Immediate Adverse Drug Reactions in Computed Tomography with Slow Injection Rate: Comparing Iothalamate Meglumine with Iopromide

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Non-ionic iodinated contrast media (NICM) are believed to cause less immediate adverse drug reactions (ADRs) than ionic iodinated contrast media (ICM). We undertook an observational study to compare the immediate ADRs caused by ICM and NICM during computed tomography (CT) examinations with a slow injection rate not greater than 2.0 mL/sec.

This study was designed to compare the immediate ADRs by using Iothalamate meglumine (Conray® 60%) and Iopromide (Ultravist® 370) for patients undergoing CT examinations in a period of 8 months. The injection rate was equal or less than 2.0 mL/sec. Immediate ADRs were classified by severity grading system. The statistical methods used were Fisher’s exact test and odds ratio with 95% confidence intervals.

Totally 8776 subjects were enrolled in our study, including 2766 subjects using Iothalamate and 6010 subjects using Iopromide. The overall incidence of immediate ADRs had statistical but small difference (p=0.04) between Iothalamate (1.84%) and Iopromide (1.26%). In each group classified by severity grading system, the incidence of immediate ADRs between subjects using Iothalamate and Iopromide did not show statistical difference.

Under the setting of slow injection rate (≤ 2mL/sec), Iothalamate was associated with a higher total incidence of immediate ADRs than Iopromide, but the difference was small. When patients were classified into groups of different ADR severity, no significant difference was found between these two contrast media. Therefore, at an injection rate not greater than 2.0 mL/sec, using Iopromide may not cause less immediate ADRs than using Iothalamate.

Iodinated contrast media (CM) are widely used in computed tomography (CT) and other X-ray examinations. When administered intravenously (IV), ionic iodinated contrast media (ICM) are believed to cause more immediate adverse drug reactions (ADRs) than non-ionic iodinated contrast media (NICM) [1-3]. The incidence of ADRs reported in the literature varied widely, from 4.17% to 31.20% in ICM and from 0.20% to 3.13% in NICM [2, 4-7].

Because of the greater incidence of immediate ADRs and the associated risks [1, 2, 8], ICM is no longer used in some hospitals. However, NICM are more expensive than ICM, thus practically they cannot totally replace ICM in examinations [2, 8]. Previous study indicated that at slow injection rate, ICM were not associated with significantly higher incidence of nausea than NICM [9]. The purpose of this study is to compare the incidence of immediate ADRs between Iothalamate and Iopromide during CT scan with slow injection rate.

Subjects and Methods

Contrast media usage and subjects

This study compared the immediate ADRs
of an ICM, Iothalamate meglumine (Conray®60%, Mallinckrodt Inc, USA) with a NICM, Iopromide (Ultravist®370, Schering AG, Germany). The characters of these two contrast media were listed in Table 1 [10]. We recruited patients undergoing CT scan from May 2004 to December 2004 in our hospital. Totally 8776 subjects were enrolled in this study, in which 2766 subjects receiving Iothalamate and 6010 subjects receiving Iopromide. The age of patients was 15-88 years old (mean age, Iothalamate group: 57.0 years; Iopromide group: 58.2 years). Totally four CT scanners were used in this study (G.E., HiSpeed, United States; G.E., ProSpeed, Japan; Siemens, Somatom Sensation 16, Germany; Siemens, Somatom Volume Zoom, Germany). Each patient received a fixed dose of CM, equally 100mL in volume. The patients receiving CT scan with less than 100 mL CM, such as those receiving enhanced brain CT scan, were excluded in this study. Before injection, intravenous access route (BD, Insyte™IV. Catheter 20G or 22G, Singapore) was established, and the CM were warmed to the temperature of 37°C [11]. The CM were infused by portable mechanical injector. The maximal injection rate of the injector was 2.0 mL/sec. The injection rate of CM for each patient was decided according to the grading system introduced by the manual on contrast media established by American College of Radiology (ACR Manual) [16]. They were classified into (1) grade I: mild immediate ADRs, including limited symptoms without need of further management, such as nausea, vomiting, urticaria, or diffuse erythema; (2) grade II: moderate immediate ADRs, including symptoms not immediately life-threatening but requiring management, such as symptomatic urticaria, vasovagal reaction, bronchospasm, tachycardia, and mild laryngeal edema; (3) grade III: severe immediate ADRs, including symptoms potentially or immediately life-threatening, such as complete cardiovascular collapse, severe vasovagal reactions, moderate to severe bronchospasm, moderate to severe laryngeal edema, loss of consciousness, seizure, and cardiac arrest.

Table 1. Characters of Iothalamate and Iopromide

<table>
<thead>
<tr>
<th>Character</th>
<th>Iothalamate</th>
<th>Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Structure</td>
<td>Ionic monomer</td>
<td>Non-ionic monomer</td>
</tr>
<tr>
<td>Concentration (mg/mL)</td>
<td>282</td>
<td>370</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg-water)</td>
<td>1400</td>
<td>774</td>
</tr>
<tr>
<td>Osmolality to plasma</td>
<td>Hypertonic</td>
<td>Hypertonic</td>
</tr>
<tr>
<td>Viscosity (cps)</td>
<td>4 (37°C)</td>
<td>10 (37°C)</td>
</tr>
</tbody>
</table>

Immediate adverse drug reactions

No statistical difference was noted in age distribution between subjects using Iothalamate and
Table 2. Enrolled Subjects

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (YR ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iothalamate</td>
<td>2766</td>
<td>57.0 ± 14.9</td>
</tr>
<tr>
<td>Iopromide</td>
<td>6010</td>
<td>58.2 ± 16.0</td>
</tr>
<tr>
<td>Total</td>
<td>8776</td>
<td></td>
</tr>
</tbody>
</table>

Note: N = number of enrolled subjects

Table 3. Subjects with Immediate Adverse Drug Reactions Classified by Grading System with Comparison

<table>
<thead>
<tr>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iothalamate</td>
<td>21 (0.76%)</td>
<td>30 (1.08%)</td>
<td>0</td>
</tr>
<tr>
<td>Iopromide</td>
<td>27 (0.45%)</td>
<td>48 (0.80%)</td>
<td>1 (0.02%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.09</td>
<td>0.22</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Data are the number of subjects with immediate adverse drug reaction. Data in parentheses are percentages

Table 4. Subjects with Immediate Adverse Drug Reactions Classified by Symptoms

<table>
<thead>
<tr>
<th>Symptoms*</th>
<th>Iothalamate</th>
<th>Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or vomiting</td>
<td>22 (0.80%)</td>
<td>24 (0.40%)</td>
</tr>
<tr>
<td>Cutaneous symptoms</td>
<td>32 (1.16%)</td>
<td>54 (0.90%)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>4 (0.14%)</td>
<td>17 (0.28%)</td>
</tr>
<tr>
<td>Cyanosis, severe laryngeal edema</td>
<td>0</td>
<td>1 (0.02%)</td>
</tr>
<tr>
<td>Shock</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Cutaneous symptoms include urticaria or erythema with any degree. Respiratory symptoms include sneeze, vasovagal reaction, bronchospasm, and laryngeal edema of any degree but not life-threatening. *Each adverse event may have more than one symptom

Table 5. The Past History of Subjects with Immediate Adverse Drug Reactions

<table>
<thead>
<tr>
<th></th>
<th>Iothalamate</th>
<th>Iopromide</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>4</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1</td>
<td>0.84</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>0</td>
<td>1</td>
<td>0.84</td>
</tr>
<tr>
<td>History of Allergy</td>
<td>1</td>
<td>4</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Note: ADR = adverse drug reaction. CM = contrast media

Iopromide (Table 2). Totally 127 subjects with immediate ADRs were observed (1.45%), including 51 subjects using Iothalamate (1.84%) and 76 subjects using Iopromide (1.26%). Significant difference of total incidence of immediate ADRs between subjects using Iothalamate and those using Iopromide (p=0.04, odds ratio 1.47 [95% CI 1.03-2.10]) was noted (Table 3). However, no significant difference of immediate ADR incidences was found between subjects using Iothalamate and those using Iopromide in each grade of ADRs (p>0.05) (Table 3). The presentation of immediate ADRs was showed in Table 4. The past history of subjects with immediate ADRs was summarized in Table 5.

Discussion

Under the setting of slow injection rate that equal or less than 2.0 mL/sec, the total incidence of immediate ADR in patients receiving Iothalamate was higher than those receiving Iopromide (p<0.05), although the difference between them was small. The reported incidence of immediate ADRs in literature varied widely [2, 4-7, 17] from 4.17% to 31.20% in ICM and 0.20% to 3.13% in NICM. Our results showed relatively low incidence of ADRs when compared with the previously reported data. In our study, we excluded transient discomforts, such as heat sensation or pain at injection site, while most studies with higher incidence of ADRs counted these findings [1, 4, 5, 18]. Furthermore, we limited the route of contrast administration to intravenous administration, while some retrospective studies included ADRs arising from angiography or urography as well [1, 4, 18]. To our knowledge, no studies have compared the incidence of immediate ADRs between Iothalamate and Iopromide.

Concerning injection rate of CM, controversial results were found in the literature. Some studies reported no significant relationship between the injection rate and contrast reaction [19-22]. Federle et al. [9] reported that at slow injection, there was no increase in the incidence of nausea in subjects using ICM when compared with that in subjects using NICM. But at rapid injection, using NICM was associated with a significantly reduced incidence of nausea.

No significant difference was found between patients using Iothalamate and those using Iopromide when they were classified into groups according to severity of ADRs. This may be explained by small difference of the overall incidence of immediate ADRs between Iothalamate and Iopromide. Therefore, in each group of severity, the difference may be even smaller and failed to show a statistical significance. Transient discomforts without observable sign (heat sensation or pain at the injection site) were excluded in our study, but were included in previous studies [4, 5, 18]. According to the ACR Manual, warmth/heat sensation was a physiological
response to the high-osmolality contrast agents, and
the pain on injection was largely a function of hyper-
tonicity [23]. These discomforts did not progress to
moderate severity and usually did not need any man-
agement, so we did not record them. This was con-
sidered the major reason that the incidence of grade
I ADRs in our study was less than the incidences of
grade II and III ADRs, disaccorded the findings of
previous reports [6, 11, 24].

A detailed discussion of reactions to the con-
trast agents, their mechanisms, and nephrotoxicity
was beyond the scope of this study, but a relevant
comparison of these two different CM might help.
Concerning the characters of the Iothalamate and
Iopromide, many differences were noted between
them (Table 1). Iopromide had higher concentration
than Iothalamate, that might induce more heat sen-
sation but no proven influence to the frequency of
ADRs or local pain sensation [25]. The Iopromide
had higher viscosity than Iothalamate. Some litera-
ture indicated that higher viscosity caused less and
slower cardiac electrophysilogic effects [26] and
delayed change to the composition of interstitial
fluid [27], resulting in less cardiovascular discom-
forts. But higher viscosity caused more significant
reduction of cutaneous microcirculation [28], which
induced transient ischemic change and pain sensa-
tion at the injection site. Through Iothalamate and
Iopromide were both hypertonic contrast media,
Iopromide presented lower osmolality to plasma than
Iothalamate. This difference may explain less cardio-
vascular effects, vasodilatation, and heat sensation
while using Iopromide [1, 2, 5, 18, 26]. Some litera-
ture supported that CM with low osmolality caused
less nausea/vomiting and cutaneous symptoms [2, 5,
18], while others did not support it [1].

In our study, cutaneous symptoms were the
most frequent immediate ADRs, similar to the find-
ings in previous literature [17, 29]. Nausea/vomiting
and respiratory symptoms were the next most fre-
quent discomforts in both CM. One severe imme-
|diately ADR was observed with Iopromide, none was
seen with Iothalamate. In this particular event, the
patient developed hypotension, cough, diffuse ery-
|thema, laryngeal edema, and cyanosis immediately
after IV administration of Iopromide, but he kept
consciousness and was not in shock status. The
patient was stabilized after emergent managements
including IV administration of steroid, oxygen and
IV fluid supplements. The patient was soon trans-
ferred to emergency room for further monitoring and
completely recovered later.

Several possible limitations presented in this
study. First, body weight was not taken into account
during contrast administration. The same volume
(100 ml) of CM was used for every subject in our
study. This may result in higher osmolality in thin
patients than in fat patients. Some studies have indi-
cated that osmolality can affect the overall incidence
of immediate ADRs [15, 18]. Moreover, subjects
who experienced mild and tolerable symptoms may
have been underestimated, because they may not
report such events. Also, because NICM were pre-
sumed as safe contrast agents, patients with severe
disease or old patients may be convinced to use
NICM by family, or medical personals, including
duty radiologists, technicians, nurses, or clinical
doctors. Additionally, Iopromide was compulsorily
used for the patients in ICU, patients older than 85
years, and patients who had previously experienced
severe adverse drug reactions. Age was not a factor
affecting the frequency of immediate ADRs [6], and
no statistic difference between the age distribution
of the subjects using Iothalamate and Iopromide in our
study was found. The status about inpatient or out-
patient might influence the frequency of immediate
ADRs [6]. We did not record this, so the influence
to our result could not be evaluated. Because our
study was an observational study, the past history of
subjects was only recorded for those who had expe-
rienced immediate ADRs. Although concerning the
past history of the patients with immediate ADRs, no
statistic difference was noted between Iothalamate
and Iopromide (p>0.05) (Table 5). Furthermore, the
past history of immediate ADRs was not recorded in
every subject. Though it was a confounding factor
that may influence the frequency of immediate
ADRs in our study [30], we could not evaluate it.
Another interesting point was the previous experi-
ence of the administration of CM in the subjects with
or without immediate ADRs, and its relationship
with the frequency of immediate ADRs in our study.
Due to the incomplete information in our study, this
topic could not be discussed in this study.

In clinical practice, informing patients of the
differences between ICM and NICM is important.
The NICM is believed to cause less adverse drug
reactions than ICM. Adapting a slow injection pro-
|ocol, our study showed significant but small dif-
ference of the overall immediate ADR incidence
between patients using Iothalamate and those using
Iopromide. When patients were classified into
groups of different ADR severity, no significant dif-
ference was found between those using these two con-
trast media. Therefore, at an injection rate not
greater than 2.0 mL/sec, using Iopromide may not
cause less immediate ADRs than using Iothalamate.

References
16. Committee on Drugs and Contrast Media. Manual on Contrast Media Version 5.0, American College of Radiology 2004
23. Committee on Drugs and Contrast Media. Manual on Contrast Media Version 5.0, American College of Radiology 2004
27. Chai CM, Almen T, Baath L, Besjakov J. Adding sodium and calcium ions to the contrast medium iodixanol reduced the risk of ventricular fibrillation during perfusion of the left coronary artery in pigs: effects of electrolytes, viscosity, and chemotoxicity of an isotonic perfusate. Acad Radiol 2004; 11: 583-593
以慢速給藥進行電腦斷層檢查發生立即性藥物不良反應之情形：比較 Iothalamate Meglumine 與 Iopromide

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長庚大學  林口長庚紀念醫院  影像診療科部

一般認為非離子性含碘顯影劑較離子性含碘顯影劑產生較少的立即性藥物不良反應。我們試著觀察以慢速給藥（每秒不超過 2.0 毫升）執行電腦斷層檢查時發生立即性藥物不良反應之情形。

此研究是觀察 Conray®60%（康利造影剤 60 注射液）與 Ultravist®370（優照維斯 370 注射液）用於電腦斷層檢查時發生立即性藥物不良反應之情形。收案時間為八個月。注射速率控制在等於或小於每秒兩毫升。在百分之九十五信心水準下以費雪法 (Fisher’s exact test) 及勝算比 (odds ratio) 作為統計分析之工具。

收案時間內共有 8776 筆在本醫院的電腦斷層檢查紀錄，包含 2766 筆使用 Conray 與 6010 筆使用 Ultravist 的紀錄。總共的立即性藥物不良反應發生率於 Conray 為百分之 1.84，於 Ultravist 為百分之 1.26，具有統計上很小的差異性。而以嚴重度區分開來的話，則這兩種顯影劑比較起來並無明顯的差異性。

在慢速給藥（等於或小於每秒兩毫升）的前提下，此研究顯示 Conray 和 Ultravist 比較起來只有稍高的總和立即性藥物不良反應發生率。而當病人之藥物不良反應的嚴重度區分開來時，這兩種造影剤並無明顯統計上的差異性。因此，以慢速給藥時，使用 Ultravist 並不會比使用 Conray 產生較少的立即性藥物不良反應。