April 30, 2021

PharmacologyOnLine

Special issue • 2021 • vol.1 • 158-165

CONTRAST MEDIA PHARMACOVIGILANCE IN DIAGNOSTIC IMAGING: A TOOL TO ENHANCE

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Abstract

The use of contrast media is necessary to some diagnostic procedures; unfortunately, the administration is associated in some cases with adverse drug reactions (ADRs); some reactions are common and the probability increases expecially in pluripathological patients; in these cases the polypharmacotherapy can increase drug interaction risk.

Frequency, severity and other features of adverse drug reactions due to contrast media should be monitored; however contrast media ADR are often underreported for many reasons, such as the habit of the radiologist to report these reaction, the availability of standard forms and the interaction between radiologists and pharma-covigilance referents. It is necessary to promote and implement pharmacovigilance actions for constant moni-toring of patients undergoing media contrast agents to diagnostic procedure sand an electronic consultation system on the incidence of hypersensitivity reactions to contrast media should be introduced.

Keywords: *contrast media, adverse drug reaction, pharmacovigilance.*

INTRODUCTION

Considering the growing use of imaging techniques and contrast agents, it is necessary for the radiologist to expand safety information on contrast media (CM) to improve their tolerability profile [1].

Even if the use of CM is necessary to some diagnostic procedures [2-4]; unfortunately, the administration is associated in some cases with adverse drug reactions (ADRs); some reactions are common and the probability increases expecially in pluripathological patients; in these cases the polypharmacotherapy can increase drug interaction risk, also in relation to patient's phenotype, with consequent clinically relevant ADRs, which should be promptly reported [5,6] [**Tab. 1**].

More used intravenous contrast media in Diagnostic Imaging are Iodinated contrast media, used for CT exams and in some cases also in contrast-enhanced spectral mammography (CESM); a correct and immediate diagnosis in breast radiologist, such as in other field of application is essential for a rapid and effective management of the disease and of the patient [7-12].

Severe acute adverse reactions after a few minutes from the administration of the contrast media are possible, but rare. Although these reactions may have the same manifestations as anaphylactic reactions, they are not true IgE-mediated hypersensitivity reactions and a previous sensitization is not necessary. However, low osmolar non-ionic iodinated compounds are preferred for their lower toxicity, such as monomers like Ioexol (Omnipaque®), Ioversol (Optiray®), Iopromide (Ultravist®), Iopamidol (for example Iopamiro®) or dimers like Iodixanol (Visipaque®) [**Fig. 1**].

In Magnetic Resonance Imaging procedures, different contrast media are used, such as paramagnetic (containing gadolinium or manganese) and superparamagnetic (containing iron compounds) contrast media.

The most used are those containing gadolinium with the risk of acute nephrotoxicity just as for radiographic iodinated compounds. Furthermore, expecially in nephropathic patients, the possibility of developing nephrogenic systemic fibrosis, with scleroderma-like alterations of the skin, of the connective tissues and other organs, sometimes with fatal evolution, has been described after exposure to gadolinium. For the latter adverse reaction, a release of toxic free gadolinium ions was hypothesized. The most used gadolinium-based contrast agents in Italy are: gadodiamide (Omniscan®), gadobenic acid (Multihance®), gadobutrol (Gadovist®), gadofosveset (Vasovist®), gadopentetic acid (Magnevist®), gadoteric acid (Dotaren®), gadoteridol (Prohance®) and gadoxetic acid (Primovist®).

ADVERSE DRUG REACTION FEATURES

The *frequency* of adverse reactions is often related to the osmotic concentration of the CM: high- osmolality molecules can cause more reactions if compared with low-osmolality media.

ADRs can be classified in acute, delayed effects and contrast-induced nephropathy; acute reactions that occurs within an hour and are more frequent for a ionic, monomeric, high-osmolality agents [13].

The *severity* of reactions can go from mild to severe; in the first case, pain on site of intravascular injection, nausea and vomiting, rash and hemodynamic changes can occur. Pruritus, hives, bronchospasm, dyspnea, hypotension up to cardiovascular collapse can be the expression of anaphylaxis. Cardiovascular side effects occur rarely after iodinated contrast media administration. The most frequent are due to risk factors associated with cardiopulmonary comorbidities of patients or vasomotor reactions, in particular vagal effect of peripheral vessels [14].

According to Cutroneo et al., no significance difference regarding acute reactions between men and women exposed to contrast media has been observed. In particular, females were shown to be at risk for delayed reactions [15]. The impact of sex on fatality is not well studied, but the US FDA database showed that male patient deaths exceeded those of females by a ratio of 2:1. All fatal reports were associated with males, and no such

ratio could be evaluated. However, it is important to note that for all fatalities, cardiac arrest was the cause of death, and only one patient had a previous cardiac complication.

ADVERSE DRUG REACTION REPORTING

Although spontaneous reporting is considered to be the most important pharmacovigilance tool for identifying clinically relevant side effects, in some medical setting, such as radiology, this method may be linked to the problem of under-reporting and it should not be overlooked. From Kalaiselvan analysis, pediatric case reports of suspected adverse reactions to contrast media need to be closely monitored. In addition, serious and fatal reactions could suggest that it would be useful to ascertain whether radiology centers give prophylaxis to patients at increased risk for contrast media allergic reactions and take measures to reduce the risk of arrhythmias, as there was nothing in the indian reports to indicate whether such measures had been taken [16].

Hypotension and heat sensation can be linked to osmolarity and the injected volume of the contrast medium. Low osmolarity molecules have a lower incidence of these adverse reactions but are not exempt; the status of any coronary disease also affects the possible development of side effects. Iopromide and iodixanol induce dilation under normal coronary conditions but constriction under stricture conditions; also depressions of the atrioventricular node, ventricular fibrillation and tachycardia can occur. However, these phenomena most often involve asymptomatic changes in electrocardiography (ECG), with a more favorable profile than low osmolar media [17].

ADVERSE DRUG REACTION UNDERREPORTING

While underreporting is a common phenomenon in pharmacovigilance, for contrast media it is particularly marked for many reasons. The critical role of CM in adverse reactions is evident from previous epidemiological studies. CM may be categorized as drugs, although safety information is lacking. Indeed, necessary details for good reporting can be recorded with difficulty in the standard forms. Other reasons may be sought in the radiologist 's attitude to report ADRs. Various evaluation tools have been developed and used to analyze ADRs.

However, these tools have not been adapted to CM-ADRs. These evaluation tools would be helpful to understand CM-ADRs and to compare them with non-CM induced ADRs to different causality assessment [*Ryu J,*]. The physicians' perception of the risk / benefit ratio of a treatment is generally conditioned by the severity of the prognosis of the disease. Adverse reactions to contrast media could be considered as secondary problems, placing spontaneous reporting among the low priority activities in the routine of hospital setting. The tendency is therefore to report sporadic cases of serious or unknown ADRs [18].

Another problem for the underreporting in radiology is the absence of no certain pharmacological treatments for the prevention of contrast nephropathy although several molecules have been proposed including sodium bicarbonate, acetylcysteine, calcium channel blockers, theophylline, endothelin receptor antagonists. More important seems to be careful hydration before the examination and the suspension of drugs potentially capable of worsening kidney function. A prospective controlled and randomized Japanese study indicates that rehydration does not change the risk of adverse events from iodinated contrast medium during abdominal or pelvic CT. One patient group candidate in this survey was assigned to the rehydration arm (n = 2,244, 1,379 men, age 18-90 years, mean 65.2 years) or the standard preparation control arm (n = 3,715, 2,112 men, age 17 to 96 years, mean 65.8 years); from the control arm a small subgroup was selected, similar in age and gender to the intervention arm and of the same number. Rehydration consisted of the oral administration of 500 ml of a solution available on the market, with a balanced composition of carbohydrates and electrolytes and an ideal osmotic pressure to promote gastrointestinal absorption, according to a questionnaire completed before the examination, 997 patients were classified as subclinical dehydrated and 4,962 as adequately hydrated. The onset of adverse reactions to the contrast medium was investigated before patients left the radiology room at the end of the examination. The overall incidence was 4.3% (254 cases out of 5,959

exposed); 136 events were allergic and 118 were classified as physiological (vasovagal reaction, headache, flushing, chills). There were no significant differences in the frequency of adverse events between the intervention group and the narrow control group (4.4% vs 4.5%, p = 0.9), even considering the starting hydration status (patients with subclinical dehydration vs patients with dehydration: allergic reactions 2.5% vs 2.2%, p = 0.6062, physiological reactions 2.2% vs 1.9%, p = 0.5793). Hydration before a CT with contrast medium remains a practice indicated to reduce the risk of nephropathy but does not seem to have any impact on the other adverse events associated with the examination [19].

Severe acute idiosyncratic reactions (for example shock, syncope, ventricular cardiac arrhythmias, bronchospasm, urticaria) must be recognized and treated promptly, remembering that even pre-treatment with antihistamines and corticosteroids in risk cases does not provide safe protection. In any case, it is advisable to agree with the interventional doctor, generally the radiologist, who will carry out the examination the correct indication for the contrast examination based on clinical information.

Furthermore, the identification of a causal link is rather complex, and it is easier to attribute an adverse reaction to genetic variability, comorbidities or politherapy. Iodinated contrast-induced thyrotoxicosis is relatively rare. Patients with Graves' disease and multinodular goiter are at increased risk, and those with thyrotoxicosis should receive iodinated contrast media only with close monitoring since patients with preexisting hyperthyroidism may develop a thyroid crisis. Individuals with underlying Hashimoto's thyroiditis or other autoimmune thyroid diseases and those with a history of partial thyroidectomy are at particular risk for the development of iodine-induced hypothyroidism [20].

Predisposing conditions, such as pre-existing renal insufficiency, dehydration, diuretic therapies, the use of drugs that can cause renal toxicity (for example NSAIDs or ACE inhibitors that must be discontinued before the examination) must be carefully evaluated, especially for prevention (or aggravation) of nephrotoxicity. For this purpose, it is mandatory to consider in each patient who must undergo intravenous contrast examination not only creatinine, but also the GFR (glomerular filtrate), which many laboratories provide together. Above 60 ml / min the contrast can be performed with confidence, below 30 ml / min it is contraindicated, as well as the paramagnetic contrast for resonance. Caution should also be taken for interactions with other drugs (for example metformin to be suspended before or at the time of the examination and up to 48 hours after) [21].

Moreover, according to a systematic review funded by the US Agency for Healthcare Research and Quality, only N-acetylcysteine can contain the renal damage induced by the administration of contrast medium. The authors excluded studies referring to hyperosmolar contrast media, no longer used in clinical practice, and reconsidered 86 randomized controlled studies published from 1998 to 2015 that compared N-acetylcysteine, sodium bicarbonate, statins, and ascorbic acid added to intravenous or intra-arterial infusion of physiological versus physiological alone. A clinically and statistically significant reduction in the risk of iatrogenic renal damage (defined as an increase in creatinine> 25% compared to baseline or> 0.5 mg / dl in the first 3 days following the radiological investigation) emerged with N-acetylcysteine.About the other drugs (ascorbic acid, sodium bicarbonate and statins) significant conclusions have not been reached from a statistical point of view, sometimes also due to the limited availability of data. However, there was a protective tendency of sodium bicarbonate with respect to the physiological one in the case of hyperosmolar contrast agents, of statins more physiological than physiological alone and of ascorbic acid with respect to physiological. Contrast-induced nephropathy is a problem that is anything but negligible in clinical practice, also because patients who require radiological examinations with contrast often have an impairment of renal function already in place, due to comorbidities or more simply for personal reasons. The latest generation contrast agents are less harmful, but it is important to have the possibility to improve nephroprotection with targeted interventions. [22].

NUCLEAR MEDICINE RADIOPHARMACEUTICALS

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy. [22-25] A carrier, in the form of inactive material, either isotopic with the radionuclide, or non-isotopic, but chemically similar to the radionuclide [26] , may be added during processing and dispensing of a radiopharmaceutical preparation to permit ready handling. [27] At the end of the expiry period, the radioactivity will have decreased to the extent where insufficient radioactivity remains to serve the intended purpose or where the dose of active ingredient must be increased so much that undesirable physiological responses occur. [28] In addition, chemical or radiation decomposition may have reduced the radiochemical purity. [29-32]

Adverse reactions to radiopharmaceuticals are comparatively few in number. [33,34] The very low numbers of reported adverse effects probably reflect the tiny amounts of material which are used in the formulation of radiopharmaceuticals. [35] Adverse reactions to radiopharmaceuticals are usually mild and transient and require little or no medical treatment. [36]

CONCLUSION

Considering the above reasons, it is necessary to promote and implement pharmacovigilance actions for constant monitoring of patients undergoing media contrast agents to diagnostic procedures [37,38].

An accurate drug history should always be collected, whenever possible. Equally important are a careful clinical examination of the patient and the evaluation of some laboratory parameters, such as renal, hepatic, thyroid, haemocoagulative and serum protein electrophoresis. Obviously the first consideration to be made, also in relation to possible risks, is the real usefulness of the exam.

The pharmacist in charge of Pharmacovigilance can promote training initiatives aimed at ensuring the availability of the necessary knowledge to all health personnel for an appropriate and valid approach to reporting an adverse event. It is believed that a quality report can contribute to the creation and maintenance of an electronic consultation system on the incidence of hypersensitivity reactions to contrast media which, where introduced, significantly reduced the frequency of allergic reactions.

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Table 1 Contrast media (CM) adverse reactions, differentiated in chemotoxic and anaphylactoid events.

CM ADVERSE REACTIONS	CHEMOTOXIC REACTIONS*	ANAPHYLATTOID REACTIONS**
PREVENTABILITY	YES	NO
DOSE-DIPENDENCE	YES	NO
RISK FACTORS	CARDIOPATHIES, NEPHROPATHIES, LIVER DISEASES, ENCEPHALOPATHIES	ATOPY, PREVIOUS REACTIONS TO CM
PRETREATMENT WITH STEROIDS	NOT EFFECTIVE	NOT ESTABLISHED

**Chemotoxic reactions are linked to the intrinsic toxicity of the molecule and fundamentally depend on theits chemical-physical characteristics and the dose administered*

***There is no universally accepted definition of anaphylactic and anaphylactoid reaction.Many mechanisms can result in severe symptoms either signs triggered by the activation of mast cells and basophils. The term anaphylaxis is generally used for reactions from hypersensitivity mediated by immunoglobulins E. The reactions defined as anaphylactoid are similar but do not depend on hypersensitivity.These too, like the anaphylactic ones, are of varying severity, rapidity and progression; they are rarely biphasic or persist for more than 24 hours.*

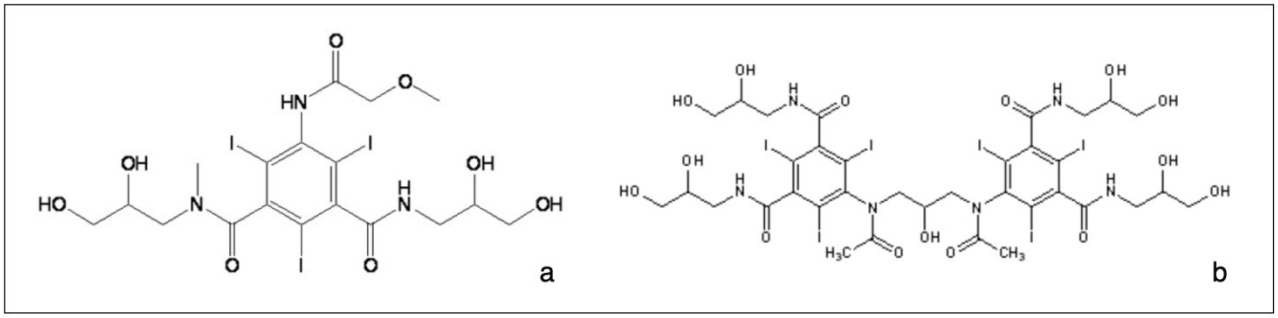

Fig. 1 - a) Iopromide and b) Iodixanol formula