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Safety asssessment of iopromide contrast media: a narrative review focusing on adverse events

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ABSTRACT

Many clinical contexts require radiological exams based on contrast media administration. Iodinated contrast media (ICM) represents one of the most studied contrast agents often used in radiological examinations. ICM vary widely in their physicochemical properties, clinical uses, as well as in the incidence of adverse reactions (ARs). Therefore, a basic understanding of ARs occurrence, risk factors, clinical features, and management of ICM is increasingly important in clinical practice. Iopromide is a nonionic ICM widely used in clinical practice due to its favourable safety profile and numerous applications. This narrative review provides a comprehensive report of the available data concerning iopromide ARs. It also analyses iopromide ARs occurrence and frequency with diverse potential risk factors such as age, sex and pre-existing conditions.

INTRODUCTION

Medical imaging has become a fundamental field of medicine, playing a pivotal role in early detection of, for example, cancer, by facilitating accurate diagnosis. It is also crucial in advancing drug development [1]. These techniques developed in the science, allow observations through internal structures for various clinical purposes such as medical procedures, diagnosis, or medical science, including studying normal anatomy and function [2]. Such type of biological imaging incorporates radiology, which includes a panoply of imaging technologies like X-ray radiography, X-ray computed tomography (CT), endoscopy, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), thermography, medical photography, electrical source imaging (ESI), digital mammography, tactile imaging, magnetic source imaging (MSI), medical optical imaging and single-photon emission computed tomography (EIT) [3]. The sophistication process of these techniques greatly contributes to correctly evaluate the patient's clinical situation.

Contrast agents are chemical compounds used in many imaging examinations (e.g. radiology) to enhance the effectiveness of visualisation and detection rate of internal structures [4]. Currently, iodinated contrast media (ICM) and gadolinium-based contrast media (GBCM) are the two most used contrast agents for enhancing CT and MRI scanning, which are the primary imaging modalities applied in daily clinical practice [5,6]. According to estimates, more than 120 million doses of ICM and GBCM are administered worldwide per year [7,8], with ICM mainly used for enhanced CT scanning and GBCM predominantly used for enhanced MRI scanning.

Iopromide ($C_{18}H_{24}I_3N_3O_8$), also known as Ultravist®, is a non-ionic contrast-enhancement agent used in clinical imaging applications and is considered one of the most favourable [9]. It comprises a monomeric structure with low osmolality and is mainly applied by the intravascular route [10]. It is commonly used in cerebral and peripheral coronary arteriography applications and for neoplastic visualisation of the brain [11]. Despite its favorable safety profile, as with all contrast agents, iopromide carries the risk of the adverse reactions (ARs) that are present in the application of any contrast agents, which can be fatal in rare cases [12].

Ars are the undesired, harmful events that arise following the administration of a medication or substance, such as contrast agents. These reactions to contrast agents can vary in severity, ranging from mild symptoms (e.g. nausea or hives), to severe and potentially life-threatening reactions, such as anaphylactic shock. Therefore, it is imperative to study ARs associated with contrast agents in clinical practice to ensure patient safety and mitigate potential risks of harm.

Given the lack of consistent studies specifically dedicated to the occurrence of iopromide ARs, this review aims to

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provide an overview of all collected studies and shed light on the ARs of iopromide.

METHODS

Search strategy and selection criteria

A comprehensive literature search was performed using the electronic databases PubMed, Scopus, and Web of Science to conduct this narrative review. The search was carried out from inception up to September 2021. The keywords and phrases used in the search strategy included "iopromide", "adverse reactions", "contrast media", "contrast agents", "safety" and "hypersensitivity". Both Medical Subject Headings (MeSH) terms and free-text terms were combined using Boolean operators "AND" and "OR" Additionally, the reference lists of relevant articles were manually searched for further eligible studies.

The search strategy identified a total of 84 publications. After removing duplicating records, a total of 72 publications remained, which were screened by title and abstract, excluding 26 studies which were not relevant for the review. After a deeper analysis of the full-text, 7 documents remained. All the results were organised in the Table 1.

Inclusion and exclusion criteria

The inclusion criteria for selecting studies were as follows: (1) original research articles, including observational, experimental and randomised controlled trials; (2) studies focusing on the adverse reactions and safety profile of iopromide; (3) studies published in peer-reviewed journals; and (4) articles written in English. Exclusion criteria included: (1) review articles, editorials, letters to the editor and conference abstracts; (2) studies with insufficient or unclear data on adverse reactions; and (3) articles that did not specifically investigate iopromide or did not provide separate data for iopromide.

Study selection and data extraction

Full-text articles were obtained and assessed for eligibility according to the predefined inclusion and exclusion criteria. Two independent reviewers screened the titles and abstracts of the identified articles for relevance. Any reviewer disagreements were resolved by discussion and consensus or, if necessary, by consulting a third reviewer.

The following data were extracted from the included studies: study design, study population, sample size, main outcomes, and relevant findings. Due to the heterogeneity of the study designs and outcomes, a narrative synthesis approach was applied to summarise and discuss the results.

ICM: classification, chemical properties, and overall safety profile

ICM agents have greatly contributed to diagnostic aid in clinical practice since their introduction in the late 1950s [13]. Intravascular ICM are currently one of the most widely used pharmacological agents, with approximately 75 million annual applications worldwide [7]. Therefore, their development has led to substantial advances in the design of safer and more effective compounds [14,15].

These compounds are classified in different categories based on their different properties, namely ionisation in solution (ionic vs non-ionic agents), osmolality (high vs low), and structure (monomeric vs dimeric) (Figure 1) [16]. The chemical structure of ICM includes a 2, 4, 6 tri-iodinated benzene ring, which produces radiopacity, and different structural elements attached to the ring that determine their pharmacological and physicochemical properties [17]. High-contrast density, firm binding to the benzene molecule,

Table 1. Summary of developed studies for iopromide adverse reactions

Study type	Population	Main outcomes	Ref.
Pooled analysis	132,850 patients F – 57,864 (43.6%) M – 74,986 (56.4%)	HSR were significantly less frequent in children (0.47%; p<0.042) and elderly (0.38%; p<0.001) compared with adults (0.74%). The reporting rate for HSRs in children (0.0114%) and elderly (0.0071%) was significantly lower as compared with adults (0.0143%) (all p<0.0001).	[31]
Pooled analysis	133,331 patients F – 58,074 (43.6%) M – 75,257 (56.4%)	822 patients with HSR: 766 patients (0.7%) and 56 patients (0.2%) after IV or IA administration, respectively (p<0.0001). Major risk factors for hypersensitivity reactions were the injection route of administration (IV vs IA), age (18 to <50 years vs ≥65 years), history of allergy or previous contrast media reaction (all p<0.001), and asthma (p=0.005)	[10]
Randomised clinical trial	137,473 patients F – 53,614 (39.0%) M – 83,859 (61.0%)	AARs (in iopromide and iopamidol) were observed in 428 patients (0.31%): 330 mild (77,1%), 82 moderate (19,2%), and 16 severe (3,7%), including 1 death. More incidence of AAR in iopromide than in iopamidol (0.38% vs 0.24%, P<0.001), but only for mild AARs (0.32% vs 0.16%, p<0.001). Higher risk of AAR in female patients (n=221, 0.43%, p<0.001), emergency patients (n=11, 0.51%, p<0.001), elderly patients aged 50 to 60 years (n=135, 0.43%, p<0.001), and patients who underwent CTA (n=55, 0.51%, p<0.001)	[25]
Prospective cohort	132,012 patients F – 59,517 (45.1%) M – 70,911 (53.7%) NS – 1584 (1.2%)	3823 patients (2.49%) reported an AR (2632; 1.99% mild). More AR frequency in female patients (n=1680; 2.8%) than men patients (n=1586; 2.2%). Most common ARs: injection site heat, nausea/vomiting, and dysgeusia. Increased AR in patients with established risk factors: previous CM reaction	[34]
Prospective cohort	120 patients (block randomisation method)	Associated pain and heating sensation were more frequent in iopromide, compared to iodixanol (p=0.03). ↑ frequency of immediate reactions (e.g., nausea and vomiting) in iopromide (p=0.01). ↓ frequency in delayed skin reactions in iopromide (p<0.01)	[26]
Retrospective cohort	74,717 patients F – 16,852 (47.1%) M – 39,192 (52.9%)	1069 (1.5%) patients with at least one AR, 14 (0.02%) of them serious. ↑ incidence of AR in women aged between 18 and 30 years. ↑ AR rate reported following intravenous administration, compared with Intraarterial use (2.1% versus 1.1%, respectively; p<0.0001). Increased risk for developing AR in patients with established risk factors: previous CM reaction (7,4%; 6.2-fold increase) or allergic diathesis (7.4%; 3.4-fold increase). No alterations in AR incidence with the use of premedication	[32]
Pooled analysis	29,508 patients F – 16,852 (56%) M – 12,656 (43%)	ARs were observed in 211 patients (0.7%): 188 mild (89%), 19 moderate (9%), and 4 severe (2%), including 1 death. ARs required treatment in 89 patients (42%). History of allergies in 92 patients (44%), and 29 (14%) had a previous AR to a contrast medium. No relationship between the occurrence of AR and patient age or dose. ↑ incidence of AR in female (p<0.001) and outpatients (p<0.001)	[33]

AAR - Adverse acute reaction; CTA - computed tomography angiography; F - Female; HSR - Hypersensitivity reactions; M - men; NS - non-specified

and low toxicity are the major properties that justify the safety and effectivity of iodine for contrast media use [18]. Ionic ICM are those that ionize in aqueous solutions, while non-ionic ICM remain electrically neutral in the solution. The ionisation capacity of a given medium is directly related to the frequency and severity of ARs [17].

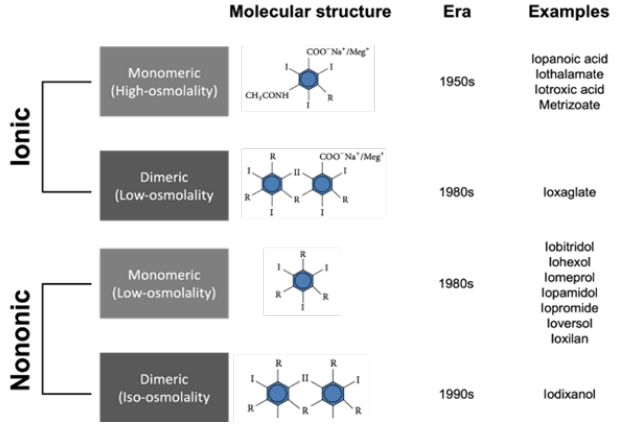

Figure 1. Figure 1. Classification of iodinated contrast media according to structural and chemical properties

The pharmacokinetic properties of ICM determine the imaging efficiency. They undergo rapid distribution to the extracellular fluid, present limited plasma protein binding, are not metabolised, and are rapidly excreted through glomerular filtration (50% in 2h) in patients with normal kidney function [19,20]. However, despite their recognized safety profile, ICM use is not devoid of risks [21] and ARs can range from mild to life-threatening reactions [22]. According to some reports, ARs to ICM can range from 1 to 12%, with severe reactions comprising 0.01 to 0.2% [23].

The incidence of ARs may vary depending on the ICM used, as the ICM properties change according to their structure [16]. Non-ionic ICM, including iopromide, have been shown to have a lower incidence of ARs compared to their ionic counterparts [24]. However, certain studies have found that iopromide and other non-ionic ICM may have a higher frequency of ARs than other non-ionic agents such as iopamidol and iodixanol [25,26]. While non-ionic ICM are generally regarded as safer than ionic ICM, patients with pre-existing medical conditions may still face potential risks. Therefore, understanding the incidence rate and severity of ARs associated with each ICM is essential to ensure patient safety [27].

The mechanisms underlying the ARs associated with iopromide are not fully understood, but may be related to the chemical properties of iopromide. Some studies suggest that iopromide has higher osmolality compared to other non-ionic contrast media, resulting in a higher particles concentration in solution, leading to more significant changes in blood chemistry and a greater risk of adverse reactions. Additionally, iopromide's higher viscosity may enhance tissue irritation and inflammation [28,29]. Another potential factor relies in the immunogenic nature of the iopromide molecular structure, increasing the risk of hypersensitivity reactions. Hypersensitivity reactions occur when the immune system overreacts to a foreign substance, such as iopromide, and can range from mild to severe, including anaphylaxis [25,26,30]. Overall, the mechanism behind iopromide causing frequent adverse reactions is complex and multifactorial, and may vary depending on the individual patient's health status and immune system, among other factors. Despite these plausible explanations, further research is needed to fully elucidate the underlying mechanisms behind iopromide's ARs.

Iopromide adverse events assessment

The safety profile of iopromide has been characterised through extensive studies reporting the ARs, possibly by applying it to the databases records. Regardless the vast clinical experience with contrast media, including iopromide, many safety issues still need elucidation [31]. Despite being described as safe with rare serious ARs, ICM use can be potentially severe and even lethal [25,32,33].

The summary of safety results from the studies is shown in Table 1. In all studies, the population was considered homogenous concerning gender, which bespeaks the important role of these compounds in medical practice for all patients. However, two recent studies performed by Endrikat et al. demonstrated a higher risk of iopromide hypersensitivity reactions in adults, particularly when administered via the intravenous route, when compared with children and older individuals [31]. Still, other studies have reported conflicting results regarding the relationship between age and ARs [27,28]. Accordingly, two studies reported a higher risk of acute ARs in elderly patients (50-69 years) [25] and no relation between the occurrence of ARs with age [33]. Patients with established risk factors such as allergy to previous contrast reaction media or asthma, and those undergoing undergoing CTA, had a higher frequency and severity of ARs [10,25,32,34].

Interestingly, a significant number of studies have reported a higher incidence and frequency of ARs in female patients compared to male patients[25,32-34].

Commonly reported adverse reactions associated with iopromide use include nausea, vomiting, headache and diverse allergic reactions, although severe adverse reactions like anaphylaxis are rare [35]. Additional studies have revealed other specific adverse reactions associated with iopromide use, including contrast-induced nephropathy (CIN), skin vasculitis [35] and colitis. [35-39].These studies highlight the importance of careful monitoring for adverse reactions associated with iopromide use in clinical practice.

DISCUSSION

Since its introduction in the 1950s, ICM have been among the most commonly prescribed drugs in the history of modern medicine[16, 40-42]. Although contrast media agents are routinely used in clinical practice and are broadly recognised as safe, an in-depth knowledge of the susceptibility, prevention, and overall impact of ARs is still warranted.

Although some studies have investigated the occurrence of ARs in ICM [16,40-42], ARs have typically focused on individual agents rather than comparing multiple substances. Therefore, a more comprehensive analysis of each ICM is needed to better understand the patterns of ARs associated with compound's chemical structure [16].

The pharmacological and physicochemical properties are also directly implicated in the frequency and severity of Ars [16]. Thus, we performed an overview of ARs, including some perspectives about patients' characteristics of iopromide reported in the literature. To the best of our knowledge, this is the first review focused on the safety profile of iopromide, the intent being to provide useful analysis and extremely relevant information for professionals in clinical practice, and to encourage researchers to further scrutiny the profile of ARs in contrast media compounds.

Some findings indicate that iopromide-associated hypersensitivity reactions were higher in adults compared to children and the elderly [31] and correlates the IV route to increase incidence of ARs [10,32]. However, other studies reported conflicting findings, with higher risks of ARs observed in elderly patients [25] or no clear relationship between age and the occurrence of ARs [33]. This discrepancy highlights the need for further research to better understand the risk factors for iopromide-associated ARs across different age groups. Furthermore, several studies found a higher frequency and severity of ARs in female patients [25,32-34], suggesting a potential gender-related predisposition that warrants further investigation.

The importance of patients and healthcare professionals reporting adverse events related to iopromide cannot be overstated. Just like any other medication, a clear, thorough and timely reporting system for adverse reactions is critical to ensuring the safety and efficacy of iopromide. It provides a feedback loop for continuous monitoring and evaluation of its safety profile, aiding in identifying previously unrecognized or underreported side effects. Additionally, these reports could, firstly, spur more research into developing safer contrast media, and, secondarily, inform regulatory authorities on decisions related to drug safety [43-45].

Strengths and limitations

This review presents several strengths, namely, the large sample sizes in included studies that enhance findings' reliability and help to identify even rare ARs. It also highlights several risk factors associated with ARs to iopromide, providing useful information for the clinical use of contrast media.

The limitations identified in this study rely on some inconsistent findings, which may be attributed to differences in study designs, populations or methodologies. In addition, most of the included studies focused on short-term or immediate ARs, which may not fully capture the long-term safety profile of iopromide. Lastly, while the review discloses potential associations between certain risk factors and ARs, other confounding factors might not be considered or controlled for in these studies, which could influence the findings.

CONCLUSIONS

This review examined the ARs associated with iopromide, revealing their variating frequency according to diverse factors such as age, gender and pre-existing conditions. As some studies reported a higher incidence of ARs with iopromide compared to other contrast agents, such as iopamidol and iodixanol, although iopromide is generally considered safe (with few serious adverse reactions), patients should be carefully assessed for risk factors before receiving this contrast agent. Further research is needed to fully elucidate the long-term safety of iopromide and identify strategies to minimize ARs associated with its use. Future studies should include well-designed prospective studies and randomised controlled trials that address research gaps and incorporate knowledge about risk factors that could lead to severe Ars so as to expand the knowledge of iopromide safety profile. It is also important for healthcare providers and clinicians to be aware of the benefits and limitations of different types of contrast agents to enhance patient outcomes.

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The authors declare no conflict of interest.

CONSENT FOR PUBLICATION

Participants consented to submit the manuscript to the journal.

AUTHORS' CONTRIBUTIONS

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