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The Delayed Adverse Reactions of Low Osmolar Contrast Media

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低浸透圧性造影剤の遅延性副作用

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1988年12月から1990年8月迄に、経静脈性造影検査（3,765件）を受けた外来患者を対象に造影後一週間以内に発生した症状を、用意した調査用紙に自宅で記入してもらった上回収し、遅延性副作用の発生頻度を調査した。回収した1,070件の内、症状があったものは290件であった。この内の59例は今回訴えた症状が造影剤を使用しなかった過去一年間にも同様な症状があったため、これらを副作用から除き、1,011例を分析処理の対象とした。

致死性の又は入院を必要とする重篤な症状はなかった。これらの遅延性症状の発生頻度は上肢痛6.0%、頭痛3.6%、かゆみ2.3%、発疹1.5%、倦怠感1.4%であった。しかし、発生頻度は女性が高く、特に中高年女性では頭痛、倦怠感などの主観性の強い症状において同年齢層の男性と比べより高い発生頻度を得た。これより、性別や、精神的因子は症状の発生頻度に影響する因子であることが窺える。鼻炎と薬剤アレルギー性既往歴を持つ群は待たない群より高い発生頻度を示したが(p<

0.05)、各症状では主観性の強い症状であり、同様に女性に多く見られ、危険因子とするには不十分である。調査期間中2回以上の造影検査を受けた群（129件）と1回のみ受けた群と比較すると、客観的な発疹の発生頻度は2回以上造影を受けた群が1回のみ受けた群より低くなっていた。これは、造影回数が増えれば、増えるほど副作用の発生率が高くなるという一般的な考えと異なった結果であった。

遅延性症状の発生は造影剤を注射して数時間を経ってから起こるもので、症状と造影剤の因果関係の証明がなければ副作用とは言い難い。この点を考慮すると、今のような調査方法で得られた発生頻度は他の因子にも影響され、実際の発生頻度を正確に示すものかどうか疑問である。今後は調査件数を増やし、より高度な分析方法を用いて解析する必要があり、更に遅延性副作用を慎重に判定していかなければならない。

Abstract

A computer scale survey to inspect the occurrence of delayed symptoms (adverse reactions) associated with the intravenous injection of low osmolar contrast medium (LOCM) was carried out. Of the recovered 1070 questionnaires, 290 had the delayed symptoms. Excluding 59 patients having the same symptoms in the past one year without contact with the contrast medium, the overall incidence of the delayed adverse reaction is 22.8% (231/1011). The delayed symptoms include arm pain (6.0%), headache (3.6%), itching (2.3%), rash (1.5%), general fatigue (1.4%), gastrointestinal symptoms, etc. Though the chi-square test had shown significance of the occurrence of the delayed symptoms for the group with a past history of drug allergy and nasal allergy ($p < 0.05$), the delayed symptoms were mainly distributed in the middle-aged female to indicate that the sexuality is the cause of the foresaid significance. Furthermore, the incidence of the objective delayed symptoms such as rash in the group who had accepted more than two examinations is lower than the incidence in the group who accepted only one examination in the survey period. The disagreement to the fact that the repeated usage of the contrast medium is the risk factor to increase the incidence of the adverse reactions indicates the contrast medium may not be the only cause for the occurrence of the delayed symptoms, e.g. other factors such as sexual and psychological factors etc. may play a more important role than the contrast medium under this type of survey.

Introduction

Adverse reactions (acute) due to the contrast medium is well known to occur immediately after the injection and have been on large scale inspected in the past twenty years. It is well known that the incidence of the acute adverse reaction is affected by the type of contrast medium, the race, age, risk factors and even the physical or psychological condition¹⁻⁶). Recently, the incidence of adverse reactions significantly reduced owing to the new low osmolar contrast media that is available¹⁾²⁾.

It has been reported that delayed adverse reactions may occur either after the examination ends in the hospital or when the patients return home and thereafter. A large scale survey was carried out by Panto and Davis⁷⁾. The reported symptoms are commonly seen in a person even without administration of any contrast medium and there is a time span between the injection of the contrast medium and the onset of the symptoms, it is therefore important to prove the causal reasons, i.e. using the contrast media, before calling them adverse reactions. Yet, it is unknown. We have designed a survey to inspect these questions in the group using the low osmolar contrast media (LOCM).

Object, Material and Method

All the out-patients, in the period from December 1988 to February 1990, who accepted the radiological contrast enhanced examinations, including the studies of computed tomography (CT) and intravenous urography (IVU), are the objects of this study.

The LOCM of iopamidol (300 mg iodine/ml) and iohexol (300 mg iodine/ml) are used. The method of contrast enhanced examinations for either CT or IVU is performed by using 100 ml of contrast medium (50 ml fast drip infusion soon after a 50 ml bolus injection). For the children whose body weight are under 50 kg, the quantity of the contrast medium is 2 ml/kg. If the calculated quantity of contrast media was less than 50 ml, only the bolus injection is performed.

Two kinds of questionnaire sheets were designed for computer analysis. Patients were asked to fill out the one that contained the queries concerning the risk factors of the past history before the examination. The other questionnaire was handed out to the patients to record the data of the delayed symptoms at home that occurred within one week after the injection. The day the symptoms onset after the examination, the

Table 1 Incidence of delayed symptoms (Among 1011 cases)

Reactions	Cases(%)	Averaged days	
		Onset	Continued
Arm pain(injection site)	44(4.0)	1.2	3.1
Arm pain(above injection site)	12(1.1)	1.1	2.7
Arm pain(unspecified)	5(0.5)	1.0	2.2
Parotid pain	9(0.8)	1.6	3.2
Parotid swelling	1(0.1)	1.0	1.0
Gum pain	4(0.4)	1.8	3.3
Itching	25(2.3)	1.6	3.4
Rash	17(1.5)	2.0	4.0
Headache	40(3.6)	1.2	2.0
Fatigue	15(1.4)	1.5	2.7
Dizziness	5(0.5)	1.4	1.8
Nausea	8(0.7)	1.0	1.8
Vomiting	1(0.1)	2.0	1.0
Epigastralgia	7(0.6)	2.0	3.4
Diarrhea	13(1.2)	1.5	2.0
Constipation	7(0.6)	1.7	2.6
Aching joints	5(0.5)	1.4	2.6
Asthmatic attack	2(0.2)	1.5	1.0
Others	11(1.0)	1.3	3.2

number of days it lasted, the treatment of the symptom and whether the patient experienced the same symptom before were also surveyed. 18 delayed symptoms that have been reported in the literature were listed in the questionnaire handed out (Table 1). Since the "iodide mumps" was reported as a delayed adverse reaction, the symptoms of pain and swelling around the parotid area and gum pain that were not caused by caries were also listed⁸⁻¹⁰⁾. Though, up to five spaces were available for the patient to fill in one the delayed symptoms, the severest and most irritating symptom that patient was asked to fill in the first space was statistically analyzed. A total of 67 registered items for each patient were obtained from these two questionnaires.

All data were input into the NEC-PC 9801 RA and analyzed by using a programmed DBASE III plus system. All the statistical significances were analyzed by chi-square test.

Result

Of 3765 questionnaires handed out, 1430 were returned. The recovery rate was 38%. Among these returned questionnaires, a total of 1070 remained the complete record for analysis. 290 patients declared that the delayed symptoms occurred. 59 of them also remarked that they had had the same delayed symptom in the past one year in their daily lives without having contact with the contrast medium. After deleting these 59 cases the overall incidence of the delayed symptoms was 22.8% (231/1011). The sex distribution of the males is 487 persons and the females is 524. The average age was 46 years old with a range from 0 to 92. The lethal symptoms such as respiratory or cardiac arrest and death did not occur during the study.

(A) Delayed Symptoms (Table 1)

Arm pain was the most frequent delayed symptoms registered. The incidence of arm pain was 6.0%. The other delayed symptoms were headache 3.6%, itching 2.3% and rash 1.5%. 11 cases of delayed symptoms that were not listed on the questionnaire include limb edema and limb numbness and none of them accepted the treatment.

One patient had both parotid pain and swelling but he did not receive any therapy and recovered within one day. The other eight patients had painless parotid swelling and all of them cured naturally without medical therapy.

Ten of 231 patients accepted medical treatment (Table 2). The topical treatment and oral drug therapy were applied. None of them was admitted in the hospital due to these symptoms.

Table 2 Frequency of treated cases

Reactions	Cases
Itching	2
Rash	4
Headache	1
Epigatralgia	1
Fatigue	2

Table 3 Sexual distribution of delayed symptoms

(Among 1011 cases: Male 487, Female 524)		
Reactions	Male	Female
Arm pain(injection site)	14	30
Arm pain(above injection site)	4	8
Arm pain(unspecified)	1	4
Parotid pain	4	5
Parotid swelling	1	—
Gum pain	2	2
Itching	9	16
Rash	10	7
Headache	15	25
Fatigue	2	13
Dizziness	2	3
Nausea	4	4
Vomiting	—	1
Epigastralgia	4	3
Diarrhea	6	7
Constipation	3	4
Aching joints	—	5
Asthmatic attack	—	2
Others	7	4
Subtotal	88	143

Table 4 Frequency of sex and age distribution of delayed symptoms (Among 1011 cases)

Reactions	0 to 10 cases(M/F)	11 to 20 cases(M/F)	21 to 30 cases(M/F)	31 to 40 cases(M/F)	41 to 50 cases(M/F)	51 to 60 cases(M/F)	61 to 70 cases(M/F)	71 to 80 cases(M/F)	81 to 90 cases(M/F)	above 91 years old cases(M/F)
Arm pains	—	7(2/5)	6(1/5)	7(4/3)	15(5/10)	12(1/11)	10(5/5)	4(1/3)	—	—
Parotid pain	—	—	—	1(1/0)	6(3/3)	2(0/2)	—	—	—	—
Parotid swelling	—	—	—	—	—	—	1(1/0)	—	—	—
Gum pain	—	—	—	2(1/1)	1(0/1)	1(1/0)	—	—	—	—
Itching	1(1/0)	—	1(0/1)	2(1/1)	6(2/4)	4(1/3)	6(2/4)	3(2/1)	2(0/2)	—
Rash	—	2(1/1)	2(1/1)	1(1/0)	4(1/3)	3(2/1)	1(1/0)	3(2/1)	1(1/0)	—
Headache	—	6(1/5)	3(2/1)	4(3/1)	10(1/9)	11(3/8)	3(3/0)	3(2/1)	—	—
Fatigue	—	—	—	7(0/7)	3(0/3)	4(2/2)	—	1(0/1)	—	—
Dizziness	—	—	1(1/0)	1(0/1)	—	2(0/2)	1(1/0)	—	—	—
Nausea	—	1(1/0)	1(1/0)	2(1/1)	3(1/2)	—	1(0/1)	—	—	—
Vomiting	—	1(0/1)	—	—	—	—	—	—	—	—
Epigastralgia	—	—	—	3(2/1)	—	1(1/0)	1(1/0)	2(0/2)	—	—
Diarrhea	—	—	2(1/1)	2(1/1)	2(0/2)	3(2/1)	2(1/1)	2(1/1)	—	—
Constipation	—	1(1/0)	1(0/1)	2(1/1)	1(0/1)	1(1/0)	—	1(0/1)	—	—
Aching joints	—	—	—	1(0/1)	2(0/2)	1(0/1)	1(0/1)	—	—	—
Asthmatic attack	—	—	—	—	1(0/1)	—	—	1(0/1)	—	—
Other	—	—	1(0/1)	3(1/2)	—	1(0/1)	3(3/0)	3(3/0)	—	—
Cases examined	14(8/6)	46(25/21)	58(30/28)	130(55/75)	216(73/143)	221(111/110)	199(106/93)	95(61/34)	31(17/14)	1(1/0)

(B) Contrast Media and Examination Methods

There is no statistical significance in the incidence between the different examination methods of the CT and IVU. The incidence of rash was higher in iohexol (1.8%: 13/727) than in iopamidol (1.4%: 4/284). But the statistical significance is not proved yet.

(C) Sex and Age Distribution

The incidence of arm pain and the overall incidence of delayed symptoms were higher in females than in males with a statistical significance of $p < 0.01$. Though the frequency of rash was higher in males than in females, the statistical significance is not shown. Most of the other delayed symptoms occurred more often in females (Table 3).

The age distribution of the frequency of delayed symptoms was a two-tail curve with a peak at ages from 41 to 50 (Table 4). The distribution of the incidence for each delayed symptom according to the age was random.

Table 5 Frequency of delayed symptoms with risk factors

Risk factor	No. of delayed arm pain	No. of other delayed symptoms	No. of patient with risk factors
Acute reaction	27	70	393
Drug	3	13*	47
Nasal allergy	22	48*	225
Food	3	7	28
Asthma	6	8	33
Hypertension	6	11	67
Gastric ulcer	11	39	190
Diabetes mellitus	2	4	49

* $p < 0.05$

Table 6 Sexual distribution of delayed symptoms for nasal allergy group

Reactions	Male	Female
Parotid pain	—	2
Parotid swelling	—	—
Gum pain	1	—
Itching	1	5
Rash	2	2
Headache	5	11
Fatigue	—	4
Dizziness	—	—
Nausea	2	1
Vomiting	—	1
Epigastralgia	2	1
Diarrhea	3	1
Constipation	—	1
Aching joints	—	2
Asthmatic attack	—	—
Others	1	—
Subtal	17	31

Table 7 Comparison of the incidence of delayed symptoms between the groups of one and repeated enhancement

Reactions	One group Cases (%)	Repeat group Cases (%)
Arm pain(injection site)	41(4.6)	3(2.3)
Arm pain(above injection site)	10(1.1)	2(1.6)
Arm pain(unspecified)	5(0.6)	—
Parotid pain	9(1.0)	—
Parotid swelling	—	1(0.8)
Gum pain	4(0.5)	—
Itching	22(2.5)	3(2.3)
Rash	16(1.8)	1(0.8)
Headache	35(4.0)	5(3.9)
Fatigue	13(1.5)	2(1.6)
Dizziness	5(0.6)	—
Nausea	8(0.9)	—
Vomiting	1(0.1)	—
Epigastralgia	6(0.7)	1(0.8)
Diarrhea	10(1.1)	3(2.3)
Constipation	6(0.7)	1(0.8)
Aching joints	4(0.5)	1(0.8)
Asthmatic attack	2(0.2)	—
Others	19(2.1)	1(0.8)
Cases examined	882	129

(D) Risk Factor Analysis

The risk factors that have been surveyed include allergy histories to drugs and food, hypertension, cardiac infarction and angina, asthma, diabetes mellitus and gastric ulceration. The statistical significance ($p < 0.05$) was shown in the groups with the past history of nasal allergy and drug allergy compared to the groups without a past history (Table 5). Yet, looking into the occurrence of individual symptoms of group with nasal allergy, the female group was found to have more frequent complaints in either symptoms than in male group (Table 6).

(E) Repeated Enhancement

33 males and 29 females who accepted more than two examinations during the survey period composed a repeated enhancement group, a total of 129 examinations. None of them had experienced any objective delayed symptom, i.e. rash, in the first examination but not in the following examination. Compared to the group who had only one examination, the repeated enhancement group had a lower incident of rash (Table 7).

Discussion

The incidence of arm pain in the present study for LOCM was 6.0%. It was compatible with the reported values by Panto et al, a survey of 841 cases in 1986, 13% (6.2%: 9/145 for LOCM and 14.8%: 103/696 for high osmolar contrast media: HOCM). The significantly reduced incidence of arm pain for LOCM was owed to the well known fact that the lower the osmolarity of the agent the lesser damage to the vascular epitheliums to induce arm pain. The incidence of the average delayed rash was 1.5% in this study, the result was also compatible with the values reported by Panto and his coworker, with a total of 5% (LOCM 2.8%: 4/145 and HOCM 5.6%: 39/696).

In contrast to the acute adverse reactions that occur after completion of the examination in the hospital, the so-called delayed adverse reactions happen when the patients return home and thereafter. Because most of the delayed symptoms are commonly seen in normal people and since there is a time span between the onset of the symptoms and the usage of the contrast medium, it is important to prove the causal reasons, i.e. using the contrast media, before calling them adverse reactions.

Two methods can be used to prove the relation between the delayed symptoms and the contrast media. One is to biochemically observe the hematological change, another is to statistically check the deviation of the frequency or incidence influenced by the considerable variables such as sex, age, risk factors, social factors and even the personal background, e.g. the education, income etc. Yet, considering the privacy, some of the variables were impossible to survey. Based on the consideration of the possible inducing mechanisms either the acute or the delayed adverse reactions were the same, we chose the recognized variables to affect the incidence of the acute adverse reactions and the past diseases such as gastric or duodenal ulceration as the variables of inspection.

Our results have shown that the sex is an important variable that influences the incidence of the delayed symptoms. Especially middle aged females had a tendency of claiming the delayed symptoms than the same aged male. The incidence of the delayed symptoms for the group with a past history of nasal allergy and drug allergy ($p < 0.05$) show a differing significance from that of the incidence of the group without the past history. But the sexual distribution of either symptoms showed that the females had more complaints of delayed symptoms than males and indicate the contrast medium may not be the only causal reason for the foresaid significance.

Further evidence to question the true relationship of the delayed symptoms with the contrast media injected is that the repeated examination group had a lower incidence of rash than that the one examination group had. The result disagrees with the common belief the repeated use of the contrast media would increase the occurrence of the adverse reaction. So far, none of the patients had the delayed symptom of rash in the first examination but it did not manifest in the following examination. Since the delayed symptoms may not only be induced by the contrast media under this kind of survey, prolonged continuation of this survey is expected to bring about some patients declaring the delayed rash with this pattern.

Though the result of this study did not show any absolute evidence to support that the delayed symptoms was related to the contrast media, the contrast media seems to be playing a minor role on the delayed symptoms. To understand what degree the contrast media affects the patient, a larger survey is necessary in the future. Currently, to differentiate from the truly delayed adverse reaction we suggest that the terminology for all the symptoms stated by the patients to be called "delayed symptoms".

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