

“Iohexol in Diagnostic Imaging: A Narrative Review of Its Safety and Adverse Reaction Profile”

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Abstract

Iodinated contrast agents such as Iohexol are commonly used to diagnose vascular anomalies due to efficacy. Though Iohexol has a good safety profile, it is responsible for Adverse Drug Reactions (ADRs), which vary from minor symptoms to life-threatening complications. This review combines evidence from literature regarding the safety of Iohexol in terms of incidence, type, and management of ADRs to inform clinical practice. Systematic searching of PubMed and Scopus until March 2025 employed search terms: "Iohexol," "Adverse reactions," and "angiography." Original studies that reported on Iohexol safety were included, while reviews and uncertain data were not. Two reviewers assessed titles/abstracts/full texts independently, having discrepancies resolved through consensus or third reviewer. Collected data covered study design, population, sample size, and outcomes. Twelve studies found Iohexol-related ADRs were predominantly mild-to-moderate (Nausea, vomiting, and urticaria). Severe reactions (anaphylaxis, cardiovascular collapse) were uncommon (<1%). Contrast-induced nephropathy (CIN) was notable in high-risk patients (renal impairment/diabetes). Comparative studies indicated Iohexol had fewer ADRs than ionic agents. Pre-treatment (antihistamines) and hydration minimized risks. Iohexol safety profile in angiography is good, with the majority of ADRs being mild and controllable. Rare severe reactions need special attention, particularly in high-risk populations. Preventive procedures (hydration, pre-treatment) also decrease risks. Patient evaluation, informed consent, and monitoring need to be prioritized by clinicians. Additional research should optimize risk stratification and management strategies.

Keywords: Iohexol, Angiography, Adverse drug reactions.

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Introduction

Angiography is a specialized medical imaging procedure that visualizes blood vessel and is essential for detecting anomalies like blockages, narrowing, and deformities in blood arteries.¹ It would be challenging to differentiate blood arteries from surrounding tissues without contrast chemicals. In angiography, a variety of contrast agents are used, however iodinated contrast agents are the most frequently used.²

Iohexol is a common non-ionic, water-soluble contrast agent, especially for Computed Tomography (CT) and X-ray treatments. The chemical formula for it is C₁₉H₂₆I₃N₃O₉. Its molecular weight is 821.142 g/mol. Its IUPAC designation is 5-[acetyl(2,3-dihydroxypropyl)amino]-1-N,3-N-bis(2,3-dihydroxypropyl)-2,4,6-triodobenzene-1,3-dicarboxamide with CAS number 66108-95-0 being its assigned number.³ As a low-osmolar contrast agent in comparison to its earlier counterparts, It has a melting point between 174 and 180 °C (345 and 356 °F) and an osmolality between 322 mOsm/kg and 844 mOsm/kg.⁴

Pharmacokinetics of Iohexol

Iohexol has a three-compartment pharmacokinetic model, with a distribution half-life of 22 minutes, excretion half-life of 2.1 hours, and terminal elimination half-life of 12.6 hours.⁵ In people with normal kidney function, approximately 87% of an administered dose is renally eliminated within 3 hours, with a mean renal clearance of 120 mL per minute. The total body clearance is around 131 mL/min, and the distribution volume ranges from 165 to 270 mL/kg. Excretion delays occur in renal failure, resulting in increased biliary clearance. Notably, Iohexol undergoes little metabolism in humans, and remains mainly unaltered during excretion.⁶

Iohexol can be administered orally, intravenously, intrathecally, or by other body cavity routes due to its water solubility, which makes it useful for a variety of imaging procedures. It is frequently used to view blood arteries and other internal structures in myelography, Nephroangiography, arteriography, and CT imaging. Despite Its overall safety record, Adverse Drug Reactions (ADRs) can occur, ranging from minor symptoms like headache and nausea to serious events like anaphylactic shock low blood pressure, headache, itching, vomiting, skin flushing, and kidney issues, and renal failure.⁶ Safe clinical use of it requires a thorough understanding of these effects. Existing data must be consolidated because it is dispersed. The necessity for a thorough assessment of safety of Iohexol is addressed in this review. This study

intends to evaluate organ-specific side effects, compare the safety of Iohexol with other contrast agents, characterize the frequency and types of adverse reactions to Iohexol, and offer suggestions for safer clinical use.

Methodology:

Search strategies and selection criteria

To conduct this narrative review, articles were collected thorough literature search using the PubMed and Scopus databases. The search was conducted from the beginning to March 2025, and the key words and phrases used in the search strategy were "Iohexol," "Adverse reactions," and "angiography." The Boolean operators "AND" and "OR" were used to combine free-text terms and medical subject headings (MeSH) terms, and the reference lists of pertinent articles were manually searched.⁷

Criteria for inclusion and exclusion

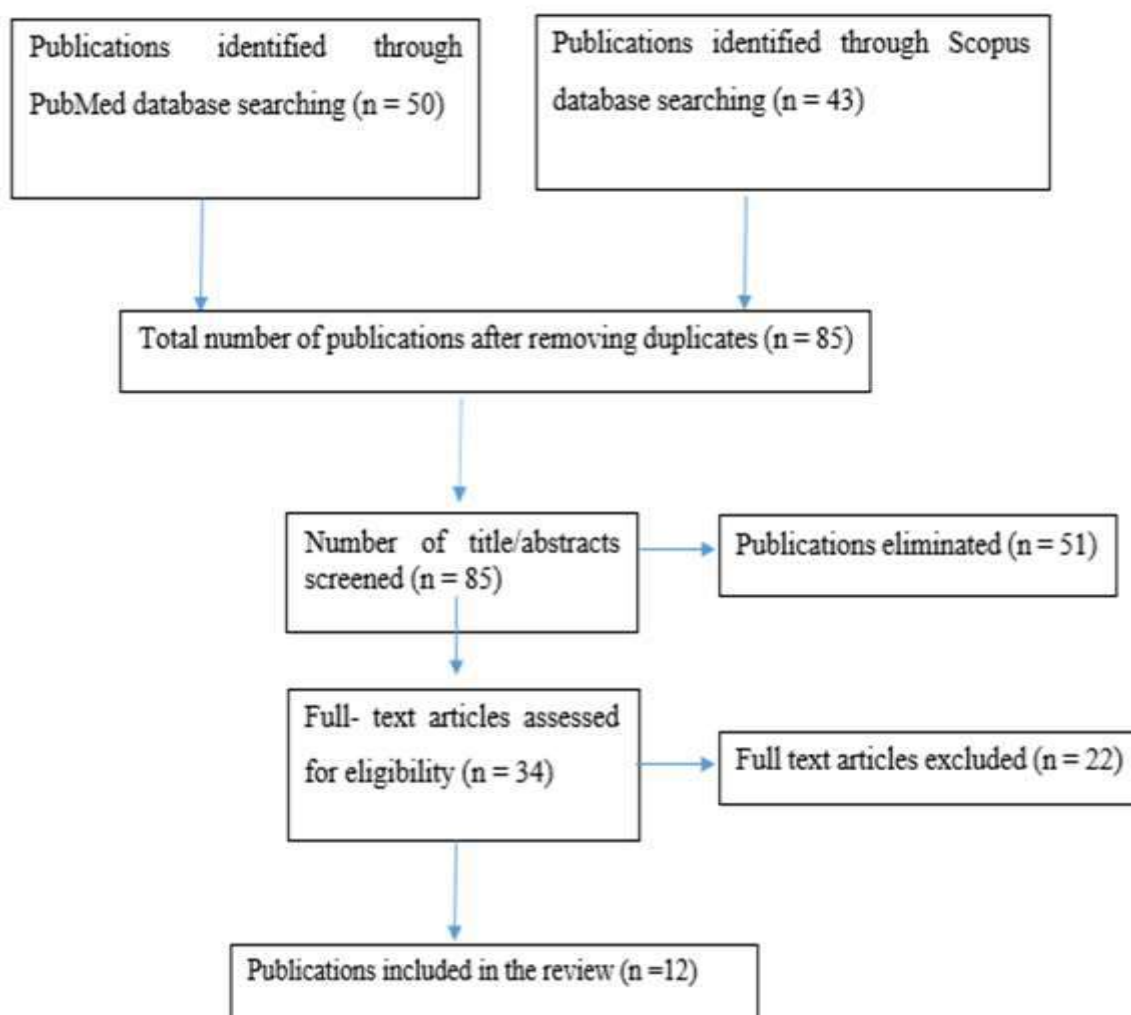
Original research publications, such as observational, experimental, and randomized controlled trials, studies concentrating on safety profile and adverse reactions of Iohexol, studies published in peer-reviewed journals, and English-language papers were included. Research having inadequate or ambiguous data on adverse responses, review papers, editorials, letters to the editor, and conference abstracts, and articles that did not clearly examine Iohexol or did not offer distinct data for Iohexol excluded.

Study selection and extraction of data

The predetermined inclusion and exclusion criteria were used to evaluate the eligibility of full-text articles two separate reviewers (BA, SA) checked the identified articles' titles and abstracts for relevancy.⁸ Discussion and agreement among the reviewers, or, if required, the consultation of a third reviewer (PA), were used to settle any discrepancies. The included studies were analysed to extract the study design, study population, sample size, and outcomes of the study.

Figure caption:

Figure 1. Search strategy and study selection process



Results:

The search strategy found total of 93 publications among which 50 from PubMed and 43 from Scopus respectively. After deleting 8 duplicate records, a total of 85 publications remained. These were filtered by title and abstract, 51 studies which were irrelevant to the review were discarded. After a thorough examination of the complete text 12 publications were remained. The results search strategy and articles selection is represented in figure1. The findings of selected 12 publications were organized in Table 1.

Table:

Table 1. Summary of selected articles

Sl No.	Study type	Population	Main outcome
1	Multicentre, double-blind, randomized, phase 3 study.	Total = 225 subjects, 115 received Iohexol-380 and 110 received Iohexol-350	In the iohexol-380 group, 56 (48.7%) of the 115 patients experienced 75 adverse events, while 51 (46.4%) of the 110 participants in the iohexol-350 group experienced 74 occurrences ($p = 0.690$). In neither group were there any documented serious adverse medication responses. ⁸
2	Prospective, observational, multicentre study	Total = 83 patients,	35 (42.1%) patients out of 83 injected with Iohexol 240 mgI/mL developed adverse events. 32 (38.5%) cases of acute adverse events and 3 (3.6%) cases of delayed adverse events. ⁹
3	Phase III, double-blind, randomized, parallel-design clinical trial	Total = 49 adult patients	Adverse events occurred in 25% of patients in the iohexol-300 (IOH-300) group. Headache was the most frequent adverse effect. ¹⁰
4	Double-blind, randomized, parallel group trial	Total = 39 patients, Male=14, Female=25	Adverse events occurred in 7 (17%) in the Iohexol group ($P = 1.0$): nausea (2), vomiting (4), headache (2), dizziness (1), paraesthesia (1), and visual abnormalities (1) were the events that were recorded. 31 (79 %) in the Iohexol group ($P = 0.59$) reported discomfort. They were all moderately or somewhat intense. ¹¹
5	Prospective cross-sectional study	Total = 1,020 patients referred for cardio angiography	9% of Iohexol-treated participants experienced cardiac adverse effects, including angina pectoris, arrhythmia, and dyspnea. 11% of patients aged 65 years had developed Cardiac adverse events. 2 patients developed ventricular fibrillation. ¹²
6	Double-blind, randomized, parallel group trial	Total = 42 patients undergoing intra-arterial cerebral digital subtraction angiography. Male =18, Female = 24	5 (11%) in the Iohexol group reported Nausea(1), Paraesthesia(1), Visual disturbance (1), and Dizziness (2). ¹³
7	Prospective, double-blind,	Total = 125 patients	54 (43.2%) patients have developed ADRs. ¹⁴

	randomized clinical trial.		
8	Two-centered, prospective, double-blind study	Total = 50 patients	Total adverse event = 5 (10%), Taste perversion 3 (6%), Injection pain 1 (2%), Purpura 1 (2%). ¹⁵
9	Retrospective cohort study	Total = 851 patients	14 (1.7%) patients out of 851 developed late responses with iohexol. ¹⁶
10	Randomized, double-blind, phase III clinical trial	Total = 74 patients	27 (36.4%) patients reported pain, 67 (90.54%) patients reported Warmth. ¹⁷
11	Randomized, double-blind, crossover clinical trial	Total = 59 patients	5 (8.47%) patients developed ADRs, out of which Chest pain/angina pectoris - 2 (40%), Bradycardia - 1 (20%), Discomfort/pain - 1 (20%), Urticaria - 1 (20%). ¹⁸
12	Retrospective analysis	Total = 201 patients, 151 with type 2 diabetes mellitus and 50 non-diabetic patients.	CIN occurred more frequently in diabetic patients (40.4%) compared to non-diabetic patients (16%) ($p < 0.002$). ¹⁹

Table 1. Summary of selected articles

Incidence of Side Effects Related to the Application of Iohexol during Angiography in the Total Population

General Incidence of Adverse Effects

The incidence of adverse events with Iohexol is low compared to ionic contrast agents. A comparative study with sodium meglumine diatrizoate showed lower adverse event rates with Iohexol (10.2%) compared to diatrizoate (31.6%).²⁰

Mild to Moderate Reactions- Common mild to moderate reactions include nausea, vomiting, and urticaria. In a study of 899 patients, mild reactions were observed in 19.47%, while moderate reactions occurred in 1.33%.²¹

Severe Reactions- Severe reactions such as anaphylactic responses, hypotension, and cardiovascular collapse are rare. Most studies report severe reactions in less than 1% of cases.²²

Specific Adverse Events

Nausea and Vomiting- These are among the most frequent adverse effects of Iohexol. A study comparing Iohexol with ioxaglate and iopamidol showed that nausea and vomiting were lower with iohexol (1%) compared to ioxaglate (16%).²³

Urticaria and Cutaneous Reactions- Generally mild and self-limiting. A study on 300 coronary angiography patients noted a very low incidence of urticaria with iohexol.²³

Cardiovascular Effects- Iohexol causes minimal hemodynamic alterations. In a comparative study, iohexol showed no significant effects on systolic arterial pressure, PR interval, or ventricular extrasystole.²³ another study found it induced smaller changes in heart rate and blood pressure than ionic agents.²⁴

Delayed Allergy-Like Reactions- Delayed reactions (occurring more than 1 hour post-injection) are rare. They are typically mild to moderate, manifesting as maculopapular exanthema or urticaria. Incidence is estimated to be between 0.5% and 2%.²⁴

Contrast-Induced Nephropathy (CIN) - CIN is a known complication, particularly in patients with pre-existing renal impairment. In patients with chronic kidney disease and diabetes, CIN incidence with iohexol was 10.5%, comparable to iodixanol (9.8%).²⁵ Increased risk in patients with renal impairment, diabetes, dehydration, and congestive heart failure. Hydration with low-osmolar contrast media is recommended to reduce CIN risk.²⁶

Comparative Analysis of Side Effects of Iohexol in Angiography in Different Body Systems

The comparison of side effects of Iohexol in angiography in the cardiovascular, nervous, renal, gastrointestinal, respiratory, and integumentary systems has been carried out based on data from different studies.

Cardiovascular System

The cardiovascular system is usually involved during angiography, particularly by hemodynamic changes caused by contrast media. Moderate to severe cardiovascular reactions, including changes in blood pressure and heart rate, have been described for iohexol. Numerous studies have proven that iohexol is not significantly associated with the risk of severe cardiac events compared to other LOCMs, but in patients with known cardiovascular disease, for instance, hypertension or coronary heart disease, the potential risk of adverse cardiovascular events could be higher.²⁷

In a single trial to compare iohexol versus ioversol in patients who underwent Percutaneous Coronary Intervention (PCI), no difference between the two agents in the frequency of CIN or in renal function was found. The number of stents delivered via coronary arteries and diabetes, but not the test agents, were found to be independent predictors for CIN.²⁸

Nervous System

The nervous system is also affected by iohexol, particularly in the presentation of mild to moderate neurological signs. The mild and very common side effects include headache, dizziness, and, rarely, seizures. In a prospective observational study of iohexol adverse drug reactions during CT scans, the investigators found all the acute adverse effects were mild and self-limiting, with none of the adverse reactions found to be potentially life-threatening. Another study on acute adverse effects of intravenous iodinated contrast agents, including iohexol, stated that the majority of the effects were mild, with none of the serious neurological effects.²⁸ Iohexol was less prone to cutaneous and respiratory adverse effects than iopromide in a comparative study, suggesting that iohexol possesses an even better safety profile regarding the nervous system.⁶

Renal System

The renal system is one of the most commonly affected systems by contrast media, particularly in patients who already have renal insufficiency. Iohexol, like other iodinated contrast media, can cause contrast-induced nephropathy (CIN), which is a reversible impairment of renal function. Numerous studies have contrasted nephrotoxicity of iohexol with other contrast agents.

A double-blind, randomized, prospective study comparing iohexol and iodixanol in diabetic and chronic kidney disease patients revealed no difference in the incidence of CIN between the two drugs. The overall CIN incidence was, however, noted at 10.5% and highlighted the importance of careful patient selection and hydration protocols.²⁵ A clinical trial comparing iohexol and ioversol in PCI patients found no difference between the two drugs for the incidence of CIN or renal function. There was a higher rate of CIN with iohexol compared to iodixanol in a comparative study including patients with chronic heart failure undergoing coronary angiography or coronary angioplasty.²⁹

Gastrointestinal System

Gastrointestinal system is also impacted by iohexol, and nausea and vomiting are some common side effects. A prospective observational study of iohexol adverse drug reactions with CT imaging reported gastrointestinal symptoms such as nausea and vomiting as the most common acute adverse effects.³⁰ A comparison between iohexol and iopromide showed that iopromide produced a higher rate of gastrointestinal adverse reactions and therefore iohexol may be more tolerable in this regard.⁶

In a study on acute adverse reactions to intravenous iodinated contrast media, including iohexol, the majority of the reactions were mild, with no severe gastrointestinal complications noted.²⁸

Respiratory System

The respiratory system is also involved with iohexol, with dyspnea, bronchospasm, and coughing as frequent side effects in sporadic cases. In a study comparing iopromide and iohexol, it has been observed that there was a greater incidence of respiratory side effects of iopromide, showing that iohexol is more tolerated regarding this.⁶

In a study of acute adverse reactions to intravenous iodinated contrast media, the majority of reactions were mild and no severe respiratory adverse effects occurred.²⁸ A comparative study of iohexol and iodixanol in patients with chronic heart failure undergoing coronary angiography or angioplasty found that the administration of iodixanol was found to have a lower incidence of respiratory adverse reactions compared with the use of iohexol.²⁹

Integumentary System

The integumentary system can also be affected by iohexol, with common side effects including skin rashes, urticaria, and pruritus. A prospective observational study of iohexol adverse drug reactions in CT imaging revealed that cutaneous reactions such as rashes and urticaria were among the most common acute adverse reactions.³⁰ But another comparison study between iohexol and iopromide observed that iopromide included a greater incidence of cutaneous adverse reactions and concluded that iohexol was probably better tolerated regarding this result.⁶

In one test that investigated acute adverse reactions to intravenous iodine contrast agents like iohexol, the majority of reactions were found to be mild and none were documented concerning severe cutaneous complications.

DISCUSSION

It is critical to emphasize the rarity of severe adverse drug reactions associated with iohexol contrast media during angiography, (ADRs) while also recognizing their potential severity. According to studies, the incidence of ADRs associated with non-ionic iodinated contrast media, such as iohexol, is between 0.3% and 0.7%, with only a tiny fraction leading in severe consequences. Notably, a case report reported a fatal reaction during carotid artery angioplasty in which the patient developed significant allergic-like reactions that resulted in cerebral oedema and renal failure despite the fact that preoperative tests revealed no previous contrast allergies. This emphasizes the unpredictable nature of ADRs and the necessity for rigorous monitoring during and after the administration of iohexol in clinical settings.⁷

Adverse responses to iohexol can appear in a variety of ways, from mild symptoms like nausea and skin rashes to more serious results like seizures, hypotension, and anaphylaxis.⁷ Neurotoxic effects have been described, with individuals developing tonic-clonic seizures and abrupt renal failure after using iohexol. The osmotic characteristics of Iohexol, which are lower than those of first-generation contrast agents, may contribute to these undesirable effects by increasing vascular pressure and tissue oedema.³¹ Furthermore, research reveals that intravenous administration of iohexol may have a larger risk for adverse drug reactions compared to arterial injection, showing that the mode of administration plays a crucial role in the safety profile of this contrast agent.

Comparative Safety with Other Contrast Agents indicated that Iohexol, as a non-ionic agent, has a superior safety profile. A study comparing iohexol and sodium meglumine diatrizoate reported lower adverse event rates for iohexol (10.2% vs. 31.6%).²⁰ Iohexol is well tolerated in patients with heart failure or unstable ischemic syndromes. A study comparing iohexol with ioxaglate found severe adverse event rates were lower with iohexol (2% vs. 16%).³² Allergic Patients are at an increased risk of adverse reactions. Pre-treatment with antihistamines and corticosteroids is recommended.^{22, 33} Antihistamines and corticosteroids effectively reduce acute reaction rates. A study showed pre-treatment reduced reaction rates from 35-60% to 9%.²² Hydration is critical in preventing CIN. Isotonic saline or sodium bicarbonate infusions are recommended for high-risk patients.^{26, 34} Post-contrast monitoring for at least 30 minutes is advised, especially in high-risk patients.

Despite the low prevalence of severe ADRs, their impact on patient safety is significant. The prevalence of catastrophic events raises questions about the sufficiency of pre-procedural assessments and emphasizes the need for enhanced protocols in handling patients who may be at risk for adverse reactions. Ongoing study is required to understand various adverse reactions and to create risk reduction techniques. Clinicians must be watchful and prepared to quickly address unexpected problems, particularly in high-risk patients such as those with past contrast media allergies or underlying renal impairment.

CONCLUSION

The incidence of adverse events related to iohexol during angiography is relatively low, with most reactions being mild to moderate. Severe adverse effects are rare, and iohexol demonstrates a superior safety profile compared to ionic contrast media. Delayed reactions and CIN remain concerns, particularly for high-risk patients. Implementing prevention and treatment strategies, such as pretreatment and adequate hydration, can further mitigate adverse event risks. Careful patient evaluation, informed consent, suitable agent selection, careful delivery by trained staff under supervision, close monitoring, and preparedness to handle adverse responses are all necessary for health care workers to utilize contrast agents safely.

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