence, the other names of the two contrast agents are high osmolar contrast medium (HOCM) (ie, ionic) and low osmolar contrast medium (LOCM) (ie, nonionic), respectively.

In terms of viscosity, the larger the molecule, the more viscous is the contrast agent. Therefore,

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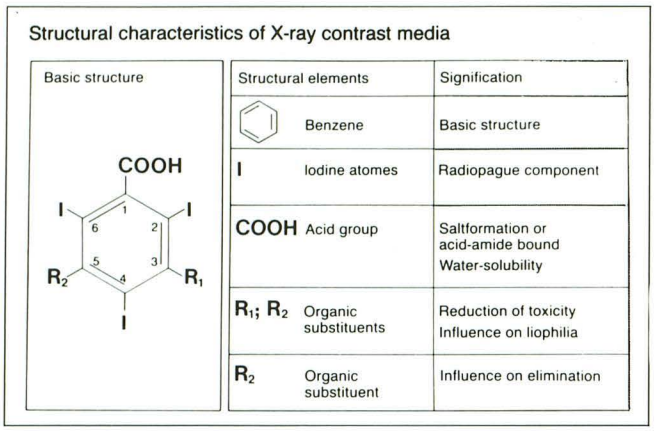

Fig. 1. Basic structure of iodinated contrast agent; benzene ring; ionic monomer.

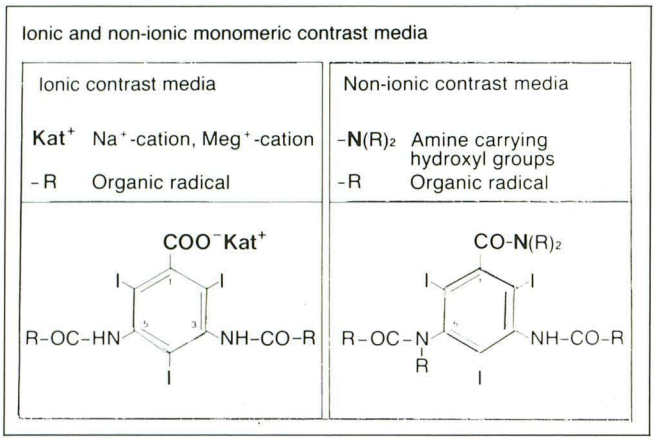

Fig. 2. Nonionic monomer contrast chemical structure; hydrogen atom in acid group replaced by hydroxyl group.

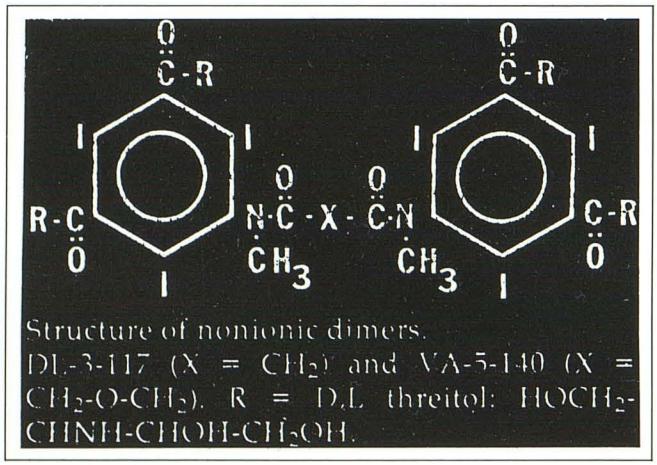

Fig. 3. Dimer contrast agent with two benzene rings; ionic or nonionic dependent on the acid group.

the most viscous contrast agents are the nonionic dimers, as opposed to the ionic dimers and the nonionic monomers. The least viscous are the ionic monomers (Table 3). The viscosity, however, changes with temperature (10). The higher the temperature, the less viscous the contrast becomes. For this reason, nonionic contrast agents are warmed to body temperature for intravenous or intraarterial injections, so as to make the injection easier and more rapid.

Because the nonionic contrast agents have a lower complication rate than the ionic contrast agents in intravenous and intraarterial usage, they are the only contrast agents that can be used intrathecally for myelography and ventriculography (11–13). With the advent of MR imaging, there are now fewer indications for myelography and ventriculography; however, in cases of isolated tethered cord (or tight filum terminate syndrome) and in patients who have difficulty in cooperating, myelography is still a more useful diagnostic tool (14). Ventriculography is still useful in analyzing the communication and compartmentalization of the ventricular system and cisterns (15).

The dosage used for ventriculography is approximately 1–2 mL of isotonic nonionic contrast

TABLE 1: Low osmolar contrast medium commonly used in North American

Contrast Medium	Manufacturer
Hexabrix-Ioxaglate	Mallinkrodt
Iohexol-Omnipaque	Sterling-Winthrop
Iopamidol-Isovue	Squibb
Ioversol-Optiray	Mallinkrodt

TABLE 2: Osmolality and viscosity of nonionic contrast agents

Contrast Agent	Viscosity at 37°C (cps)	Concentration (mg Iodine/mL)	Osmolality (mOsm/Kg H_2O)
Optiray 320 (Ioversol)	5.8	320	702
Iohexol	6.3	300	672
Iopamidol	4.7	300	616
Iohexol	2.0	180	408
Optiray 160 (Ioversol)	1.9	160	355
Iopamidol	1.4	128	290

TABLE 3: Viscosity of contrast agents of 300 mgI_2/mg at 37°C

Contrast	Viscosity	Type
Sodium trizoate	2.4	Ionic monomer
Meglumine trizoate	5.0	Ionic monomer
Meglumine ioglicate	6.0	Ionic dimer
Iohexol	5.7	Nonionic monomer
Iopamidol	4.6	Nonionic monomer
Iotrolan	9.0	Nonionic dimer

TABLE 4: Complete myelography dosage table

	Concentration mg I/mgL	mL/kg
Less than 2 mo	180–210	1/2
2 mo–2 yr	180–210	2–4
3 yr–7 yr	180–210	4–8
8 yr–12 yr	180–210	7–12
13 yr–17 yr	180–210	8–14

TABLE 5: Cerebral angiography—contrast dosage

	Under 10 kg	10–20 kg	20–40 kg	Over 50 kg
Internal carotid artery	2–4 cc	4–6 cc	6–7 cc	7–8 cc
External carotid artery	1–2 cc	2–3 cc	3–4 cc	4–5 cc
Common carotid artery	4–5 cc	5–7 cc	6–8 cc	9–10 cc
Vertebral artery	2–3 cc	3–5 cc	5–7 cc	6–8 cc

agent. The dosage used for myelography is listed in Table 4. The dosage varies with the patient's age rather than weight because the size of the subarachnoid space tends to vary with age rather than with weight (16).

We have done a comparative study of 180 mg % I_2 versus 210 mg % I_2, in myelography and found that if same amount of Iodine is given, ie, larger volume of 180 mg % I_2 as compared to 210 mg % I_2, there is little appreciable difference in the quality of the myelogram (17); however, if the same volume is given, then the more concentrated 210 mg % I_2 does provide a better myelographic study. This is *not* the case in CT myelography.

Contrast dosage for cerebral angiography is listed in Table 5. For good visualization of the arterial, capillary, and venous phases, the total volume of contrast medium should be given in less than 1.5 seconds. The concentration of the contrast medium, however, can be substantially less in digital angiography than in the conventional film technique; thus, isotonic concentrations of contrast can be used in digital studies.

Some authors have shown by animal experiments that, for intravascular usage, the LOCM is less neurotoxic than HOCM (18–20). However, the comparison is made with the same dosage and iodine concentration; adjustments or experiments were *not* made for comparing isotonic LOCM and HOCM to see if osmolality is really the key element in the factor.

As mentioned previously, adverse drug reactions are more common and may be more severe with the ionic contrast agents. The incidence of ionic contrast reaction is 4.17% versus 0.69% in the nonionic group. In intravascular usage, adverse reactions appear to depend on three factors, namely chemotoxicity, osmotoxicity, and low toxicity (6, 21, 22). The chemotoxicity effect causes red cell crenation and rigidity with direct effect on cell membranes and organelles causing endothelial damage in vessels. There is also release of vasoactive substances from cells (6). (The vasoactive substances include histamine, sertonin, fibrolysin, kallikreins, prostaglandins, leukotrienes, complements, and bradykinin.) The osmotoxicity or osmotic effect causes pain during arteriography, vasodilatation with hypotension, and rigidification of red blood cells. The osmotoxicity of the contrast agent is governed by a ratio that comprises the number of iodine atoms over the number of particles in an ideal solution, and is equal to the imaging effect of contrast medium over the osmotic effect of contrast medium. The higher the ratio, the lower the osmotoxicity.

Adverse reactions can be classified as mild or severe: mild reactions include urticaria, generalized pruritus, sneezing, rhinitis, nasal stuffiness, coughing, and lacrimation; severe reactions include wheezing, dyspnea, laryngospasm, status asthmaticus, subglottic oedema, angioneurotic oedema, anaphylactic shock, and cardiovascular collapse. Laryngotracheal edema and urticaria are part of the immune response, although no specific antibodies IgG or IgE have been isolated (23). The cardiovascular effect is probably related to chemotoxicity as well as to osmotoxicity. In addition to endothelial damage, hyperosmolality causes decrease in smooth vascular muscle tone as well as cardiac contractility (6).

Hypotension may be secondary to a vasovagal response from anxiety, but may also result from the vasodilatory effect of contrast agent. The HOCM cause an increase in the circulatory volume, with an increase in peripheral blood flow and a decrease in systemic resistance resulting in reduced blood pressure and hypotension (6). The hemodilution effects are due to the shift of extracellular water into the blood stream, which further contributes to hemodynamic perturbation associated with the use of HOCM (6). On the other hand, contrast-induced nephropathy does not correlate well with the volume of contrast medium injected or with HOCM versus LOCM (24). Decrease in renal blood flow and glomerular filtration rate can lead to proteinuria or anuria (25).

Premedication with steroids has not been shown to prevent damage; rather, it suppresses the symptoms of the adverse reactions (6). This

is why we have chosen to use nonionic contrast agents for all intravascular studies instead of only in high-risk patients, despite the apparent cost benefit.

Ionic contrast media cannot be used in myelography because of high neurotoxicity. Even the first nonionic contrast agent—metrizamide—is more neurotoxic than the newer contrast agents, such as iohexol, iopamidol, or ioversol (26–29). Despite different reports by different authors, no significant differences have been shown to exist among the newer nonionic contrast agents (11, 20, 29–34).

The incidence of adverse drug reactions following intrathecal usage of nonionic contrast agents varies from 26% to 44% (35, 36). The commonest reactions are headache and vomiting, although it is often uncertain whether the reaction is caused by the lumbar puncture or the contrast agents. No seizures have been recorded in our experience with the newer nonionic contrast agents but have been reported by others (37, 38). With metrizamide, the incidence of seizures is approximately 1 per 300.

Four rules provide guidelines for the tolerance of intravascular contrast agents (6): **Rule I**, Use of CM with a ratio of 3 or higher almost completely eliminates pain during arteriography; **Rule II**, The lower the number of particles in the solution (higher ratio), the lower the number of carboxyl groups; the higher the number of hydroxyl groups in relation to the number of iodine atoms in the CM molecule, the higher its intravenous tolerance will be; **Rule III**, Low neurotoxicity in the subarachnoid space requires absence of carboxyl groups and the presence of many hydroxyl groups evenly distributed around the CM molecule; and **Rule IV**, A high venous CM concentration in arteriography is obtained when diffusion of CM is slowed down by using large molecules (dimers), and osmotic dilution is decreased by using CM with low osmotic effects (ratio 3 or ratio 6).

Applying the above principles to the properties of the nonionic contrast agents, it can easily be understood why the nonionic contrast agents have a lower toxicity and a higher patient tolerance.

Despite all precautions adverse reaction can still occur. Initial and immediate management of these patients may then be crucial to patient survival. The treatment of the adverse reaction often rests in the hands of the radiologist and management should consist of the following (22): 1) monitor vital signs frequently; 2) ensure patient airway; 3) observe for aspiration; 4) oxygen when necessary; 5) establish intravenous route; and 6) administer specific drug therapy (Table 6).

It is as important not to overreact. Most of the medications listed in Table 6 do not cause harmful effects in a single dose; the dose of adrenalin, however, is more critical and it should be administered carefully.

Paramagnetic Contrast Agents

The three basic types of MR contrast agents are paramagnetic, supraparamagnetic, and ferromagnetic. The supraparamagnetic and ferromagnetic agents reduce T2 relaxation much more than T1 relaxation and come in the form of particles. Therefore, they are unfit for neuroradiology usage (intravascular injections) (Table 7) (39). In addition, reducing T2 relaxation is a disadvantage, because it causes a decrease in signal intensity on spin-echo images (39).

The only contrast agents presently usable for neuroradiology imaging are the paramagnetics. The paramagnetic ions used have magnetic dipole moments 1,000 times that of protons (40).

TABLE 6: Medications

Chlortripolon:	oral, IM, IV 0.2–0.3 mg/kg Maximum dose—20 mg
Diphenhydramine: (Benadryl) 50 mg = 1 cc	IV I mg/kg maximum dose—75 mg q 6 hr
Decadron:	IV 0.2 mg/kg Maximum dose—10 mg
Solu-cortef:	IV 2 mg/kg given over at least 10 min
Adrenalin: vial	1:1000 s.c. 0.01 mg/kg 0.01 ml/kg
Diazapam:	IV up to 0.2 mg/kg
OR	
Adrenalin:	1:10,000 IV 0.01 mg/kg 0.1 mg/kg
Maximum q. 15 mins × 2 doses	

TABLE 7: MR contrast agents

	Paramagnetic Chelate	Supraparamagnetic Particles	Ferromagnetic Particles
T1	↓		
T2	↓	↓↓↓	↓↓↓↓
Physical form	Chelates dissolved in solution	Fe aggregates as small particles	Fe aggregates as large particles
Number of paramagnetic atoms per molecule	1	10^{10}	10^{12}
Examples	Fe EDTA Mn EDTA Gd DTPA	Dextran plus Magnetite	Microspheres plus Magnetite

This affects the relaxation rate of the protons in the vicinity.

The formula for the relaxation rate is as follows (40):

$$1/T_1 \text{ obs} = 1/T_1 \text{ o} + 1/T_1, \text{ p}$$

where T_1 obs = observed relaxation time; T_1 o = intrinsic value; and T_1 p = contribution contrast agents makes to the relaxation rate.

The increased relaxation rate is proportional to the concentration of the paramagnetic agent and to square of the magnetic moment and inversely proportional to r^6, where r is the distance between the paramagnetic center and the protons to which it is bound.

Paramagnetic agents affect both T1 and T2 relaxation rates, although they affect T1 at a much lower concentration. Multiple paramagnetic agents have been tested and Gd^{3+} (gadolinium) had the largest magnetic moment (Table 7) (41). Gadolinium is attached to a chelating agent to decrease toxicity, as well as to increase the effectiveness of the paramagnetic centre (42–44).

Therefore, the selection of useful MR contrast agents is dependent on the following factors (40): 1) paramagnetic ion of a high spin number and a large electron-spin relaxation time; 2) small radius; 3) large complexes to retard molecular motion; 4) chelating agents for increasing stability and reducing toxicity; and 5) paramagnetic concentration > 100 μm. Other considerations include biodistribution, metabolism, and cost (40).

The chelating agent currently being used by Berlex is diethylenetriamine pentacetic acid (DTPA). The compound is ionic, although nonionic Gd contrast agents are being developed by other drug companies, eg, Squibb's (Princeton, NJ) Gd-DO3A is currently undergoing trial in North America.

Gd-DTPA (Magnevist) has an extremely low incidence of adverse drug reactions, ie, lower than nonionic iodinated contrast agents (Table 8) (45). It is not certain whether a nonionic Gd compound would further reduce the rate of contrast reaction.

Contrast reactions reported with Gd-DTPA include headache, nausea, and vomiting, which are the most common symptoms (45). Other reactions include hypertension, local burning sensation, and hiccups (45). Sensations of warmth or cold at the injection site are not included, since these may just represent temperature of the injected solution. The incidence of drug reactions varies from 0.7% without known history of allergy to 2.6% with known history of allergy (45). The overall incidence is approximately 1.46% (45). There is no significant difference between pediatric and adult population, and the reported pediatric incidence is 1.21%.

On the biochemical level, there is a reported incidence of 10%–20% transient increase in serum concentration of ions and less often with bilirubin as well (45). In neuroradiology practice, the use of both iodinated contrast agents for CT and paramagnetic contrast agents for MR relies mainly on breakdown of the blood-brain barrier.

TABLE 8: Adverse drug reactions comparing Gd-DTPA and LOCM

Symptoms	LOCM		Gd-DTPA	
	No.	%	No.	%
Nausea/vomiting	2363	1.40	57	0.42
Local warmth/pain	1635	0.97	55	0.41
Allergy-like skin reactions	1548	0.92	14	0.104
Allergy-like mucosal reactions	698	0.41	7	0.052
Flush	271	0.16	8	0.059

Because of the sensitivity of MR, the dosage of contrast medium given is much less than in CT.

Our regular pediatric dose for CT has been 3 mL/kg of 300 mg I_2/mL up to a maximum of 100 mL. The contrast is given in a bolus, since it is extremely difficult to infuse rapidly. The net effect by the bolus is as good as a rapid infusion. For MR scans, the recommended *adult* dose is 0.1 mmol/kg. We feel this is too low for children and that 0.25 mmol/kg is more appropriate. Experiments have shown that use of an increased dose does give better enhancement of lesions, with little increase in normal tissue and areas of edema (46).

The indications for contrast agents in CT and MR are similar, although CT usually has one or two additional uses. The commonest use in CT and MR are infection, tumor and tumor-like conditions, vascular diseases, and neurodegenerative disorders. CT also uses contrast media routinely for seizure disorders and, on rare occasions, to localize the tentorium and the falx for anatomical purposes.

Gd-DTPA is expensive. Recently, we looked into the cost-benefit ratio of Gd-DTPA for tumor diagnosis. In no case has T2 missed an abnormality, although T1 MR with Gd-DTPA often shows the lesion better than T2. However, there are some cases in which T2 is better than T1 with Gd-DTPA. In a few cases, Gd-DTPA brings about no enhancement (47). This often happens in low-grade glioma where there is little blood-brain barrier breakdown. Other than pituitary tumors, we have found little value in precontrast T1 studies. Therefore, in order to make Gd-DTPA more cost effective, we have proposed skipping the T1 precontrast study in selected cases.

Xenon CT

Inhalation of inert xenon gas mixed with oxygen has been used for studying perfusion of the brain. The theory of inhalational xenon CT is based on Fick's Principle and that xenon is a freely diffusible contrast agent. As xenon is carried by the blood flow to the brain, the changes seen on CT in Hounsfield units is proportional to: 1) percent concentration of inhaled xenon gas; 2) xenon solubility in arterial blood; 3) xenon blood brain proportional coefficient; and 4) local cerebral blood flow.

It is the cerebral blood flow we are interested in measuring; indications for xenon CT are: 1) occlusive vascular disease; 2) seizures; 3) trauma; 4) brain death; and 5) aneurysm and arteriovenous malformations.

Future Developments

In the iodinated contrast agents, new nonionic dimers are currently being developed. Berlex (Cedar Knolls, NJ) has introduced iotrolan for clinical trial in North America (48), while Sterling-Winthrop has introduced iodixanol. The advantages of the nonionic dimers include lower osmolality (isotonic intravascular injection) with high-iodine dose delivered. The contrast is of low toxicity, highly hydrophilic with low protein-binding capacity and, therefore, has a low incidence of contrast reactions (49, 50). The disadvantage will be that of high viscosity.

In MR, emphasis has been on low osmolar agents with increased tolerance such as Gd-DTPA bismorpholide, high relaxivity such as Gd-DTPA polylysine, and tissue-specific uptake from Gd-DTPA derivatives that are lipophilic (51). For example, porphyrins are endogenous chelating agents and metalloporphyrins tend to accumulate preferentially in tumor tissues (46). Nitroxide spin labels are synthetic paramagnetic organic molecules with one or more unpaired electrons and can be designed to lodge in cell membranes or to penetrate intracellular compartments (46).

Conclusion

We are in constant search for ideal contrast agents that manifest the following properties: 1) low toxicity; 2) high degree of efficacy; 3) wide margin of safety; 4) tissue or compartment specific distribution; 5) rapid clearance; 6) high degree of stability (in vivo and in vitro); 7) good solubility in water; and 8) uncomplicated synthesis.

Let us hope that our search continues at a goodly pace.

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