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REVIEW

Contrast media toxicity in children

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Overall, adverse reactions to contrast media (CM), either iodinated agents used primarily for CT and angiography or gadolinium-containing chelates for MRI, are unusual. Severe adverse drug reactions (ADR) are encountered only rarely. Fatal ADRs to CM have been reported but should be considered extremely rare. Most published information about ADRs to contrast media focuses on adult patients; the little epidemiologic information from pediatric populations is sparse. Part of the problem leading to this general lack of information on contrast media reactions in children is that clinical trials performed to justify governmental approval of new agents are invariably performed in adult subjects; if children are included at all they are typically a late addition Many of the contrast media formulations used commonly in children and many of the common applications for which CM are now employed were never specifically tested or governmentally approved for children; such uses are termed "off-label".

In this essay, I will review some of the clinically important forms of contrast media toxicity giving special attention to children where there is specific information.

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Contrast-induced nephropathy (CIN)

Renal impairment is one of the major side effects of intravenous iodinated contrast administration. A wide variety of risk factors for CIN have been described, of which pre-existing renal impairment and diabetes mellitus are the most important. The true frequency of contrast-induced nephropathy is difficult to establish because there are no standard acknowledged diagnostic criteria. In two large series (n=1114 and 443) of patients undergoing coronary angiography, 6 to 10% of patients had a post-procedural rise in serum creatinine of greater than 0.5 mg/dl [1, 2]. None of these patients became anuric or required hemodialysis. Another study that only included patients with impaired renal function (creatinine greater than 1.35 mg/dl) found the frequency of contrast nephropathy (defined as a rise of at least 25% in serum creatinine) depended primarily on the baseline creatinine level and presence of diabetes mellitus [3].

Routine creatinine testing prior to contrast administration is NOT necessary in all patients [4]. Indications for creatinine testing are listed in Table 1 [5, 6]. A creatinine level within the prior 30 days is sufficient in most clinical settings. Creatinine testing may be omitted for an urgent study where time is critical. This final determination should be made in consort with the requesting physician.

The decision to proceed with contrast administration in patients with a creatinine greater than 1.5 mg/dl should ALWAYS be a matter of clinical judgment, based on the individual circumstances of the patient and following consultation between the radiologist and requesting physician. The radiologist is ultimately responsible for determining the most appropriate imaging algorithm. If contrast administration is considered essential, the following options should be considered.

– Acetylcysteine. A frequently cited study claimed a ninefold reduction in contrast-induced nephropathy in

Table 1 Indications for creatinine testing prior to contrast administration

Indications
Diabetes mellitus (insulin-dependent or non-insulin dependent)
Age>70
Congestive cardiac failure
General debility (e.g., AIDS, advanced malignancy)
Solitary kidney (e.g., prior nephrectomy, congenital absence)
Collagen vascular disease
Paraproteinemia syndromes (e.g., myeloma)
Renal disease (e.g., renal transplant)
Family history of kidney failure
Liver disease (e.g., cirrhosis)
Currently receiving chemotherapy or other nephrotoxic drugs

chronic renal insufficiency patients receiving 600 mg acetylcysteine (Mucomyst®) orally twice daily on the day before and the day of a contrast-enhanced study, when compared to controls [7]. In the study, patients were randomly assigned to receive acetylcysteine and 0.45% saline intravenously or to receive placebo and saline. Only 1 of the 41 (2%) patients in the acetylcysteine group had an increase of at least 0.5 mg in serum creatinine at 48 h after administration of contrast compared to 9 of 42 (21%) patients in the control group (p=0.01). A more recent randomized study of 121 cardiac catheterization patients with chronic renal insufficiency (creatinine greater than 2.0) receiving a mean dose of 117ml of non-ionic contrast, showed 15 of 61 (24.6%) patients who received only saline infusion (0.45% at 1 ml kg^{-1} h^{-1}) from 12 h before to 12 h after angiography developed acute nephropathy (increase of creatinine by at least 0.5 at 48 h after the procedure) compared to only 2 of 60 (3.3%) patients who received saline infusion and acetylcysteine 400 mg bid on the day before and the day of the procedure (p<0.001) [8].

- Discontinue other nephrotoxic drugs.
- Hydration. IV hydration can be achieved with 1/2 normal saline [9].
- Decrease total amount of contrast administered.
- Increase the amount of time between contrast-enhanced studies.
- Infuse sodium bicarbonate solution. A trial [10] of patients with a baseline creatinine of at least 1.1 mg/dl study found a significant reduction (p=0.02) in the frequency of nephrotoxicity (defined as an increase of 25% or more in serum creatinine within 2 days of contrast) in those randomized to sodium bicarbonate infusion (1 of 60) compared to sodium chloride (8 of 59). Patients received 154 mEq/l of either sodium chloride or sodium bicarbonate, as a bolus of 3 ml kg^{-1} h^{-1} for 1 h before iopamidol contras media, followed by an infusion of 1 ml kg^{-1} h^{-1} for 6 h after the procedure. The advantage of this regime is that it can be implemented rapidly, facilitating the early scanning of patients from the Emergency Department, for example.

While these options may be helpful, it should be remembered contrast nephropathy is uncommon and usually transient. A critical diagnostic study should NOT be delayed because of excessive concern regarding possible contrast nephropathy.

Management of acute contrast reactions

Management is organized by symptom complex [11–13]. No attempt has been made to integrate symptomatology into an etiological scheme. It is prudent to administer oxygen to all patients having a contrast reaction, however mild, since the reaction may progress and become potentially life-threatening (Table 2).

Pre-medication to reduce the incidence and severity of contrast media reactions

Premedication is generally reserved for patients with a history of a significant prior contrast reaction. The risk of a repeat reaction in a patient with a history of prior severe reaction is 18.5%, even with non-ionic contrast media [14]. The use of pre-medication to prevent reactions to intravascular non-ionic contrast media is controversial [15, 16]. The most supportive study states pre-medication reduces the incidence of all reactions by approximately 60% [17]. Corticosteroids are considered by some to be the critical component of any premedication regime, and should be given at least twice, 12 and 2 h before the test. For simplicity, an oral regime is recommended: (Table 3).

Nephrogenic systemic fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an emerging scleroderma-like systemic fibrosing disorder. It develops in patients with chronic renal disease [18–20]. There is no definitive cure and the disease tends to be progressive. It can be fulminant in approximately 5% of cases and can be fatal [21]. NSF has been reported in all age groups including children. In December, 2006, the Food and Drug Administration released a Public Health Advisory discussing a possible association between NSF and the adminis-

Table 2 Management of acute contrast reactions

Acute contrast reactions	Management
"Hives" (urticaria)	Discontinue injection if not completed No treatment needed in most cases—reassure the patient Consider diphenhydramine (Benadryl®) PO/IM/IV 25–50 mg If severe/widely disseminated: epinephrine SC (1:1,000) 0.1–0.3 ml (=0.1–0.3 mg; if no cardiac contraindications)
Facial or laryngeal edema	0.1–0.3 ml epinephrine SC or IM (1:1,000; =0.1–0.3 mg) or, if hypotensive, 1 ml epinephrine IV (1:10,000) slowly (=0.1 mg). Repeat as needed up to 1 mg Give oxygen 6–10 l/min (via mask) If not responsive to therapy or if there is obvious acute laryngeal edema, seek appropriate assistance (e.g., cardiopulmonary arrest response team)
Bronchospasm	Give oxygen 6–10 l/min (via mask) Monitor: ECG, O_2 saturation (pulse oximeter), and BP Give beta-agonist inhalers, such as metaproterenol (Alupent®), terbutaline (Brethaire®), or albuterol (Proventil®; Ventolin®) 2–3 puffs; repeat as needed If unresponsive, epinephrine SC or IM (1:1,000) 0.1–0.3 ml (=0.1–0.3 mg) or, if hypotensive, epinephrine (1:10,000) slowly IV 1 ml (=0.1 mg)—Repeat up to 1 mg Alternatively, give aminophylline 6 mg/kg IV in D5W over 10–20 min (loading dose), then 0.4–1 mg kg^{-1} h^{-1}, as needed (caution: hypotension) Call for assistance for severe bronchospasm or if O_2 saturation <88% persists
Hypotension with tachycardia	Legs elevated 60∞ or more (preferred) or Trendelenburg position Monitor: ECG, O_2 saturation (pulse oximeter), and BP Give oxygen 6–10 l/min (via mask) Rapid large volumes of IV isotonic Ringer's lactate or normal saline If poorly responsive: epinephrine (1:10,000) slowly IV 1 ml (=0.1 mg; if no cardiac contraindications). Repeat as needed up to a maximum of 1 mg If still poorly responsive seek appropriate assistance (e.g., arrest team)
Hypotension with bradycardia (vagal reaction)	Monitor: ECG, O2 saturation (pulse oximeter), and BP Legs elevated 60∞ or more (preferred) or Trendelenburg position Secure airway and give oxygen 6–10 l/min (via mask) Rapid large volumes of IV isotonic Ringer's lactate or normal saline If unresponsive, atropine 0.6–1 mg IV slowly—repeat up to 2\3 mg in adult Ensure complete resolution of hypotension and bradycardia prior to discharge
Severe hypertension	Give oxygen 6–10 l/min (via mask) Monitor: ECG, O2 saturation (pulse oximeter), and BP Give nitroglycerine 0.4-mg tablet, sublingual (may repeat ×3) Transfer to intensive care unit or emergency department For pheochromocytoma–phentolamine 5 mg IV
Unconscious/unresponsive/pulseless/ collapsed patient	CALL CODE (Know the code phone number at *your hospital*. A code is not the time to look for the number in a phone book!) Institute Basic Life Support –Establish airway, head tilt, chin lift –Initiate ventilation and external chest compression –Continue uninterrupted until help arrives

Table 3 Oral pre-medication regime in patients considered at high risk for adverse contrast reactions

	Oral pre-medication regime
12 h before	50 mg prednisone OR 32 mg methylprednisolone (Medrol®)
2 h before	50 mg prednisone OR 32 mg methylprednisolone (Medrol®) 300 mg Cimetidine (Tagamet®) OR 150 mg ranitidine (Zantac®) 50 mg Diphenhydramine (Benadryl®)

tration of gadolinium-based contrast media in patients with moderate to end-stage kidney disease. A cause and effect relationship between NSF and gadolinium contrast media has not been established [22]. The preponderance of reported cases have been associated with administration of those gadolinium-containing contrast media based on open-chain chelates as compared with few, if any, cases, reported with the use of macrocyclic chelates of gadolinium. These clinical observations have raised speculation that a release of free gadolinium ions from the chelate–metal complexes

may have at least a partial causative role in the development of this disorder; other factors such as erythropoietin or co-existing inflammatory disease may also have a role. Even without knowledge of specific cause or causes for NSF, the prudent avoidance of gadolinium-chelate enhanced MRI in those patients with chronic and severe renal disease, now a common practice, appears to be having the desired benefit of reducing reports of new NSF cases. This rare condition may become almost unheard of.

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References

1. Davidson CJ, Hlatky M, Morris KG et al (1989) Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann Intern Med 110:119–124
2. Schwab SJ, Hlatky MA, Pieper KS et al (1989) Contrast nephrotoxicity: a radomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med 320:149–153
3. Barrett BJ, Parfrey PS, Vavasour HM et al (1992) Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. Kidney Int 41:1274–1279
4. Tippins RB, Torres WE, Baumgartner BR, Deborah A (2000) Are screening serum creatinine levels necessary prior to outpatient CT examinations? Radiology 216:481–484
5. Manual on Contrast Media, Edition 4.1, 1998 (revised 2001). American College of Radiology
6. Kintzel PE (2001) Anticancer drug-induced kidney disorders. Drug Safety 24:19–38
7. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W (2000) Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 343:180–184
8. Shyu KG, Cheng JJ, Kuan P (2002) Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol 40:1383–1388
9. Solomon R, Werner C, Mann D et al (1994) Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 331:1416–1420
10. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP (2004) Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 291:2328–2334
11. Manual on Contrast Media, Edition 5.0 (2004). American College of Radiology
12. Guidelines for the Management of Reactions to Intravenous Contrast Media. Royal College of Radiologists, London
13. Chapters 1–6, in: Bush WH, Krecke KN, King BF, Bettmann MA (1999) Radiology Life Support (Rad-LS): A Practical Approach. London/Arnold Publishers, New York/Oxford University Press, pp. 1–99
14. Siegle RL, Halvorsen RA, Dillon J et al (1991) The use of iohexol in patients with previous reactions to ionic contrast material. A multicenter clinical trial. Inv Radiol 26:411–416
15. Dawson P, Sidhu PS (1993) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 48:225–226
16. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K (1990) Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 175:621–628
17. Lasser EC, Berry CC, Mishkin MM et al (1994) Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. Am J Roentgenol 162:523–526
18. Deo A, Fogel M, Cowper SE (2007) Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. Clin J Am Soc Nephrol 2 (2):264–267 Mar
19. Morcos SK (2007) Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? Br J Radiol 80(950):73–76 Feb
20. Thomsen HS, Marckmann P, Logager VB (2007) Enhanced computed tomography or magnetic resonance imaging: a choice between contrast medium-induced nephropathy and nephrogenic systemic fibrosis? Acta Radiol 48(6):593–596 Jul
21. Todd DJ, Kagan A, Chibnik LB, Kay J (2007) Cutaneous changes of nephrogenic systemic fibrosis: predictor of early mortality and association with gadolinium exposure. Arthritis Rheum 56 (10):3433–3441 Oct
22. Wahba IM, Simpson EL, White K (2007) Gadolinium is not the only trigger for nephrogenic systemic fibrosis: insights from two cases and review of the recent literature. Am J Transplant 7 (10):2425–2432 Oct