Acute Adverse Reactions of Three Intravenous Iodinated Contrast Media in Computed Tomography under Routine Clinical Monitoring: Iothalamate meglumine, Iopromide and Iohexol

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ABSTRACT

Nonionic iodinated contrast media (NICM) is generally considered to have a much lower incidence of acute adverse drug reactions (aADRs) than ionic iodinated contrast media (IICM). Several studies have compared aADRs of IICM to NICM but few compared between different NICMs. There are few large local studies of adverse reactions to iodinated contrast media (ICM) in Taiwan. We undertook a retrospective study to compare the aADRs between different ICM in computed tomography (CT) under routine clinical monitoring.

All consecutive patients who received intravenous contrast-enhanced CT scans using Iothalamate meglumine, Iopromide, or Iohexol from May 2004 to February 2006 were enrolled. In total 32499 enrolled patients received either Iothalamate meglumine (7520, 23.14%), Iopromide (9830, 30.25%), or Iohexol (15149, 46.61%). Two categories of injection rate were classified: rapid (>2 mL/sec) and slow (manual injection). Acute ADRs were classified by systemic symptoms. The statistical methods used were Fisher’s exact test and Chi-squared test.

Significantly increased aADR incidence was noted with Iothalamate meglumine when compared with Iopromide (p<0.001) and Iohexol (p<0.001). Comparing aADR incidence between different NICMs, Iopromide had a higher total aADR incidence (p<0.001), and significantly increased incidence of gastrointestinal (p=0.005), cutaneous (p<0.001) and respiratory (p<0.001) aADR symptoms than that of Iohexol. When comparing slow with rapid injection, a higher incidence of gastrointestinal symptoms was noted with slow injection than rapid injection of Iopromide (p=0.008).

In this study, Iothalamate meglumine revealed a higher aADR incidence than Iopromide and Iohexol. In addition, compared to Iohexol, Iopromide had a higher total aADR incidence as well as gastrointestinal, cutaneous and respiratory aADR incidence.

Iodinated contrast media (ICM) are widely used in radiological examinations and procedures. Nonionic iodinated contrast media (NICM) has a lower incidence of acute adverse drug reactions (aADRs) than ionic iodinated contrast media (IICM) [1-7]. Some hypotheses have been proposed to explain the manner by which ICM trigger aADRs, including chemotoxic reactions, anaphylactoid reactions, IgE mediated hypersensitivity, and T-cell mediated immunity [8-13]. However, few of these studies discuss the aADRs as different systemic symptoms, and compare...
them between different NICMs. There are few large local studies of adverse reactions to ICM in Taiwan.

In order to collect local data on the incidence of NICM-induced aADRs, we conducted a retrospective study to describe the incidence of different systemic symptoms of aADRs with the use of IICM and NICM.

METHODS AND MATERIALS

Patients and Iodinated contrast media usage

The Institutional Review Board in our hospital approved the retrospective study. We reviewed the radiology medical records from May 2004 to February 2006, and selected consecutive patients who received intravenous contrast-enhanced CT scans. Patients who received ICM below the routine volume of 100 mL for contrast-enhanced CT were excluded. This consisted of patients who 1) were children (under 18 years old), 2) were under 40 kg body weight, 3) had poor renal function (eGFR < 60mL/min/1.73m²), and 4) received brain CT. In total 32499 patients were enrolled in this study: 7520 (23.14%) patients received Iothalamate meglumine, 9830 (30.25%) patients received Iopromide and 15149 (46.61%) patients received Iohexol (Table 1).

The IICM, Iothalamate meglumine (Conray®60%, Mallinckrodt Inc, USA) was used in our tertiary referral hospital over the entire review period. Because of yearly bidding of NICM in our hospital, Iopromide (Ultra-vist®370, Schering AG, Germany) was used from May 2004 to December 2004, and another NICM, Iohexol (Omnipaque®350, Amersham Health, USA), was used from January 2005 to February 2006. All patients could choose IICM (afforded by Taiwan National Health Insurance Bureau) or purchase NICM depending on their willingness after being asked about ADR history to ICM, and were fully informed of the associated risks and the different chemical properties (e.g. osmolality, viscosity…etc.) of these ICMs.

All ICMs were routinely warmed to body temperature to reduce the viscosity before CT study. The injection rate of ICM was decided by the radiologist based on tailored protocol according to the patient’s disease or clinical problem. Rapid injection of ICM was mainly used in CT angiography for detection of vascular disease and dynamic enhanced CT for detection or staging of hypervascular tumor, and slow injection rate was suitable for all other situations. Patients who received IICM Iothalamate meglumine were all in slow injection group (manual injection). Patients who received NICM, either Iopromide or Iohexol, were divided into slow (manual injection) and rapid injection groups; rapid injection rate was defined as greater than 2 mL/sec and achieved by automated contrast injector (Liebel-Flarsheim CT 9000® ADV digital injection system).

Data collection

All data were collected from radiology medical records including gender, age, the type of ICM, injection rate, enrollment date and the type of aADRs. The aADRs that were reported by patients were documented in radiology medical records. The aADRs were classified in 5 types by symptoms: 1. gastrointestinal symptoms, including nausea and/or vomiting; 2. cutaneous symptoms, including pruritus, flushing, maculopapular exanthemas, urticaria, and angioedema; 3. respiratory symptoms, including running nose, sneezing, nasal congestion, shortness of breath, dyspnea, laryngoedema and asthma; 4. shivering; 5. severe symptoms, including conscious disturbance, loss of consciousness, and shock. Delayed adverse drug reaction, defined as symptoms that developed 12 hours after ICM was injected, and contrast-related nephropathy were not included in this study. Human error, contrast extravasation and non-specific symptoms mainly owing to patient’s perception (e.g. transient dizziness, warmth at the injection site and discomfort in the injection extremity) were not collected in the analyzed data. The grading of aADRs severity was not applied in this study because interpretation of severity grading differed among clinicians.

Statistical analysis

Fisher’s exact test and Chi-squared test were used to evaluate differences in aADRs. A p-value of less than 0.05 was considered to be statistically significant. P-values for pairwise comparisons were adjusted by Bonferroni correction. All statistical operations were performed using STATA 10.1 (College Station, Texas, USA).

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tr>
<td>Contrast media</td>
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<tr>
<td>Iothalamate</td>
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<td>Iopromide</td>
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<td>Iohexol</td>
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Abbreviations: N: number of enrolled patients and (percentages); M/F: male/female.
RESULTS

Comparison between IICM (Iothalamate meglumine) and NICM (Iopromide and Iohexol)

The aADRs of iothalamate meglumine, iopromide and iohexol were classified by systemic symptoms and described in Table 2. There was no death due to ICM-induced aADRs during the study period. The incidence of shivering and severe symptoms was not significant in iothalamate meglumine, iopromide and iohexol. The incidence of aADRs of iothalamate meglumine was higher than iopromide and iohexol in total patient group ($p<0.001, p<0.001$) and slow injection group ($p=0.021, p<0.001$).

Cutaneous symptoms with iothalamate meglumine (1.02%), iopromide (0.89%) and iohexol (0.20%) was the most common type of ICM-induced aADRs, followed by gastrointestinal and respiratory symptoms. In systemic symptoms, iopromide only revealed lower incidence of gastrointestinal symptoms compared with iothalamate meglumine in total patient group ($p<0.001$) and slow injection group ($p<0.001$). Iohexol compared with iothalamate meglumine not only showed lower incidence of gastrointestinal symptoms, but also lower cutaneous and respiratory symptoms in total patient group ($p<0.001, p<0.001, p<0.001$ respectively) and slow injection group ($p<0.001, p<0.001, p=0.004$ respectively). In slow injection groups with shivering symptom, comparison of the three ICMs showed significance ($p=0.037$), but no significance with paired comparison. This may be due to extremely few patients with shivering; only four patients in iohexol, and no patient in iothalamate meglumine or iopromide.

Comparison between NICMs: Iopromide vs. Iohexol

Iopromide had higher total aADR incidences than iohexol in total patient group ($p<0.001$), slow injection group ($p<0.001$) and rapid injection group ($p<0.001$). Iopromide increased the incidence of gastrointestinal and respiratory symptoms in total patient group ($p=0.005, p<0.001$ respectively) and slow injection group ($p=0.005, p<0.001$ respectively), and also increased the incidence of cutaneous symptoms in total patient group, slow and rapid injection groups ($p<0.001, p<0.001, p<0.001$ respectively) compared with iohexol. When comparing slow with rapid injection, a higher incidence of gastrointestinal symptoms

<table>
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<th>Table 2. Acute Adverse Drug Reaction of Iodinated Contrast Media</th>
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<td>Patients with aADR</td>
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<tr>
<td>Iothalamate meglumine</td>
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<td>132 (1.76)</td>
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<td>Slow injection</td>
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<td>132 (1.76)</td>
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<td>Rapid injection</td>
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<td>Systemic symptoms</td>
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<td>Gastrointestinal</td>
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<td>Slow injection</td>
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<td>Rapid injection</td>
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<td>Cutaneous</td>
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<td>Respiratory</td>
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<td>Severe</td>
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<td>Slow injection</td>
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<td>Rapid injection</td>
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Abbreviations: Data denote patient number and (percentages).
was noted with slow injection than rapid injection of iopromide ($p=0.008$).

**DISCUSSION**

In our study, the total incidence of aADRs was 1.76% (iothalamate meglumine) for IICM and 0.34% (iohexol) for NICM. There are quite different incidence rates from different studies, and the total incidence of aADRs is 2.31%-12.66% for IICM, and 0.35%-3.13% for NICM [4-7, 14, 15]. Petersein et al.(2003) observed a higher total incidence of aADRs for NICM (2.3%), but nearly half of the aADRs (1.1%) presented with only a warmth feeling [15] which was not included in aADRs in other studies [6, 13, 16]. Our reported incidence was lower than prior studies which may be due to the exclusion of patients with contrast extravasation and non-specific mild symptoms such as transient dizziness, warmth and discomfort in the injection extremity, and transient dysosmia and/or parageusia.

In general, ICM-induced adverse reactions are classified into extravasation, aADR, delayed ADR and nephropathy [9, 17]. The severity of extravasation is associated with the extravasated volume and the osmolality of ICM. Nephropathy is related to the osmolality of ICM [17]. Delayed ADR is thought to be a type IV T-cell mediated hypersensitivity [17, 18]. The pathophysiology of most ICM-induced aADRs is poorly understood. Many reports focus on the definition and classification of aADRs based upon severity, timing, signs and symptoms, or presumed pathophysiology. Currently, the mechanism of ICM-induced aADRs can be divided into two broad categories: chemotoxic and anaphylactic/anaphylactoid reactions [8-13, 17, 19-21]. Vasovagal reactions, such as nausea, vomiting and hypotension, are related with chemotoxic reactions, although some patients develop vasovagal reactions from IV needle placement even before ICM injection. ICM-induced anaphylactic/anaphylactoid reactions are subdivided into immediate and delayed. Immediate anaphylaxis develops within one hour after contrast administration and includes cutaneous symptoms (pruritus, flushing, urticaria and angioedema), respiratory symptoms (running nose, sneezing, nasal congestion, dyspnea, laryngoeedema and asthma), loss of consciousness and shock [19, 22]. A rare population with ICM-induced anaphylaxis was proved to be an immunoglobulin E-mediated reaction [22]. The anaphylactoid reaction to ICM is caused by histamine release from mast cells and basophils either due to direct ICM osmolality effect or indirect complement–kinin activation [19]. Delayed T-cell mediated hypersensitivity develops from hours to several days after ICM injection and is a rare ICM-induced ADR [21]. Early recognition and treatment of aADRs can prevent a reaction from getting worse and becoming severe. These adverse symptoms to ICM can also be limited by pretreatment with prednisone, diphenhydramine, and either ephedrine or a histamine H2-receptor antagonist [8-13, 17, 19, 23, 26, 27].

Many studies differentiated ICM-induced aADRs by grade of severity [2, 4, 7, 9, 10, 23-27] but only some literature differentiated them by symptoms [1, 14, 28], and discussed incidence of adverse symptoms with different ICMs [6, 12, 15]. In our study, cutaneous symptoms were the most common type of ICM-induced aADRs followed by gastrointestinal and respiratory symptoms which is similar to report of Yang et al.(2001) [14]. It is well known NICM has a lower aADR incidence than IICM. In our study, iopromide reduced total aADR incidence compared with lothalamate meglumine. However, concerning systemic symptoms, iopromide only reduced the incidence of gastrointestinal symptoms while iohexol can reduce the incidence of gastrointestinal, cutaneous and respiratory symptoms compared with lothalamate meglumine. The cause for this is not known and may be related to different chemical structure and properties of iopromide and iohexol.

Chemotoxic reactions are related to the chemical properties of ICM (osmolality, viscosity, hydrophilicity, calcium-binding properties, and sodium content) [17], and generally considered dependent upon dose and infusion rate [8, 17]. In contrast, ICM-induced hypersensitivity reactions are idiosyncratic and not related to dose and infusion rate [28]. This may be why some studies showed no correlation between the incidence of adverse reactions and the applied volume of ICM [15, 16, 29], or injection rate [16, 29-31]. However, our study showed slow injection of iopromide had a higher incidence of gastrointestinal symptoms than rapid injection. The cause is not known and may be related to the chemical structure and pharmacological mechanism of iopromide. The result is similar to a previous report [28].

Previous studies showed iopromide and iohexol revealed no significant differences in adverse events [28, 32-36]. However, our study shows significantly higher aADR of iopromide compare with iohexol. The result is consistent with a prior prospective randomized comparative study in Japan [29]. Further, we observed iopromide had higher aADR incidences than iohexol with gastrointestinal, cutaneous and respiratory symptoms which has not been previously discussed. Gomi et al.(2010) consider that the discrepancy of these results may reflect the relatively small number of enrolled patients in previous reports, or perhaps racial differences because previous reports are all from Europe and the United States [29].

There are some limitations in our study. First, the analyzed aADR data did not include the symptoms of warmth and pain, and current studies do not classify them into aADRs either [6, 13, 16]. The significance of injection site and ICM volume were not analyzed because the data on injection site in our medical record was incomplete. A routine volume 100mL of ICM was used for enrolled patients, prior studies showed no correlations between aADR incidence and the applied ICM volume [15, 16, 29], or injection site [16,
factors for adverse reactions. Information about benefits of NICM and find out the risk further prospective trials should be taken to provide more and respiratory symptoms. As the result of controversy, incidences than Iohexol with gastrointestinal, cutaneous compared with another NICM, Iopromide had higher aADR symptoms compared with Iothalamate meglumine. When incidence of gastrointestinal symptoms, and no significant difference in the incidence of cutaneous and respiratory symptoms compared with lothalamate meglumine. When compared with another NICM, Iopromide had higher aADR incidences than Iohexol with gastrointestinal, cutaneous and respiratory symptoms. As the result of controversy, further prospective trials should be taken to provide more information about benefits of NICM and find out the risk factors for adverse reactions.

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