Adverse delayed reactions to the intravenous injection of non-ionic iodinated contrast media

Abstract Adverse delayed reactions (ADRs) to the intravenous injection of non-ionic iodinated contrast media (NICM) were first recognised in the mid-1980s and a growing number of articles in the literature have described such reactions as increasingly common. The aim of this article is to increase the understanding of the risk factors, frequency, signs and symptoms of ADRs amongst healthcare staff especially radiographers, nurses, radiologists and physicians who regularly use contrast media (CM). A literature review of multiple studies assessing ADRs performed from 1990–2010 has revealed various misconceptions, particularly in the frequency of ADRs and the influence of ethnic background most likely due to methodological limitations. Therefore, the use of improved research methods and design has the potential to increase our knowledge in this area. Furthermore, new areas of study such as blood testing as a screening tool can assist in risk assessment and prevention of ADRs.

Keywords: adverse delayed reactions, non-ionic iodinated contrast media, risk factors, signs, symptoms.

Introduction

Background

Non-ionic iodinated contrast media (NICM) is currently amongst one of the most used drugs in the medical field. First introduced in the 1950s, it has now become the standard in diagnostic imaging due to its high level of safety and tolerability and is currently the most commonly used drug in radiological imaging. Despite its relatively good safety record, no drug is without risks and potential side effects. The existence of adverse acute reactions has been long well-established by the literature in large-scale prospective studies by Katayama, et al. and Shehadi but these studies did not assess adverse delayed reactions (ADRs) as ADRs were not recognised until the mid-1980s and since then a wide range of studies have investigated these reactions.

Over the last two decades, a review by Webb, et al. described the frequency as gradually increasing and that the “frequency of late adverse reactions to non-ionic monomers has been reported to be between 0.52–23%” (pp. 182). Despite this review, there is still much controversy pertaining to the risk factors, frequency, signs and symptoms of ADRs. It appears inconsistencies amongst research findings may have left healthcare staff uncertain when confronted with ADRs in the clinical situation and without appropriate knowledge, staff may inadvertently compromise their patients’ safety.

In a recent study performed by Loh, et al., the frequency of delayed reactions was 14.3%. Common manifestations of these reactions were skin rash or erythema, swelling and headache. A media report attributed Loh as describing ADRs as generally mild and non-life-threatening, although some can be moderate to severe. To ensure patient safety when administering NICM, further study is required in this area due to the rapidly increasing use of NICM especially in the field of radiological imaging.

New and precise data is required in order for clinicians to ensure patient safety prior to contrast administration, to evaluate the risk factors to their patients and to diagnose an ADR. Healthcare personnel especially those who administer CM including radiologists, physicians and radiographers must be knowledgeable in identifying the patient risk factors, signs and symptoms of ADR to ensure patient safety.

Definitions

Various definitions of ADRs were observed throughout the literature. Some ranged from 30 minutes or 1 hour to 7 days after injection. In the majority of studies, a delayed or late reaction was defined as one occurring after one hour but within 7 days of the administration. This definition will also be used throughout this literature review.

Literature review

Patient risk factors

In three key studies by Mikkonen, et al., Munechika, et al. and Yasuda, et al., the main risk factors identified were being of female gender, history of drug allergy, underlying disease, previous CM reaction, asthma and previous exposure to CM.

Gender

The link between the female gender and a higher incidence of ADRs was observed consistently across the literature. To ensure this is valid, it is ideal to have equal numbers of each gender in the study sample. The study by Mikkonen, et al. consisted of 54.6% male and 45.4% female and Yasuda, et al. study consisted of 54.5% male and 45.5% female. Both studies had equally adequate numbers of each gender. Cattroneo, et al. on the other hand reported a higher incidence of ADRs in males than females. However, their results were obtained...
from spontaneous data reporting and diagnosis of ADRs was subject to researcher bias.

Asthma

Key studies which evaluated asthma as a risk factor for ADRs concluded that there was no increased risk of late reaction and data was not statistically significant. However, the sample size for these studies were relatively small (n = 239; n = 67; n = 73 respectively) and potentially problematic for precision during data analysis. Even for Mikkonen’s, et al. larger sample size, symptoms of ADRs were identified by the patients themselves, resulting in bias.

History of allergy

Numerous studies reported that any previous history of allergy significantly increased the risk of delayed reactions. Similar rates were observed in Mikkonen, et al.7 (8.0%) and Munechika, et al.6 (7.4%). Yasuda, et al.9 reported an incidence of 20.2% although this was not the true rate. To obtain this true rate, a control group was included in the study. The control group did not undergo contrast-enhanced CT but only plain CT. Interestingly, 14.5% of patients with a history of allergy in the control group claimed to have experienced an ADR. Therefore, the true rate of ADR was only 5.7% although this was not statistically significant. In all studies, a patient’s allergy was confirmed by a physician or nurse to ensure accuracy. However, symptoms of ADRs were identified by the patient. Furthermore, it cannot be established whether a reaction was due to CM or perhaps the patient was exposed to an allergen after the CM injection during the data collection period.

Previous exposure/reaction to contrast media

A prospective study by Bartolucci, et al.22 found that previous exposure to a contrast agent contributed to the risk. In fact, the P values for previous exposure to contrast were equal to the risk factor for female gender and history of allergies (P = 0.001), both of which were identified as greater risk factors in other studies. On the other hand, key studies by Munechika, et al.6 and Yasuda, et al.9 observed slightly higher rates of ADRs although it was not statistically significant. In fact, Mikkonen, et al.7 did not include previous exposure as a risk factor. However, some patients had indicated “unknown”. Therefore, data collection was subject to the accuracy of the patient’s memory, even when the information was collected by a nurse or radiologist.

Conversely, Higashi, et al.11 reported that patients who had more than two contrast-enhanced examinations had a lower incidence of developing a rash in comparison to those who only had one, purporting that repeated usage of contrast medium did not increase the advent of ADRs. Patients who experienced the documented symptoms in the past one year were excluded from the data analysis. Although the purpose was to reduce false ADRs that mimicked symptoms, this may have also excluded true ADRs.

Underlying disease

Only two of the key studies evaluated underlying disease as a function for the risk of ADRs. It is expected that underlying disease may be difficult to assess due to its diverse range. Munechika, et al.6 evaluated this factor very broadly by placing patients with underlying disease into the following categories: cardiovascular disease, hepatic disease and urinary disease. More specific conditions included diabetes and hypertension and an “others” category. Interestingly, the highest rate of ADRs was observed in the “others” category. Diseases included under that category have not been published, perhaps due to the diversity of diseases. However, none of these delayed reactions in patients with underlying disease were statistically significant. Furthermore, Munechika, et al.6 made no further discussion and comparison of these results with other literature and thus, results remain inconclusive. Then again, Mikkonen, et al.7 identified diabetes mellitus, heart, liver and kidney disease as contributing factors.

In considering underlying disease as a risk factor, both studies were problematic. In the first-phase questionnaire of the Mikkonen, et al.7 study to obtain data prior to administration of CM, patients were offered a closed-ended question and forced to choose from heart, liver and kidney disease and diabetes mellitus. Although this excluded patients with diseases that did not fit into these categories, the amount of data for this variable was controlled. On the other hand, Munechika, et al.6 collected data in a semi-structured interview, allowing for all types of underlying diseases to be considered, although this resulted in a diverse range of answers, complicating statistical analysis.

Ethnicity

Across the literature, there appeared to be greater emphasis placed on the comparison of the incidence of ADRs between Japanese and European populations than any other ethnicity. Studies from Japan and European countries produced an average of 7.8% and 19% respectively (Table 1).

Only two studies by Mikkonen, et al.7 and Bartolucci, et al.22 evaluated risk factors in the Caucasian population. As seen in Table 1, a large number of Japanese studies have taken place more than any other country.

Table 1: The prevalence of adverse delayed reactions during the last two decades

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Adverse delayed reactions</th>
<th>Locality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loh, et al.6</td>
<td>258</td>
<td>14.3%</td>
<td>USA</td>
</tr>
<tr>
<td>Kishore, et al.23</td>
<td>292</td>
<td>65.6%</td>
<td>UK</td>
</tr>
<tr>
<td>Schild, et al.1</td>
<td>772</td>
<td>51.9%</td>
<td>Germany</td>
</tr>
<tr>
<td>Munechika, et al.6</td>
<td>7505</td>
<td>2.8%</td>
<td>Japan</td>
</tr>
<tr>
<td>Hosoya, et al.13</td>
<td>15690</td>
<td>9.5%</td>
<td>Japan</td>
</tr>
<tr>
<td>Bartolucci, et al.21</td>
<td>403</td>
<td>12.4%</td>
<td>Italy</td>
</tr>
<tr>
<td>Pedersen, et al.20</td>
<td>2656</td>
<td>0.52%</td>
<td>Norway</td>
</tr>
<tr>
<td>Rydberg, et al.27</td>
<td>3408</td>
<td>2.0%</td>
<td>Sweden</td>
</tr>
<tr>
<td>Yasuda, et al.3</td>
<td>2370</td>
<td>12.4%</td>
<td>Japan</td>
</tr>
<tr>
<td>Oi, et al.28</td>
<td>512</td>
<td>6.4%</td>
<td>Japan</td>
</tr>
<tr>
<td>Niendorf29</td>
<td>783</td>
<td>0.62%</td>
<td>Europe</td>
</tr>
<tr>
<td>Niendorf29</td>
<td>179</td>
<td>3.0%</td>
<td>Japan</td>
</tr>
<tr>
<td>Mikkonen, et al.7</td>
<td>4875</td>
<td>4.7%</td>
<td>Finland</td>
</tr>
<tr>
<td>Yoshikawa22</td>
<td>2382</td>
<td>8.0%</td>
<td>Japan</td>
</tr>
<tr>
<td>Yamaguchi, et al.21</td>
<td>715</td>
<td>4.9%</td>
<td>Japan</td>
</tr>
<tr>
<td>Miyamoto, et al.22</td>
<td>3411</td>
<td>0.41%</td>
<td>Japan</td>
</tr>
<tr>
<td>Higashi, et al.12</td>
<td>1070</td>
<td>22.8%</td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td><strong>12.5%</strong></td>
<td></td>
</tr>
</tbody>
</table>
No single comparative study was found between Japanese and Caucasian populations nor were any other Asian populations such as Chinese or Indian ethnicities evaluated. Some literature has suggested that being of Japanese descent was the main risk factor. In fact, scientific theories have been put forward to explain this trend based on the differences between the immune system of Japanese and Caucasian populations.

Both literary pieces referenced Niendorf's 1996 study. In 1996, Niendorf performed a controlled study in Europe and a comparative study in Japan, concluding that the Japanese had a higher incidence of ADRs compared to Europeans. However, it is limited in various aspects and should be interpreted with caution. Firstly, only the use of Iotrolan 280 (Isovist 280, Schering, Berlin, Germany) was evaluated and the results produced were collated from two separate studies. Secondly, the original studies in Europe and Japan have remained unpublished and no reference was made within the published article. There was also minimal discussion on the methodology and limitations of these studies. Thirdly, according to media reports, Schering AG, the manufacturer of Iotrolan 280 (Isovist 280) suspended and recalled this product due to increasing reports of ADRs by physicians. In response, Niendorf, a Schering researcher performed these studies to re-assess the safety of their product. This professional affiliation gives rise to the potential for bias. Fourthly, the writing style used in this article is persuasive and defensive in nature rather than objective.

Another reason for this notion may be due to the large number of studies in Japan, which may have artificially increased the frequency of ADRs due to the fact that they have been reported and published more than any other region. As a result of the plethora of data in Japanese populations, other studies have also used this to support their hypothesis in their study of ADRs.

**Signs and symptoms and the frequency of ADRs**

There was an extremely diverse range of signs and symptoms presented by multiple studies. The most common signs and symptoms observed across the literature were urticaria, itching, headache, nausea, diarrhoea, vomiting and dizziness.

A major challenge across all studies into ADRs was to attribute symptoms accurately to the injection of CM. The frequency of reported ADRs across the literature could be much higher than in reality due to methodological problems. To resolve this issue, various methods have been employed to ensure true ADRs are reported and false ADRs are eliminated.

The most commonly used method of data collection was questionnaires. In several studies, the limitations of this method were acknowledged. To record delayed ADRs, some studies completed the questionnaires. In several studies, the limitations of this method were acknowledged. To record delayed ADRs, some studies completed the questionnaires. In several studies, the limitations of this method were acknowledged.

To reduce these false ADRs, some studies completed the questionnaires with the guidance of a physician, radiologist or nurse to attribute ADRs to CM injection. This potentially reduced the number of false ADRs. However, this posed new problems. Diagnosis of an ADR would be subject to the judgement and experience of the staff. Furthermore, there is the potential for staff to influence patient's answers.

Few studies involving a control group have been performed. Yasuda, et al. first introduced the control group in their study to further reduce false ADRs and to eliminate the effects of 'background noise'. Patients in the contrast-enhanced group underwent computed tomography (CT) with contrast media administration while the control group underwent plain CT without contrast media. Yasuda, et al. reported that 12.4% of the contrast-enhanced group and 10.3% of the control group experienced an ADR. Therefore, the true frequency of ADRs was 2.1%. However, the process of assigning patients to each group was not randomised and thus, subject to selection bias. Even when radiologists completed the questionnaire for inpatients from the control group, 5.1% of those reported ADRs when they did not receive CM.

Studies involving control groups were later on performed by Loh, et al. and Schild, et al. In addition to the control group, Schild, et al. was the only study to document the patient's symptoms before CT. This enabled further elimination of a range of false ADRs. For example, ear, nose and throat (ENT) symptoms which mimicked allergy-like reactions could be eliminated. By eliminating patients with ENT symptoms from the data analysis, the incidence of ADRs became statistically significant \((P < 0.0001)\). However, if a patient were to have ENT symptoms prior to CT and experience an ADR afterwards, they could not be differentiated.

Only two studies were found to include inpatients in their sample which may have increased the accuracy of data collection. Unlike Munechika, et al. study, Yasuda, et al. failed to address other potential confounding variables such as the patient's surgery or procedure, concomitant medications and underlying disease. Furthermore, data collection was performed separately over two years (1995 and 1996) resulting in potential inconsistencies such as seasonal variations or potential change in protocols.

Two retrospective studies were identified in the literature. Collection of data on post-injection symptoms was obtained from clinical trial reports. Pedersen, et al. and Rydberg, et al. reported 0.87% and 2.0% of patients experienced ADRs respectively. This is very low compared to other studies. The difference may be due to its reliance upon the diagnosis of other physicians and the quality of documentation. Even though non-allergy-like reactions were excluded, it is difficult to attribute symptoms to CM if the patient has an underlying disease or is on multiple medications. Furthermore, researchers may also introduce their own bias during the selection of patients by being overly cautious in their exclusion process. Rydberg, et al.'s method of a retrospective questionnaire was suspect because data collection and occurrence of adverse events were separated by one year. Therefore, the accuracy of data was dependent on the patients' ability to recall adverse events that occurred one year ago.

**Discussion**

All studies that were reviewed employed a questionnaire to collect data. The reason for higher frequency of ADRs may be due to higher reporting rates from patients who attributed symptoms they experienced to CM injection when in fact, it was not related. Even when a physician guided the patients through the questions in the control group, interestingly Yasuda, et al. reported that 10.3% of patients experienced an ADR in the absence of CM.

A questionnaire was also employed when assessing risk factors. The risk factor of the female gender was well-established throughout the literature. This may have been due to the fact that the answer to gender on the questionnaire would have been obvious. However, for other factors such as a history of allergy or previous exposure or reaction to...
CM, such questions are subject to patient bias. A patient may not have an allergy to a particular item when they believe they do or patients can confuse past injections they have had. By using a physician or nurse to guide the patient during the questionnaire successfully reduced the number of false risk factors. A control group first introduced by Yasuda, et al.9 in 1998 also greatly reduced the number of false ADRs although it was not completely sound. No studies before 1998 were found to employ a control group.

As a result of false reporting of risk factors and symptoms, the frequency of ADRs over the last two decades may have been over-reported and the frequency of ADRs presented in the literature is perhaps much higher than it is in reality. This has had direct implications in the clinical setting where healthcare staff may be unsure as to the true incidence, risk factors and symptoms of ADRs. Consequently, patients who do experience ADRs may be unable to determine the cause of their symptoms and the appropriate response. Therefore, further research is required to identify these relationships.

To obtain the true frequency of ADRs appears difficult due to the identified inherent ‘background noise’ but by eliminating as many variables as possible, collected data over time will approach the true frequency.

Future studies could be prospective, randomised and controlled to eliminate as many variables as possible, which may reduce reports of false ADRs. Only one such study was performed by Schild, et al.14 who reported a frequency of 3.6% after subtraction of the control group from the contrast-enhanced group, which was comparatively lower than other reported studies. Patient selection should be narrowed in order to eliminate alternative reasons for ADRs such as medication, previous surgery and underlying disease. Strict continuous observation of patients from 1 hour to 7 days after injection of CM would allow many of the variables to be controlled and observed. However, this could be highly impractical. Thus, the next best option is to perform inpatient studies where patients are monitored and the variables are relatively controlled. Patient selection should also be narrow as many inpatients would have underlying disease or take medication unless that were the variable to be studied. Repeated studies of identical design would need to be performed to obtain data that would approach the true frequency of ADRs.

Research up until now has primarily been pragmatic, in which exclusion criteria have been relatively loose to reflect real-life clinical conditions. A thorough research design could be performed in order to test the efficacy of a variety of risk factors on the incidence of ADRs. Diagnosis of risk factors could be made purely on evidence-based medicine. For example, a history of allergy should be documented if a positive allergy test had been observed. Likewise, any underlying disease should be evident from a history of allergy should be documented if a positive allergy test had been observed. This would help ensure no false results in cases when patients may confuse past injections they have received. It is understandable that this would result in a lengthy patient selection process under the pressure of time and financial constraints. However, it may be feasible to apply at least one of the various exclusion criteria.

Further studies could also be conducted in determining the degree to which each risk factor contributed to the incidence of an ADR. This could be achieved by enrolling patients with a specific risk factor or through comparative study. Multivariate analysis should be performed in future studies to statistically define the relationships between the risk factors. Results of such a study would increase the effectiveness of screening patients at risk and to predict whether an ADR would occur.

Overall, a great deal of research had been performed in Japan but very limited studies in other Asian populations as well as Caucasian populations in comparison. Comparative studies between different ethnicities should be performed to further investigate the higher incidence of ADRs in Japan. Furthermore, studies comparing Japanese populations living in areas outside of Japan will help to identify whether frequency rates are due to environmental or biological factors.

Studies using laboratory tests as a means of evaluating the risk factors and effects of ADR were limited. Only one study by Hosoya, et al.15 identified patients with an increased serum creatinine experienced higher rates of ADR. There is great potential for more research into the use of blood tests as a screening tool due to its availability and objectivity. Furthermore, because it is already commonly used to evaluate kidney function prior to CM injection, it can be easily adopted into general practice by radiographers, radiologists and physicians.

With further research identifying the risk factors, frequency, signs and symptoms of ADRs, healthcare staff who administer CM, equipped with this knowledge can re-evaluate current CM administration protocols and safety guidelines. Patients who present with risk factors can be properly identified, informed and educated of these risk factors and potential symptoms prior to CM injection. Patients who do experience symptoms after an injection can be diagnosed accurately, treated appropriately and reassured confidently. If such patients require repeated CM injections in the future, staff can be informed prior to injection and prophylaxis may be administered accordingly to reduce or even prevent an ADR re-occurring.

This literature review has also revealed various problems associated with research design that has had significant impact on the results and consequently, the conclusion drawn by its researchers. It is acknowledged that these studies were designed to be as efficient and effective as possible within the particular circumstances of the time. These studies can be improved and lay the foundations for future researchers from which they can learn from to further improve their research design to draw accurate conclusions that advance closer towards the true incidence of ADR. Therefore, current medical radiation students who may potentially conduct future research, not only within the study of ADRs but in all aspects of radiography, may find this paper useful as a discussion paper on research methods and design.

Limitations

English publications of several Japanese studies and one Italian study were limited to their abstract only and therefore, data could only be extracted from the abstract. The categorisation and naming of signs and symptoms varied between the studies although they were still comparable. Some studies included only "allergy-like" reactions while others recorded all types of symptoms. Data availability was also subject to duration of data collection after injection. There were few studies which observed symptoms only 24 hours after injection compared to others who observed up to 7 days. These differences resulted in slight discrepancies between the statistical outcomes. In comparative studies (e.g. dimeric vs. monomeric), data was combined between the two groups to extrapolate percentages and a total number of patients who received contrast. The majority of the studies were also conducted from 1990–2000. Although this was not a major issue because technical factors such as the type of contrast have not changed radically, protocol variations between studies
such as the amount of contrast could have changed significantly to reflect technological changes in equipment.

**Conclusion**

The first description of ADRs appeared in the mid-1980s and since their recognition, they have been investigated and documented in the literature. A survey of the literature identified the main risk factors as gender, age, previous history of allergy, previous exposure to contrast media, underlying disease and ethnicity. A critical analysis of these factors revealed that potential problems in methodology may have led these studies to draw imprecise conclusions. Despite some literature describing the frequency of ADRs as on the increase, it is possible that these figures have been overestimated due to a large number of false reports primarily because of failure to accurately recognise symptoms as caused by CM. These problems have stemmed from the methodology of the studies. Although several investigators have employed various research strategies to reduce these false reports, they were not without their drawbacks. It is recommended that prospective, randomised studies including a control group without enhancement should follow vascular administration of radiography contrast media. A comprehensive study based on a prospective survey. Am J Roentgenol 1975; 124: 145–52.

**References**


