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Clinical Survey on Adverse Reaction of Contrast Media
(Final Report)

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ヨード造影剤の副作用に関する臨床調査（最終報告）

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1983年10月より1986年6月まで2年9カ月にわたり，全国11施設においてヨード造影剤の血管内投与による副作用の臨床調査を行った．症例の総数は33,440例であった．

33,440例中，何らかの副作用がみられたのは2,523例（7.5%）であった．このうち致死例はなかった．副作用の発生に男女差はなく，40～60歳台に多い傾向がみられた．プレテストは90%の症例で行われており，プレテスト陽性者は108例であった．これはプレテスト実施例の0.4%にあたる．副作用の発生はプレテスト陽性者に高く（48%），しかし特別に重篤な症例はなかった．

アレルギー歴陽性例で副作用発生が52%であり，かなり副作用発生を予測できるものと考えられた．

以前に造影剤の投与を受けた既往の有無と副作用の発生には特に関係がなかった．

プレテストでテストアンプルが使用されたか，本剤より1mlとって行われたかは不明であった．

とくに，プレテストのpositive predictive valueは低く，dose-dependentの副作用は予知できないし，dose-independentの副作用を起す危険がある．今回の調査でも副作用を予知する最も信頼できる方法は，詳細なアレルギー歴の聴取であることが分った．しかし今回の結果から，テストアンプルの廃止はともかく，プレテストそのものを行うべきではないとは言いきれなかった．

造影剤の種類や量についてははっきりした結論を出し得なかった．また，低浸透圧造影剤の症例は少なかったので，今回の分析から除外された．

新しい造影剤の臨床使用も普及し始めた現在，更に，大規模な全国レベルの調査を行い，ヨード造影剤の副作用の実態を明らかにし，多様化した造影剤の使用に指針を示すべきと考える．

Iodine contrast media with low osmotic pressure have now been made available. Low osmotic iodine contrast media can be divided roughly into nonionic iodine contrast media and dimeric iodine ones. A background factor leading to the development of these low osmotic iodine contrast media is as follows; though the radiopacity of the conventional contrast media given at a high dose is nearly satisfactory, their side-effects have become not to be neglected. On the other hand, the production cost of low osmolar contrast media is higher than that of the conventional ionic high osmolar contrast media and their market price is also several times higher than that of the conventional ones. Thus, the new low osmolar iodine contrast media are used only in high-risk patients for the present. In this connection, it has been positively discussed from the viewpoint of medical economics what is the high-risk factor. Under such situation, clinical or basic researches on side-effects due to iodine contrast media in general seem to have been made actively.

Receiving a support of Grants for Scientific Research from Ministry of Education (General Researches A 59370030) since October 1983, the authors had continued a clinical investigation into side-effects due to iodine contrast media in 11 institutes throughout the country[1),2)], and terminated the clinical investigation in June 1986. We would like to present the result of this investigation as a final report by way of suggestion.

Subjects

Subjects were 33,440 cases from 11 institutes who were involved in the investigation in the period from October 1983 to June 1986, consisting of 18,541 male patients and 14,336 female patients. The remaining 563 could not be specified on their sex. Age ranged from 0 to 90. Many patients belonged to the age group from 40 years old to 70 years old for both sexes.

Investigation Method

At first, an investigation form was prepared. Major investigation items were; age, sex, history of allergy, history of examination with an iodine contrast medium, presence or absence of pretesting, presence or absence of premedication, kind and dose of contrast medium, subjective and objective symptoms of side-effects, presence or absence of treatment for side-effects, etc.

The investigation forms entered by each institute were collected in one place, and a worksheet was

Table 1 Side-effects by each institute

	Total Cases	Side-effect(+)	Percentage
A	5,192	361	7.0%
B	1,609	121	7.5%
C	2,941	319	10.8%
D	2,195	150	6.8%
E	4,347	325	7.5%
F	1,429	217	15.2%
G	437	58	13.3%
H	10,415	527	5.1%
I	2,035	296	14.5%
J	1,560	89	5.7%
K	1,280	60	4.7%
Total	33,440	2,523	7.5%

Table 2 Side-effects by sex

	Male	Female
Total Cases	18,541	14,336
Cases of Side-effects	1,448	1,037
Percentages	7.8%	7.2%
Nausea	848(59%)	499(48%)
Exanthema	408(28%)	361(35%)
Vomiting	355(25%)	185(18%)
Vascular pain	127(9%)	94(9%)
Cough	64(4%)	71(7%)
Itching	38(3%)	30(3%)
Edema, air-way	26(2%)	32(3%)
Hypotension	31(3%)	24(2%)
Shivering	17(1%)	11(1%)

(Sex was not specified in 38 cases with side effects.)

prepared for computer input. Information input in the computer was output by parameters. The computer used was Burroughs' B7800 (made in USA).

Results

(1) Incidence of side-effects

Some side-effect was observed in 2,523 out of 33,440 cases (7.5%). Table (1) shows the incidence of side-effects in each institute. Their incidence ranged from 4.7% at the lowest to 15.2% at the highest. The difference was caused by the fact how far angialgia upon administration of contrast medium was significantly evaluated.

(2) Incidence of side-effects by sexes and ages

There was no difference in their incidence between males and females. Table (2) shows the incidence and symptoms of side-effects by sexes. Namely, side-effects were found in 7.8% of male patients and 7.2% in female patients. The incidence of side-effects by ages was shown in Fig. (1). Side-effects were often found in patients at the age from 40 years old to 60 years old. Such side-effect symptoms as nausea, vomiting and redness were at ranking higher than 3. No fatal case was found. We investigated what treatment was given in side-effect patients: The very limited number of patients suffered from severe symptoms such as so-called shock. Patients reported in this series to have fallen into shock included those with transient fall of blood pressure which was easily improved and those with severer one for which a vasopressor was needed. In Table (2), these symptoms were summarized under "fall of blood pressure".

(3) Pretesting and side-effects

Pretesting was performed in 90% of the patients. Table (3) shows the incidence of side-effects by institutes in the pretesting group and non-pretesting group. Side-effects occurred in 7.5% and 7.8% in the pretesting group and non-pretesting group, respectively. There was no special difference between the 2 groups. Pretesting was positive in 108 cases, corresponding to 0.4% of patients in whom pretesting was performed. The incidence of side-effects was reviewed by judgements on pretesting, i.e. positive or negative; side-effects occurred in 7.4% (2,221 cases) in the negative group and 48% (52 cases) in the positive group. It was revealed that the incidence of side-effects was clearly higher in the positive group of pretesting [Table (4)]. There were slightly more patients in the positive group in whom fall of blood pressure occurred; treatment was required in 23 out of 52 patients. Among them, vasopressors such as noradrenaline, Carnigen, etc. were given only in 2 patients. Some treatment was given in 1,212 (3.6%) out of

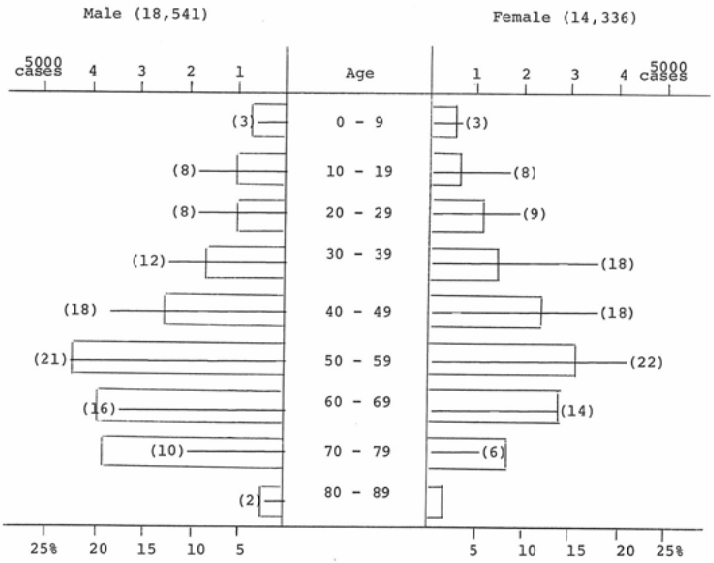

Fig. 1 Age distribution and side-effects.

Table 3 Incidence of Side-effects by pretest performed in each institute

Institute	Pretested	Side-effect(+)	non pretested	Side-effects(+)
A	5,153	357 (6.9)	20	4 (20)
B	1,608	121 (7.5)	1	0
C	2,916	313 (10.7)	24	6 (25)
D	2,076	136 (6.6)	109	14 (12.8)
E	1,361	103 (7.6)	2,986	222 (7.4)
F	1,428	217 (15.2)	1	0
G	433	58 (13.4)	4	0
H	10,412	526 (5.1)	2	1 (50.0)
I	2,031	296 (14.6)	4	0
J	1,551	88 (5.7)	9	1 (11.1)
K	1,220	58 (4.8)	60	2 (3.3)
Total	30,189 cases	2,273 cases(7.5%)	3,220 cases	250 cases(7.8%)

(drop-out : 31 cases)

all 33,440 patients. Noradrenaline was given in 10 patients, consisting of one (0.9%) in the positive group and 9 (0.03%) in the negative group. Carnigen was given in 9 patients, consisting of one (0.9%) in the positive group and 8 (0.03%) in the negative group.

(4) History of examination with contrast medium and incidence of side-effects

The relation between the result of pretesting and history of examination with contrast medium was summarized in Table (5). There was not so definite relation between history of examination with contrast medium and incidence of side-effects. The total number of patients with history of examination with contrast medium was 9,827. Among them, side-effects occurred in 689 patients (7.0%). The total number of patients without any history of examination with contrast medium was 20,357. Among them, side-effects occurred in 1,584 (7.8%). This did not suggest that the incidence of side-effects was higher in patients with history of examination with contrast medium.

Table 4 Side-effects in pretested population

	pretest-negative	pretest-positive
Total Cases	30,081	108
Cases of S.E.	2,221	52
Percentages	7.4%	48.1%
Nausea	1,335(61%)	33(63%)
Exanthema	761(34%)	17(33%)
Vomiting	536(25%)	13(25%)
Vascular pain	223(10%)	0
Cough	130(6%)	7(13%)
Itching	67(3%)	2(4%)
Edema, air-way	57(3%)	2(4%)
Hypotension	50(2%)	5(10%)
Shivering	27(1%)	1(2%)

Table 5 Side-effects in relation to pretest and previous contrast-media

		Side-effects
Pretest-negative	30,076*	2,221(7.4%)
previous CM (+)	9,803	677(6.9%)
previous CM (−)	20,273	1,544(7.7%)
Pretest-positive	108	52(48%)
previous CM (+)	24	12(50%)
previous CM (−)	84	40(48%)

*drop-out : 5cases

Table 6 Side-effects in relation to allergy and previous contrast media

		Side-effects
Allergic	329	171(52%)
Previous CM (+)	176	89(51%)
Previous CM (−)	153	82(54%)
Non allergic	32,870	2,352(7.2%)
Previous CM (+)	9,651	600(6.2%)
Previous CM (−)	23,219	1,752(7.5)

Table 7 Side-effects by mode of administration of contrast media

	IA	IV	DIV	Bolus	Others
Total Cases	1,462	9,185	12,890	4,432	4,860
Side Effect Cases	118	876	758	364	407
Percentages	8.1%	9.5%	5.9%	8.2%	8.4%
	%	%	%	%	%
Nausea	34(28.8)	574(65.5)	295(38.9)	215(59.1)	236(58.0)
Exanthema	39(33.1)	216(24.7)	320(42.2)	107(29.4)	87(21.4)
Vomiting	11(9.3)	238(27.2)	140(18.5)	67(18.4)	84(20.6)
Vascular pain	39(33.1)	55(6.3)	75(9.9)	17(4.7)	35(8.6)
Cough	0(0)	45(5.1)	51(6.7)	28(7.7)	12(2.9)
Itching	2(1.7)	18(2.1)	33(4.4)	7(1.9)	9(2.2)
Edema, air-way	2(1.7)	18(2.1)	20(2.6)	8(2.2)	11(2.7)
Hypotension	1(0.8)	22(2.5)	14(1.8)	8(2.2)	10(2.5)
Shivering	2(1.7)	17(1.9)	5(0.7)	2(0.5)	2(0.5)

(5) History of allergy and incidence of side-effects

Three-hundred and twenty-nine patients replied to have a history of so-called allergy such as asthma, urticaria, etc. Among them, side-effects occurred in 171 patients (52.0%). In 32,870 who replied to have no history of allergy, on the other hand, side-effect occurred in 2,352 patients (7.1%). Table (6) summarizes the incidence of side-effects from the viewpoint of the relation betwen history of allergy and history of examination with contrast medium. As in case of pretesting, there was not so definite relation between history of examination with contrast medium and incidence of side-effects, but history of allergy rather influenced the incidence.

(6) Administration route of contrast medium and incidence of side-effects

As shown in Table (7), the incidence of side-effects ranged from 5.9 to 9.5% in accordance with the

Table 8 Kinds of contrast media and incidence of side-effects

	Conray	DIP conray	Urografin 60	Urografin 70	Angiografin	Conray 400
Total Cases	15,018	2,041	4,095	3,888	6,164	1,444
Cases of S.E.	861	71	296	442	684	109
Percentages	5.7%	3.5%	7.2%	11.4%	11.1%	7.5%
	%	%	%	%	%	%
Nausea	450(52.3)	31(43.7)	130(43.9)	295(66.7)	385(56.3)	63(57.8)
Exanthema	266(30.9)	29(40.8)	125(42.2)	100(22.6)	210(30.7)	18(16.5)
Vomiting	199(23.1)	14(19.7)	58(19.6)	112(25.3)	117(17.1)	40(36.7)
Vascular pain	93(10.8)	1(1.4)	12(4.1)	61(13.8)	30(4.4)	22(20.2)
Cough	52(6.0)	3(4.2)	10(3.4)	13(2.9)	53(7.7)	3(2.8)
Itching	28(3.3)	1(1.4)	9(3.0)	8(1.8)	21(3.1)	2(1.8)
Edema, air-way	9(1.0)	3(4.2)	6(2.0)	13(2.9)	25(3.7)	3(2.8)
Hypotension	10(1.2)	5(7.0)	11(3.7)	8(1.8)	12(1.8)	4(3.7)
Shivering	4(0.5)	1(1.4)	3(1.0)	1(0.2)	18(2.6)	1(0.9)

Table 9 Side-effects by dose of contrast media

	≦20ml	21～50ml	51～100ml	101～150ml	151～200ml	201～250ml	250ml≦
Total Cases	790	9,439	15,493	5,213	371	1,783	147
Cases of S.E.	92	900	1,166	251	35	63	6
Percentages	11.6%	9.5%	7.5%	4.8%	9.4%	3.5%	4.1%
	%	%	%	%	%	%	%
Nausea	62(67.4)	585(65.0)	593(50.9)	80(31.9)	17(48.6)	26(41.3)	1(16.7)
Exanthema	13(14.1)	207(23.0)	433(37.1)	79(31.5)	15(42.9)	23(36.5)	2(33.3)
Vomiting	40(43.5)	223(24.8)	231(19.8)	36(14.3)	5(14.3)	12(19.0)	1(16.7)
Vascular pain	3(3.3)	70(7.8)	61(5.2)	71(28.3)	8(22.9)	5(7.9)	3(50.0)
Cough	5(5.4)	50(5.6)	58(5.0)	20(8.0)	0(0)	3(4.8)	0(0)
Itching	3(3.3)	13(1.4)	42(3.6)	9(3.6)	1(2.9)	1(1.6)	0(0)
Edema, air-way	8(8.7)	20(2.2)	25(2.1)	2(0.8)	1(2.9)	3(4.8)	0(0)
Hypotension	3(3.3)	11(1.2)	17(1.5)	4(1.6)	0(0)	3(4.8)	0(0)
Shivering	2(2.2)	13(1.4)	12(1.0)	0(0)	0(0)	1(1.6)	0(0)

administration route. The commonly used intravenous administration most often caused side-effects (9.5%). Nausea and vomiting were more frequently caused by intravenous than by intraarterial administration. Nausea was caused most by bolus injection (59.1%). Edema of the air way and hypotension occurred less frequently in intraarterial administration.

(7) Kinds of contrast media and incidence of side-effects

Table (8) shows the incidence of side-effects by kinds of contrast media. As the number of cases examined with the new low osmotic iodine contrast medium was very small, these cases were excluded from this Table. Though it was not possible to make a conclusive remark, the incidence of side-effects was slightly higher in patients examined with diatrizoate.

(8) Dose of contrast medium and incidence of side-effects

Table (9) shows the incidence of side-effects by doses. It was not possible to conclusively describe the relation between the dose and incidence of side-effects, but a conclusion was obtained that, in this series, the lower the dose is, the higher the incidence of side-effects is. This may be because side-effects checked were limited to early clinical symptoms and because many of patients examined at the dose of less than 50 ml were supposed to have received usual intravenous administration.

Discussion

The incidence of side-effects fairly varies with reports: Coleman (1964)[3] reported that some side-effects were found in 8.53% out of 10,000 cases; in 6.90% out of 32,964 cases [by Wittern (1973)[4]], 5% out of 300,000 cases [by Shehadi (1980)[5]], 10.5% out of 3,000 cases [by Kimoto (1980)[6]] and in 8.0% out of 23,000 cases [by Katayama (1986)[2]]. The larger the population is, the lower the incidence tends to be. At any rate, it may be possible to consider the incidence to be in the range of 5～10%. When side-effect symptoms are clinically checked, it is already experienced that the incidence fairly varies institute involved, observer, time of onset, etc.

The conservative or underdeveloped attitude of our country to pretesting for iodine contrast medium is well known. Kubota et al. (1984)[7] reported that pretesting was performed in 86.4%. In our present series, it was found that pretesting was performed at a remarkably high rate of 90%, but, to our regret, it was not clear whether pretesting was performed with attached test ampoule or with 1 ml taken from the contrast medium itself in 90% of patients. In our series, pretesting was positive in 108 patients. Among them, some symptom was observed in 52 patients (48%). The incidence of side-effects was clearly higher than in the negative group. Side-effect symptoms and contents of their treatment were checked, however, though a vasopressor was given in 2 patients, a conclusion could not obtained that the incidence of finding of severe side-effects was higher in the positive group. The fact that pretesting was positive means that some side-effect was observed after intravenous injection of 1 ml of the contrast medium, but side-effects were found in about the half number of patients. This suggests that the positive predictive value of pretesting is low. The negative predictive value of pretesting was as high as 80～90%, but the fact that side-effects occurred in about 10% of the negative group can not be neglected, because X-ray examination should also be safe. Kubota et al.[7] reported that severe side-effects were caused by pretesting in 26.8% of 203 institutes involved in their investigation. Fischer[8] reported that some patients died during main examination though pretesting was negative and that even pretesting might cause death. Pretesting is usually done by observing whether side-effect symptoms occur after intravenous injection of 1 ml. It is theoretically natural that the incidence of dose-dependent symptoms is lower, because the dose for pretesting is lower than that for main examination (usually 50～100 ml). There is a tendency that side-effects observed during main examination are despised, since pretesting is too much trusted. As dose-independent side-effects may occur irrespective of the volume of contrast medium given, even intravenous injection of 1 ml may cause side-effects, sometimes fatal ones. We really experience a case in daily practice where a mild symptoms which is at first easy to be over-looked may gradually lead to the severe one. Among side-effects due to contrast medium, delayed reactions[9], which appear after pretesting, can not be predicted with pretesting.

We authours still doubt if pretesting is useful, however, it is not fair to ask in general not to do pretesting with results we obtained. Even if pretesting is accepted, there are actually the following questinons: By whom, when, where and what pretesting is performed with?

By whom: Our data are not available, but according to Kubota[7], 54.5% replied that pretesting was performed by doctor and 32.4% replied that it was by nurse.

When: Pretesting was performed on the day of examination in 80%, but there was a case where pretesting had been performed more than one week before examination. If it is kept in mind that severe side-effects may be caused even by pretesting, it is obvious when pretesting should be performed.

Where: Pretesting should be performed at particular place where first-aid kit, oxygen inhalation, vacuum aspiration are immediately available, because pretesting may cause severe or fatal reactions.

What: We could not answer the guestion in this series. In other series, we found that test ampoules not attached to the contrast medium were used in more than half the number of cases. It is told that test ampoules are attached only in Japan. There is almost no reasonableness to use test ampoules. Even if the

test ampoule is manufactured by the same manufacturer and even if the test ampoule is the same kind as the contrast medium, the solution in the test ampoule is not always with the same lot number as the contrast medium for main examination. We know the actual example that test ampoules manufactured by various manufacturers are collected in one box and that pretesting is performed with one test ampoule taken out at random from the box. Such a way of pretesting must be said to be a basic error in handling of contrast medium. Though no specially severe side-effects were observed in this series, some side-effect was found in about half the number of patients with history of allergy. History of allergy has been conventionally considered to be a risk factor. In comparison with the report by Shehadi et al. (1980)[5] that the incidence of side-effects was increased by about 2 times in such patients, our data must be considered to show the very high incidence.

The possible higher incidence of side-effects in patients previously examined with iodine contrast medium is negated though a definite conclusion fails to be drawn. Even in cases with severe side-effects in the previous examination, possibility of occurrence of similar side-effects in the following examination is rather low. The possibility of mild side-effects to repeatedly develop in the examinations to follow and later is higher than in case of severe side-effects. However, experience of radiological examination does not necessarily serve for prediction of side-effects in the examinations to follow and later.

In patients with bronchial asthma, the incidence of side-effects is 3~4 times higher. Shehadi (1975)[10] reported that the incidence of side-effects in patients with history of allergy was 2 times higher than in usual patients. As important elements in the history of allergy, fish/shell, eggs, milk, chocolate, asthma hay fever and penicilline were cited. He contended that occurrence of side-effects at the time of previos use of iodine contrast medium does not become a guide to avoidance of an examination to follow.

Kimoto et al. (1980)[6] reported that out of 3,000 cases examined, side-effects occurred in 315 cases (10.5%) and out of 337 cases in which excretory urography was performed 2 times or more during the period of investigation, side-effect developed in 58 cases (17.2%). However, they reported that also in the same patient, development of side-effects showed variation in each examination and that there was no particular association between history of use of contrast medium and occurrence of side-effect. This contention is shared by us.

Mechanism of side-effects of contrast media has not been clearly established. But many people concerns to administration route, dose and kinds of contrast media. In our series, higher incidence of side effects were seen in intravenous administration as generally mentioned. Bolus injection was about the same with others in incidence of side-effects.

There are dose-dependent and independent side-effects. Our results showd that side-effects were observed more in case administered less than 20 ml of contrast media. We did not good explanation for it, but this might be possibly related to routine intravenous administration of dose less than 20 ml of contrast media.

Diatrizoate possibly induced more side-effects than iothalamate.

Because of difference in background of the cases, we could not draw a conclusive remark, allowing for possibility of major role of above-mentioned three factors in development of side-effects of contrast media.

Lastly, we would like to take up risk factors. Side-effects with contrast media show generally a less incidence by intraarterial route than by intravenous route. There is no sexual difference. In terms of age, more side-effevts are saide to develop in the age brackets of over 60. The aged people with some abnormality in the heart, aorta and hepatic artery show a higher incidence. On the other hand, the high incidence of side-effects is said to be observed in newborns or infants of below 1 year. Experience of side-effects with contrast medium, allergy including asthma, hyperuremia, diabetes mellitus, dehydration, hematological diseases, protein irregularity, anxiety, etc. are cited as risk factors.

Introduction of low osmolar iodine contrast media obviously lowered the incidence of side-effects. Side-effects associated with high osmolarity of contrast media are impairment of endothelial cells, impairment of blood-brain barrier, thrombosis and thrombotic phlebitis, increase of pressure in the vein or pulmonary artery, vasodilation and decrease of blood pressure, hypervolemia and diuresis, etc[11]. Especially from the clinical standpoint, alleviation of pain at the time of injection of contrast medium greatly contributed to X-ray examination. There is now no substantial data on how far side-effects can be reduced using low osmolar contrast media. However, Sogn et al. (1987)[12] reported that comparison between iohexol and ionic monomeric contrast medium revealed the incidence of side-effects to be about 3.5 times lower with iohexol than with ionic monomers. Further investigation in a larger number of patients may clarify those points.

Finally, we would like to refer to pretesting again. In the present investigation, patients with pretesting positive showed a higher incidence of side-effects and a higher incidence of rather severe side-effects although the number of patients in the investigation was small. The authors maintain that pretesting is useless and checking in detail of a history of allergy is more effective and more important. We would like to emphasize that attaching of test ampoules should be stopped immediately.

Conclusion

(1) The incidence of side-effects in 33,440 cases was 7.5%. There was no fatal case.

(2) Occurrence of side-effects showed no sexual difference. There was a tendency that the incidence of side-effects was higher in the age brackets of 40~60.

(3) Pretesting is still conducted in 90% of the patients. Pretesting positive was observed in 0.4% of total cases.

(4) The incidence of side-effects in patients with pretesting positive was 48%. There was no case with particularly serious side-effects.

(5) The incidence of side-effects in patients with positive history of allergy was 52% and development of side-effects can be predictable degree.

(6) There was no particular association between presence or absence of experience of previous medication of contrast media and occurrence of side-effects.

(7) The positive predictive value of pretesting is low.

(8) It is not fair to ask not to do pretesting from the result we obtained but test-ampoules should be abandoned.

(9) A difinite conclusion could not be drawn on risk factors.

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