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Original article

Incidence and severity of acute adverse reactions to intravenous iodinated contrast media: 8-year experience in King Chulalongkorn Memorial Hospital

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Background: Increasing numbers of acute adverse reactions to contrast media are being seen. Institutional information about incidence and severity of acute adverse reactions to contrast media is essential to inform radiologists of the both common and life-threatening acute adverse reactions encountered.
Objectives: We determined the overall, type-specific and severity of acute adverse reactions to intravenous iodinated contrast media at King Chulalongkorn Memorial hospital between January 2002 and December 2009.
Methods: This retrospective study reviewed 663 report forms for acute adverse reactions to contrast media among 74,010 intravenous iodinated contrast injections using five types of contrast media including meglumine/sodium ioxitalamate, iohexol, iopamidol, iopromide, and iobitridol.
Results: The overall incidence of acute adverse reactions to iodinated contrast media was about 0.9%. Of these 0.8% were minor, and 0.1% were major reactions. The majority of minor reactions were urticaria and the majority of major reactions were facial edema. One contrast-related death was reported. Incidence of acute adverse reactions to nonionic contrast media was 0.58%, and was 4.29 % in the ionic group. The type-specific incidence of acute adverse reactions was 4.29% for meglumine/sodium ioxitalamate, 0.82% for iohexol, 0.29% for iopamidol, 0.65% for iopromide, and 0.25% for iobitridol.
Conclusion: Acute adverse reactions to intravenous iodinated contrast media account for less than one percent of injections. The incidence is higher in the ionic contrast media group. The majority of reactions are mild. However, severe reactions can still be encountered and death related to contrast media exist.

Keywords: Acute adverse reactions, contrast media, intravenous, iodinated, incidence, severity

The number of imaging studies performed at King Chulalongkorn Memorial Hospital has increased dramatically over the past decade. This has resulted in increasing use of intravenous iodinated contrast media. With increased utilization of contrast media, rising numbers of acute adverse reactions were expected. Despite effort to reduce acute adverse reactions to iodinated contrast media by using low-osmolar nonionic agents and premedication in high-risk patients, severe acute reactions could still be encountered [1]. There are many factors affecting the incidence and severity of acute adverse reactions to intravenous iodinated contrast media [2-6]. The primary aim of this study was to retrospectively determine the incidence and severity of acute adverse reactions to intravenous iodinated contrast media at our institution, King Chulalongkorn Memorial Hospital.

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Our study included a subgroup analysis of the incidence and severity of acute adverse reactions from each type of iodinated contrast media [7].

Materials and methods

This study was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University. Informed consent was waived because of the retrospective nature of the study. Between January 2002 and December 2009, 74,130 patients underwent intravenous iodinated contrast media injections mainly using five different types of iodinated contrast media. These included meglumine/sodium ioxitalamate (Telebrix), iohexol (Omnipaque), iopamidol (Iopamiro), iopromide (Ultravist), and iobitridol (Xenetic).

All patients who had undergone intravenous pyelography or computed tomography with injection of intravenous iodinated contrast media at our radiology department were considered eligible.

Patients with intra-arterial contrast media use, isolated intracavitary iodinated contrast media use, contrast media injection outside our radiology department such as in the cardiology unit, sample contrast media, and incomplete data documentation were excluded from the study. All 74,010 cases in eligible patients, including adults and children who did not meet the exclusion criteria, were recruited to the study without further sampling. The number of patients using each type of contrast media was noted. If there was no documentation, the patients were categorized in the unknown group.

The volume of contrast media administration was determined by standard departmental protocol, primarily based on patients' weight, and ranged from 1 to 3 ml/kg. Manual contrast injection was used for intravenous pyelography and computed tomography of the brain while power injectors were used for the remainder. The rate of contrast injection was up to 5 ml/second.

Prior to contrast medium injection, patients would be briefly instructed about acute adverse reactions that could occur and were told to report any abnormality to attending nurses or residents. Then, after injection of iodinated contrast media, each patient would be monitored for adverse reactions for one hour, except for those already admitted to our hospital who would be send back for observation at their ward. Reactions that were not a subject of a complaint by the patients were considered mild and clinically insignificant. Reactions were evaluated and managed by the attending resident, fellow, or radiologist. Treatment was primarily based on guidelines proposed by Chaopathomkul et al. [8]. After the incident, an attending nurse at the involved station would file a report form for acute adverse reactions to iodinated contrast media. The standard report forms contained information concerning the modality of the imaging, risks for adverse reactions, type and amount of contrast media used, symptoms, onset of the first adverse reaction, longest duration of reactions, treatments given, and post treatment status. Late reactions, those occurring later than one hour after contrast injection and local reactions such as burning sensation or contrast extravasation, were not included in the documentation.

This study retrospectively reviewed all 663 report forms collected between the beginning of January 2002 and the end of December 2009.

Data analysis

The incidence was analyzed and shown as percentage. Severity grading was categorized into minor and major reactions according to our departmental classification system, which was mainly based on treatment required and is similar to that proposed by the American College of Radiology [9]. Minor reactions, were defined as those likely to be self-limiting or require no more than antihistamine or supportive treatment, including urticaria/ itching, nausea/vomiting, headache, abdominal pain, and other minor symptoms. Major reactions were defined as signs/symptoms requiring special attention and more intensive treatment, including facial edema, wheezing, hoarseness, dyspnea, apnea, hypotension, cold clammy skin, profuse sweating, confusion, loss of consciousness, and seizures. Severity of acute adverse reactions were classified as minor and major reactions were presented as a percentage. Patients who experienced major reactions were further categorized according to need for admission, and deaths if related to contrast administration.

Onset was divided into two categories, within the first 30 minutes and after more than 30 minutes. Treatments given were classified into five groups including observation, antihistamines only, antihistamines and steroids, steroids only and others such as adrenaline, bronchodilators, oxygen, intravenous fluid administration, or cardiopulmonary resuscitation.

Duration was divided into two categories, lasting no more than 30 minutes and more than 30 minutes. After treatment, we considered two outcomes, improved or need for further departmental referral. Departmental referral meant that patients required transfer to our emergency department or ward for further monitoring and treatment. General medical records were reviewed only in patients who had major reactions, required admission, or died.

Subgroup analysis of incidence of acute adverse reactions to each type of intravenous iodinated contrast media involved only data between 2006 and 2009, which comprised of 41,331 injections, because of incomplete documentation in the earlier years.

Results

There has been increasing use of intravenous iodinated contrast media at King Chulalongkorn Memorial Hospital, being 8,528 injections in 2002 and 12,267 injections in 2009. Overall incidence of acute

adverse reactions to iodinated contrast media was 0.9% (663 cases in 74,010 injections). Minor reactions occurred in 0.8% (606 cases) and major reactions amounted to 0.1% (57 cases). The majority of minor reactions were urticaria and the majority of major reactions were facial edema. Details of the signs and symptoms of acute adverse reactions are shown in **Figure 1**. Other minor reactions included shivering, sneezing/coughing/nasal congestion/nasal discharge, dizziness, eye pain, red eyes, flushing, perioral numbness, fatigue, and tinnitus. Other major reactions included episodes of chest discomfort (6 cases), hypotension (7 cases), palpitation/near syncope (3 cases), and cardiac arrest (2 cases).

The incidence of major reactions showed a decreasing trend over the years studied (**Figure 2**). Considering the major reactions, there was one ward admission and no immediate death following contrast media injection. There was one death closely related to an acute adverse reaction to contrast media in a 64-year-old man with underlying hepatocellular carcinoma post fifth transarterial oily chemoembolization who had anaphylaxis and cardiopulmonary arrest following iopromide injection for elective abdominal computed tomography. Resuscitation was successful after adrenaline administration and a 30-minute cardiopulmonary resuscitation (CPR). The patient was admitted because of complications including acute renal failure and gram positive septicemia and died after about 30 days of hospitalization. Another patient with cardiac arrest was a 50-year-old man with underlying unresectable hepatocholangiocarcinoma who had experienced a previous episode of mild urticaria following iopromide injection. Despite steroid premedication before iopromide reinjection, he went into cardiac arrest. His status improved following adrenaline injection and a 5-minute CPR. He was observed at the emergency department for one day then discharged himself against advice.

Over 98% of cases were the first acute adverse reactions within the first 30 minutes after contrast injection, while 1.4% had a 31 to 60 minute delay. All cases with an onset later than 30 minutes were minor reactions.

In terms of treatment, about 15% of cases were observed after reactions without any medication, 72% received only antihistamines orally or intravenously, 10% received combinations of antihistamines and steroids, 0.3% received steroids only, and 2.1% received other treatments such as adrenaline, bronchodilators, oxygen, intravenous fluid administration, or cardiopulmonary resuscitation.

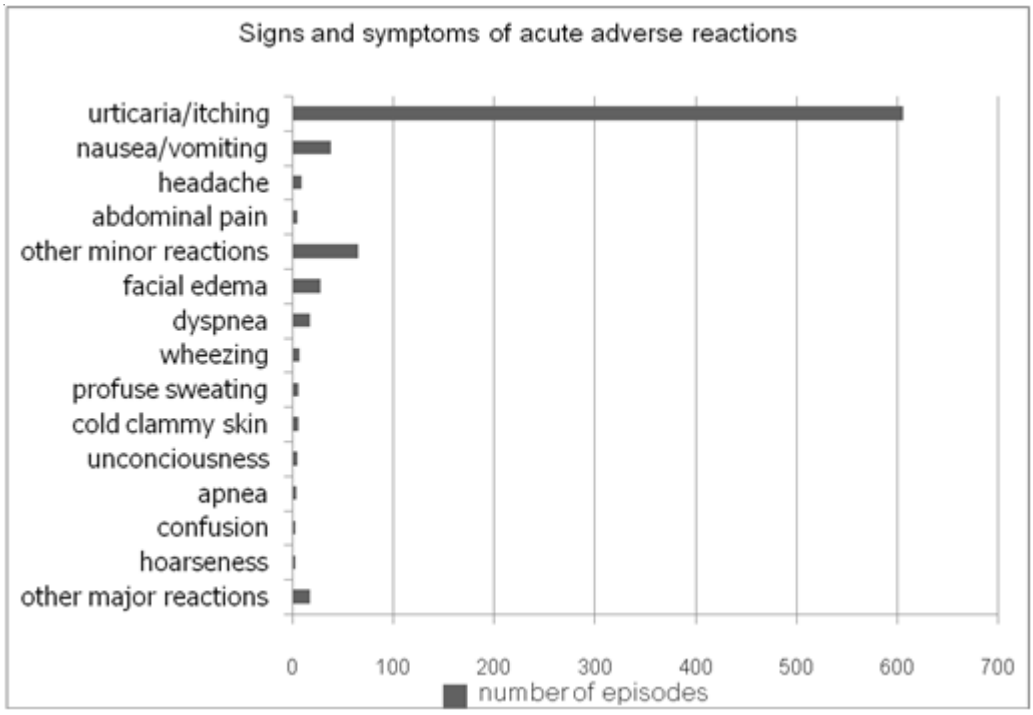

Figure 1. Details of symptoms and signs of acute adverse reactions to intravenous iodinated contrast media

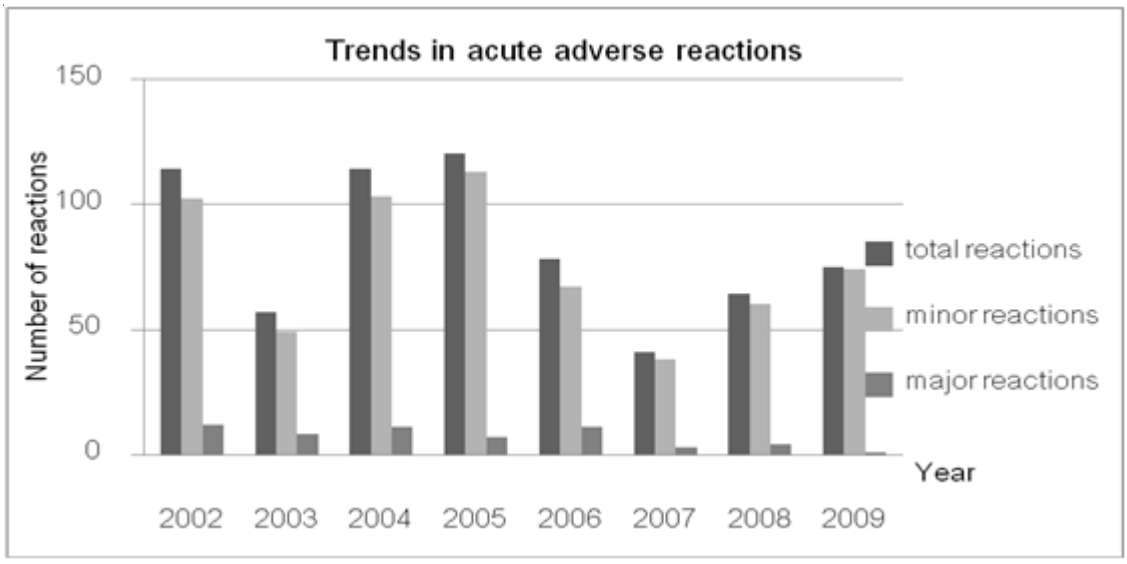

Figure 2. Trends of acute adverse reactions to intravenous iodinated contrast media in each year

The duration of symptoms lasted up to 30 minutes in about 76% of cases and prolonged more than 30 minutes in 12% of cases. The duration was not listed in 12% of cases.

After treatment, over 98% of patients improved, but 13 patients (1.96%) needed departmental referral either to emergency unit or ward for further monitoring and treatment. Ten patients had improved and were discharged from the emergency department. One was admitted and died. One was referred to a private hospital and another one left the hospital against advice.

There were 30,184 injections categorized as the unknown contrast media group between 2002 and 2005, while only 138 were listed as unknown between 2006 and 2009. Therefore, analysis of the type of intravenous iodinated contrast media was restricted to data between 2006 and 2009 involving only 41,331 injections. There were 582 (1.4%) meglumine/sodium ioxitalamate injections, 4,864 (11.8%) iohexol injections, 6,791 (16.4%) iopamidol injections, 25,444 (61.6%) iopromide injections, 3,512 (8.5%) iobitridol injections, and 138 (0.3%) unknown contrast media. Type-specific contrast media use in each year during 2006 to 2009 is shown in **Figure 3**.

Incidence of acute adverse reactions to nonionic contrast media was 0.58%, while it was 4.29 % in the ionic group. Type-specific incidence of acute adverse reactions was 4.29% for meglumine/sodium ioxitalamate (3.95% minor reactions, 0.34% major reactions), 0.82% for iohexol (0.82% minor reactions, 0% major reactions), 0.29% for iopamidol (0.28% minor reactions, 0.01% major reactions), 0.65% for iopromide (0.60% minor reactions, 0.05% major reactions), and 0.25% for iobitridol (0.25% minor reactions, 0% major reactions). Type-specific incidence of acute adverse reactions are shown in **Table 1**. The highest incidence of acute adverse reactions was in meglumine/sodium ioxitalamate group, which was the only ionic contrast media in this study. The lowest was in the iobitridol group. Meglumine/sodium ioxitalamate also revealed a high incidence of major reactions while iopromide had the highest incidence of major reactions among nonionic contrast media.

Discussion

The overall incidence of acute adverse reactions to iodinated contrast media was about 0.9%, including 4.29% for the ionic contrast media group and 0.58% for the nonionic group, which was lower than those of a large study reported by Katayama et al. [2] that reported 12.6% prevalence in ionic group and 3.1% in nonionic group. This difference may be explained because the study reported by Katayama et al. [2] had included heat sensation as an acute adverse reaction. However, our incidence of acute adverse reactions to nonionic contrast media had shown a similar figure (0.6%) as the retrospective study conducted by Wang et al. [10]. Generally speaking, there were variations of definition of minor and major reactions in each study, resulting in difficult comparisons.

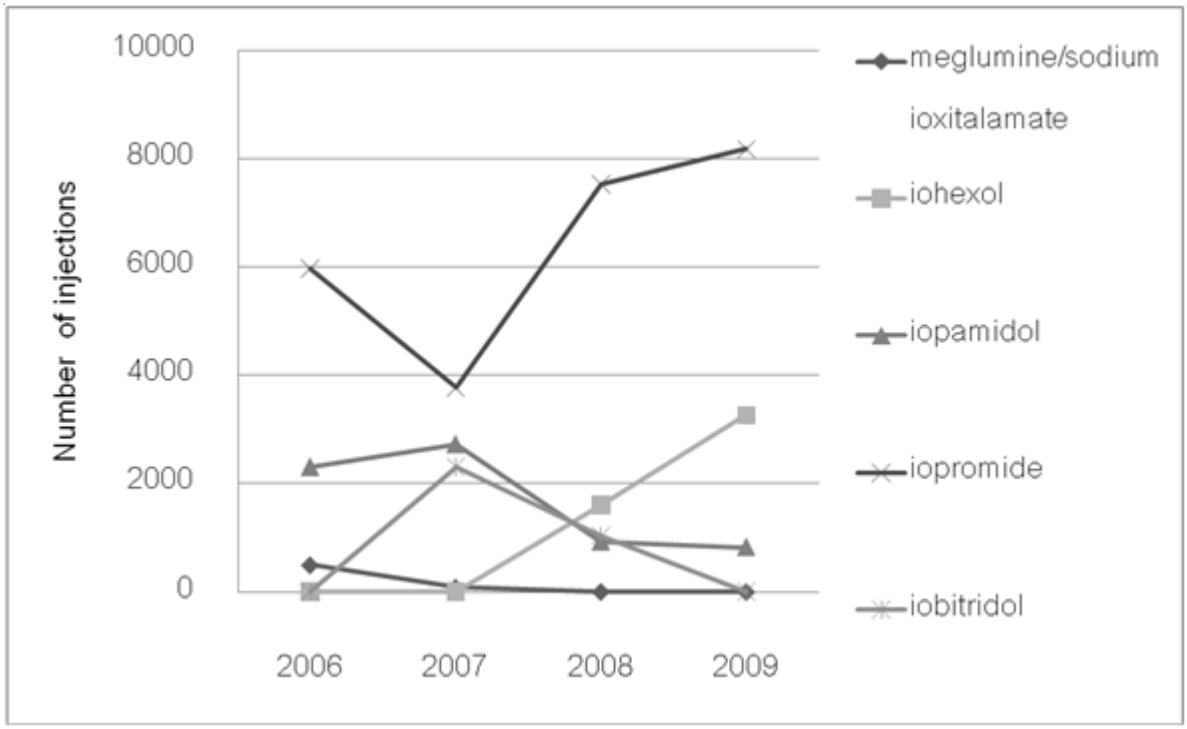

Figure 3. Type-specific contrast media used each year from 2006 to 2009

Table 1. Type-specific incidence of acute adverse reactions from January 2006 to December 2009

Type of contrast media	Sodium meglumine/ ioxitalamate			Iohexol			Iopamidol			Iopromide			Iobitridol		
No. of injections	582			4864			6791			25444			3512		
Severity	minor	major	total	minor	major	total	minor	major	total	minor	major	total	Minor	major	total
No. of reactions	23	2	25	40	0	40	19	1	20	153	13	166	9	0	9
% reactions	3.95	0.34	4.29	0.82	0	0.82	0.28	0.01	0.29	0.60	0.05	0.65	0.25	0	0.25

Researchers have reported fatalities related to iodinated contrast administration [2, 11, 12]. Our study showed a death rate of about 1:70,000 and higher than 1:170,000 reported by Katayama et al., which is quoted by others [4]. Mortele et al. [13] performed a prospective study in 29,508 injections of iopromide and reported one death related to iopromide injection.

The incidence of major reactions showed a decreasing trend, probably resulting from decreasing use of ionic contrast media. Our study corresponded well with previous studies showing urticaria and nausea/vomiting as the majority of minor reactions [2, 11] and facial edema as the majority of major reactions [13].

Our study revealed that over 98% of cases had their first acute adverse reaction within the first 30 minutes after contrast injection and all cases that had onset later than 30 minutes were minor. This implied that the first 30 minutes was the critical period for monitoring major reactions [4, 9].

There was a higher rate of antihistamine use compared with that reported by Wang et al. [10], who reported antihistamine in only 26% of cases. Additional data regarding acute adverse reactions and treatment should be collected to further evaluate the appropriateness of treatment.

In our study, iopromide possessed the highest incidence of major acute adverse reactions among nonionic contrast media (0.05%) which resembled the incidence of moderate to severe reactions shown by Mortele et al. [13]. We cannot conclude, clinically or statistically, that iopromide carried a significantly higher

risk for major acute adverse reactions because there is a wide range of number of patients injected with each type of contrast media and heterogeneity of population due to retrospective study design.

A study of 8,931 cases conducted by Gomi et al. [7] concluded that there was a significantly higher incidence of acute adverse reactions with iomeprol and iopromide use compared with three other nonionic contrast media. However, there are several smaller studies reporting no significant difference in adverse effects between iopromide and other nonionic contrast media [14-16].

A major weakness of our study is its retrospective nature, together with a lack of documented demographic data among the groups using each contrast media. Possible risk factors for acute adverse reactions to contrast media were not controlled or incompletely documented. The number of patients who received premedication, but did not have acute adverse reaction was not assessed. The group containing more cases with risk factors may have a higher prevalence to contrast reactions [3, 4].

Dillman et al. [17] reported a significantly lower rate of allergic-like reactions to intravenous iodinated contrast media in children compared to adults, but there is no documentation of the proportion of children and adult in our study.

Another limitation is the result of incomplete documentation. Incomplete documentation may result in underestimation of the incidence of acute adverse reactions. For example, debilitated patients or patients receiving multiple interventions might develop acute adverse reactions-like symptoms, but where the cause could not be determined, the incident was not included in our study.

Conclusion

The overall incidence of acute adverse reactions to intravenous iodinate contrast media is less than one percent. Incidence of adverse reactions is higher in ionic contrast media. The majority of reactions are mild. However, severe reactions can still be encountered and death related to contrast media exists.

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References

1. Davenport MS, Cohan RH, Caoili EM, Ellis JH. Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology. 2009; 253:372-9.
2. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. Radiology. 1990; 175:621-8.
3. Bettmann MA. Frequently asked questions: iodinated contrast agents. Radiographics. 2004; 24 Suppl 1: S3-10.
4. Morcos SK. Review article: Acute serious and fatal reactions to contrast media: our current understanding. Br J Radiol. 2005; 78:686-93.
5. Singh J, Daftary A. Iodinated contrast media and their adverse reactions. J Nucl Med Technol. 2008; 36: 69-74; quiz 6-7.
6. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. AJR Am J Roentgenol. 1991; 157:1153-61.
7. Gomi T, Nagamoto M, Hasegawa M, Katoh A, Sugiyama M, Murata N, et al. Are there any differences in acute adverse reactions among five low-osmolar non-ionic iodinated contrast media? Eur Radiol. 2010; 20:1631-5.
8. Chaopathomkul B RK, Leelanukrom R, Avihingsanon Y, Khovidhunkit W, Sunthornyothin S. Clinical practice guideline for contrast media administration in diagnostic imaging. Chula Med J. 2010; 54:375-90.
9. Americal College of Radiology Manual on Contrast Media, version 7. 2010.
10. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR Am J Roentgenol. 2008; 191:409-15.
11. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. AJR Am J Roentgenol. 2001; 176:1385-8.
12. Fukuda N, Shinohara K, Shimohakamada Y. Fatal cardiac arrest during infusion of nonionic contrast media in a patient with essential thrombocythemia. AJR Am J Roentgenol. 2002; 178:765-6.
13. Mortele KJ, Oliva MR, Ondategui S, Ros PR,

Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol. 2005; 184:31-4.

14. Hoogewoud HM, Neiss AC, Woessmer B. Double-blind randomized study comparing ioversol 300 versus iopromide 300 abdominal computed tomography (CT scanner). Ann Radiol (Paris). 1992; 35:273-5.
15. Hoogewoud HM, Woessmer B. Iobitridol 300 compared to iopromide 300--a double-blind randomized phase-III study of clinical tolerance in total body CT. Acta Radiol Suppl. 1996; 400:62-4.
16. Bouard JC, Lyonnet D, Illes JP, Bouard-Monnier C, Rouviere O, Pangaud C. Clinical experience with iobitridol 250-300 in digital subtraction angiography. Double-blind randomized studies vs. iopromide and iohexol. Acta Radiol. 1996; 400:85-8.
17. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. AJR Am J Roentgenol. 2007; 188:1643-7.