<table>
<thead>
<tr>
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<td><strong>Author(s)</strong></td>
<td>山口，昴一；高梨，以美；叶内，哲；星，俊子；久保田，恒</td>
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<td><strong>Citation</strong></td>
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Osaka University
A Retrospective Survey of Delayed Adverse Reactions to Ionic and Nonionic Contrast Media

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Research Code No. : 502

Key Words : Delayed adverse reactions, Ionic contrast media, Nonionic contrast media, Retrospective survey

造影剤による遅発性副作用の遡及的調査
—イオン性と非イオン性造影剤について—

山形大学医学部放射線科

山口 昇一 高梨 以美 叶内 哲
星 俊子 久保田 恒

（平成4年6月18日受付，6月26日採録）
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造影検査を終えて患者が検査室を離れた後に発生する遅発性副作用が注目されている。国内では、新しい非イオン性造影剤についての調査報告があるが、従来からのイオン性造影剤についての調査は報告されていない。この状況を踏まえて、大規模な遅発性副作用調査を行う場合の問題点を採用目的を含む本研究が行われた。

山形大学医学部附属病院で、過去に造影X線CTを受けた入院患者を対象に、検査後5日間の診療記録を遡って調査した。イオン性造影剤715例（1985，12～1986，7）と非イオン性造影剤302例（1987，5～1988，8）が分析の対象となった。

造影剤に関係したと推定されるすべての遅発性症状を取り上げると、イオン性造影剤群に36例（5.0％）、非イオン性造影剤群に44例（4.9％）であった。主観的症候として発疹を含む皮膚症状を取り上げても、その他の症状を分けて比較しても、イオン性、非イオン性の間に有意な発現率の差は見いだせなかった。また、遅発性副作用の発現と、即時型副作用、アレルギー性、造影剤の副作用ととの関にも有意の関連は認められなかった。注目すべきことに、造影剤の投与を受けた後4時間経過血圧低下で倒れた症例の記録があった。

本研究結果から、遅発性副作用は非イオン性造影剤に限らず、従来のイオン性造影剤にも発現していたことを確認した。更に、両造影剤に発現率の有意差が有るかを確実にするために、調査対象症例数を考慮して近似した。

Abstract

A comparative survey of delayed adverse reactions (DARs) to ionic and nonionic contrast media (CM) was carried out. In Japan high osmolar CM have mostly been replaced by new low osmolar CM. Therefore, a retrospective survey was performed limited to inpatients who had received an enhanced CT examination in our hospital. The material consists of 715 consecutive cases given ionic CM (iothalamate and diatrizoate)
and 902 given nonionic CM (iopamidol and iohexol). DARs were picked up based on descriptions in the medical record up to 5 days after the examination. Most DARs had occurred within two days after the examination. Overall DARs were noted in 36 cases (5.0%) of the ionic group, and 44 cases (4.9%) of the nonionic group. Skin rash as well as other symptoms revealed no significant difference in incidence between the ionic and the nonionic group. There were no significant associations with immediate reactions, allergy, previous adverse reactions to CM. One patient given an ionic CM developed hypotension (60 mmHg) after return to the ward. It should be emphasized that a delayed shock had been recorded.

Introduction

It is very important to know the incidence of delayed adverse reactions (DARs) to contrast media (CM) which occur after the patient has left the radiological department. Investigations by Panto and Davies, and McCullough et al which appeared in the British Journal of Radiology \(^1\), \(^2\) first attracted our attention. Thereafter were published in Japan several reports about DARs which were concerned, however, only with nonionic CM \(^3\)-\(^6\). Accordingly, knowledge comparing DARs after ionic and nonionic CM is still limited. Therefore, it is proposed that a comprehensive survey should be conducted like the previous large-scale survey of the Japanese Committee on the Safety of Contrast Media \(^7\).

The present study was designed as a preliminary step into a large-scale survey for the comparison of DARs to ionic and nonionic CM. At present, high osmolar ionic contrast media have been almost completely replaced by new contrast media in many institutions in Japan including our department. Because of this, our trial was undertaken also with the intention to check the availability of a retrospective method limited to previous inpatients who had received enhanced CT in our hospital.

Materials and Methods

The material for this study consists of 902 cases given nonionic contrast media (iopamidol: 900, iohexol: 2); and 715 cases given ionic contrast media (mg/l. iohalamate: 208, mg/l. diatrizoate: 2, mg/l. + Na diatrizoate: 505). As nonionic group, we used a series of inpatients from one CT room from May, 1987 to August, 1988. As ionic group, we used consecutive cases in one CT room from December, 1985 to July, 1986 before switched from ionic to nonionic CM.

DARs were picked up based on the descriptions in the medical records of these inpatients, and a period of 5 days after the examination was reviewed. Study items were as follows: (a) patient data (sex, age, body weight, previous adverse reactions to CM, history of allergy, immediate reactions to CM at this time), (b) DARs (time of occurrence, symptoms, severity, outcome). We picked up DARs on the basis of the following criteria. First, the symptoms occurred after return to the ward from CT room but within 5 days of examination. Second, the symptoms were unlikely due to administration of other drug, foods or other causes as disease itself.

Statistical analysis: Fisher exact probability test (two-tailed) was used to analyze the incidence of DARs. An association test for paired contingency table (2 by 2) was used for incidence of DARs.

Results

The incidence of DARs is summarized in Table 1. DARs were noted in 36 cases out of the ionic group, and 44 cases out of the nonionic group. Incidence rates were 5.0% for the ionic and 4.9% for the nonionic group. But, it is better to refrain from simply comparing these two values. DARs by symptoms are also described in the table. There were cases with fever. Although these patients became feverish after the examination, it was difficult to establish a definite cause: relationship considering their underlying diseases. On the other hand, we may compare the incidence of skin reactions as more objective symptoms. However, statistical analysis revealed no significant difference between the 1.4% and 2.0% obtained in skin rash, and neither between the other symptoms. There was no significant difference of the incidence between ionics and nonionics even when skin symptoms, such as rash, itching and redness of the face,
Table 1 Incidence of DARs to CM (ionic vs. nonionic)

<table>
<thead>
<tr>
<th></th>
<th>Ionic CM (n=715)</th>
<th>Nonionic CM (n=902)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall reactions</td>
<td>36(5.0%)</td>
<td>44(4.9%)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>10(1.4%)</td>
<td>18(2.0%)</td>
</tr>
<tr>
<td>Itching only</td>
<td>3(0.4%)</td>
<td>5(0.6%)</td>
</tr>
<tr>
<td>Redness of the face</td>
<td>7(1.0%)</td>
<td>3(0.3%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>8(1.1%)</td>
<td>7(0.8%)</td>
</tr>
<tr>
<td>Abd. discomfort</td>
<td>2(0.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>4(0.6%)</td>
<td>—</td>
</tr>
<tr>
<td>Drop of blood pressure</td>
<td>1(0.1%)</td>
<td>—</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>1(0.1%)</td>
<td>—</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1(0.1%)</td>
<td>1(0.1%)</td>
</tr>
<tr>
<td>Fever/chill</td>
<td>2(0.3%)</td>
<td>11(1.2%)*</td>
</tr>
<tr>
<td>Others</td>
<td>1(0.1%)</td>
<td>2(0.2%)</td>
</tr>
</tbody>
</table>

*Causal relation is uncertain.

Table 2 Overall incidence of DARs between ionic CM

<table>
<thead>
<tr>
<th></th>
<th>11/208 (5.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cofray</td>
<td></td>
</tr>
<tr>
<td>60% urografina</td>
<td>25/505 (4.9%)</td>
</tr>
<tr>
<td>Argiograftin</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Table 3 Prevalence of DARs by immediate ARs

<table>
<thead>
<tr>
<th></th>
<th>Ionic</th>
<th>Nonionic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delayed reactions</td>
<td>Delayed reactions</td>
</tr>
<tr>
<td></td>
<td>(+) (-)</td>
<td>(+) (-)</td>
</tr>
<tr>
<td>Immediate ARs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>2 26</td>
<td>1 8</td>
</tr>
<tr>
<td>Without</td>
<td>34 653</td>
<td>43 847</td>
</tr>
<tr>
<td>Association</td>
<td>NS (p=0.922)</td>
<td>NS (p=0.929)</td>
</tr>
</tbody>
</table>

The incidence of overall DARs by the kind of ionic CM is shown in Table 2. There was no statistical difference between them. Further analysis by each symptom also revealed no significant results. In the nonionic series, as a result, iohexol was used in only two cases, both without any reaction. Therefore, the data in this series are only said for iopamidol.

We analyzed association of underlying factors to the DARs. At first, Table 3 shows the incidence of DARs by immediate ARs. We could not find any significant association between them. Next, as described in Tables 4 and 5 there was no significant association also to the history of allergy and the history of ARs to previous CM application. Although the data are not shown here, analysis by gender and age revealed no significant correlation.

In Table 6 the time of occurrence of DARs is presented. Most of the DARs occurred within two days after the examination. Although the descriptions of the earliest onset was soon after return to the ward in two cases of ionic group and three of nonionic, we could not obtain detailed time data in order of minute within a hour.

As noted in Table 1, there were descriptions of drop in blood pressure and loss of consciousness. These were found in one patient. The event was as follows.
Table 4  Prevalence of DARs by history of allergy

<table>
<thead>
<tr>
<th>History of allergy</th>
<th>Ionic</th>
<th>Nonionic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delayed reactions</td>
<td>Delayed reactions</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>With</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Without</td>
<td>35</td>
<td>643</td>
</tr>
<tr>
<td>Association</td>
<td>NS (p=0.965)</td>
<td>NS (p=0.846)</td>
</tr>
</tbody>
</table>

Table 5  Prevalence of DARs by previous ARs to CM

<table>
<thead>
<tr>
<th>Previous ARs</th>
<th>Ionic</th>
<th>Nonionic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delayed reactions</td>
<td>Delayed reactions</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>With</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Without</td>
<td>36</td>
<td>661</td>
</tr>
<tr>
<td>Association</td>
<td>NS (p=0.859)</td>
<td>NS (p=0.960)</td>
</tr>
</tbody>
</table>

Table 6  Time of occurrence of DARs

<table>
<thead>
<tr>
<th>Day of exam.</th>
<th>Ionic CM</th>
<th>Nonionic CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=35)</td>
<td>(n=43)</td>
<td></td>
</tr>
<tr>
<td>1st day</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>2nd day</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>3rd day</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>4th day</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5th day</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

A case report:
A 71 years old female received tympanoplasty for chronic otitis media. She was in good course after the operation and all medication had already been stopped. But, when her discharge was close at hand, she complained of headaches and received a brain CT (10:00 a.m.) with enhancement using 100 ml of 60% Conray (mgl. iohalaminate), which revealed no abnormality. She lunched around noon. About 4 hours later (1:30 p.m.) from CM application, she developed faintness and fell down near her bed. Systolic blood pressure was 60 mmHg. Fortunately, she recovered by treatments.

Causal relationship between CM application and this event will be discussed later.

Discussion

The definition of DARs is an important problem in this type of survey. Our criteria for picking-up the reactions are as described above in the part of method. In addition to these, it has been proposed that patients did not experience the symptoms before the examination[41]. Since our survey was retrospective, it was impossible to ascertain the history. Anyway, it was sometimes very difficult to exclude some reactions by other causes.

Observation period is also a problem. It was 5 days in our survey. This was because the results of our interim analysis revealed that there was no case with DARs which was likely due to injection of CM more than 5 days. As to the time of onset in the early period after examination, it may be very difficult to draw a clear dividing line between immediate reactions and DARs assuming that there is no lucid interval between them. Yoshikawa[41] picked up the symptoms which appeared more than 30 minutes after examination but
within 2 days, and described a patient who had a severe headache and felt extremely drowsy 1 hour after examination. Our survey could not reveal information in order of minute within a hour. This problem depends on further investigation.

Table 7 shows the results of surveys of DARs in Japan, which were limited to new low osmolar contrast media. The overall incidence rates of the reactions varied in a wide range. Of course, this is due to the method (prospective or retrospective) and the criteria for picking up the reactions in each survey. Picked-up reactions are not the same in these surveys. Because of this, it is meaningless to simply compare these values. In Table 7, also are shown the incidence rates of skin rash. The range of variation is not so wide as that of the overall incidence.

Davies and his colleague in Nottingham first reported a comparative survey of delayed reactions to ionic and nonionic contrast media performed in a prospective manner. Limiting the symptom to skin rash, the incidence rates by Davies’ group are presented in Table 8. The results of our present study shown in Table 1 were obtained in a retrospective manner. There seems to be no clear-cut difference between the two surveys. We can appreciate that there were DARs after both ionic and nonionic contrast media. But, it should be said that the proof of a significant difference in the incidence between ionic and nonionic contrast media would depend on further investigation.

We calculated the sample size to detect a 0.6% difference in skin rash in our study (Table 1) at the level of a type I error (α)=0.05 (two-tailed) based on Fleiss’s formula. The necessary sample sizes are shown in Table 9. If the proportion of ionic to nonionic cases would be 1:1, the necessary sample size would be 3,567 in each group. This size is almost the same with the value calculated by McCullough et al. As mentioned earlier, at present in Japan, it might be difficult to collect large number of ionic cases. If the proportion of nonionic to ionic cases would be 4:1, it would be necessary to collect over 12,000 cases as noted in Table 9.

We presented a case with delayed shock. We carefully reviewed the descriptions of medical record and the results of examinations of this patient. All medication had already stopped. There could not be found any data or findings which might give rise to hypotension. As described in a case report, she had lunched. A hypoglycemia after fasting might be also excluded as a cause of hypotension. In such a situation, we could not but consider that the event was due to administration of CM. According to our review in Japanese reports including abstracts of meetings, there have been 4 cases of delayed shock as shown in Table 10. It is important to know that such an event may occur after the patient has left the radiological department.

Finally, we would like refer to the design of further investigations in cooperation with multiple institutions to collect the necessary sample size. The design is important if we want to perform a larger scale survey. If we want to obtain reliable results about the risk of severe adverse reactions, such as shock, the sample size would have to be very large. Therefore, it is very important to select the target symptoms
Table 9 Calculated sample size

<table>
<thead>
<tr>
<th>Proportion of case No.</th>
<th>Ionic : Nonionic</th>
<th>Sample size</th>
<th>Ionic</th>
<th>Nonionic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td></td>
<td>3,567</td>
<td>3,567</td>
<td>7,134</td>
<td></td>
</tr>
<tr>
<td>1 : 2</td>
<td></td>
<td>2,830</td>
<td>5,659</td>
<td>8,489</td>
<td></td>
</tr>
<tr>
<td>1 : 4</td>
<td></td>
<td>2,461</td>
<td>9,843</td>
<td>12,304</td>
<td></td>
</tr>
</tbody>
</table>

Table 10 Reports of delayed shock

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Contrast Med.</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawada</td>
<td>1988</td>
<td>iopamidol</td>
<td>CT:</td>
</tr>
<tr>
<td>Hama</td>
<td>1988</td>
<td>iohexol</td>
<td>CAG:</td>
</tr>
<tr>
<td>Okazaki</td>
<td>1988</td>
<td>iohexol</td>
<td>Abd. A:</td>
</tr>
<tr>
<td>ADRs report</td>
<td>1988</td>
<td>iopamidol</td>
<td>CAG:</td>
</tr>
</tbody>
</table>

Carefully.

As far as a prospective survey is concerned, it would be easier to get a large sample size. Here, it is important to select the target symptoms and to apply uniform criteria for picking up and excluding symptoms responded by patients. In regard to a retrospective survey, we might have to perform this type of survey if we would like compare old iodine and new low osmolar contrast media in Japan, and the target should be limited to more objective symptoms than in a prospective survey. Moreover, it is necessary to select the participating institutions from the viewpoint of uniformity of medical records.

Reference

4) Yoshikawa E: Late adverse reactions to non-ionic contrast media. Radiology 83: 735–740, 1982
8) Kawada T: Nakadori Byouin Hic. 29: 44, 1988 (abstract)