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POPULATION STUDIES ON DRUG HYPERSENSITIVITIES

By

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Population study dealing with drug hypersensitivity is scarce and little is known about the incidence of drug reaction. The present study is intended to clarify the incidence and the type of reaction produced by a given drug in Japan, and the factors that predispose a person to the drug hypersensitivity reaction.

SUBJECTS

Mass surveys on drug hypersensitivities were done on four occasions, i.e., in 1962, 1965, 1968 and 1971. Each group (A, B, C and D) consisted of white collar workers belonging to companies in Tokyo (department stores, a construction company, a life insurance company and a bank). No company was included twice. All companies had their own clinical offices and physicians serving the employees. The number of individuals in each group was as follows: 6893 (3873 males and 3020 females) in group A (1962); 2395 (970 males and 1425 females) in group B (1965); 2905 (1563 males and 1342 females) in group C (1968); 2629 (991 males and 1638 females) in group D (1971).

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TABLE 1
Distribution of Sex and Age in the Surveys.

Group	Age of subjects (years)										Sex ratio		
	-19		20-		30-		40-		50-			Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female			
A	255	684	1179	1593	818	257	595	118	468	30	3315	2682	1.24
B	23	227	414	925	177	105	171	41	75	9	863	1307	0.66
C	0	101	467	774	446	227	260	99	128	37	1301	1238	1.05
D	18	356	121	739	161	90	147	41	77	21	524	1247	0.42

METHODS OF SURVEILLANCE

A questionnaire was delivered to each member of the group through the clinical office of that company. The contents of the questionnaire included age, sex, use of drugs in the past, and past and family histories of allergic diseases. Answers to the questionnaire were; 5997 (87.0 per cent) in group A, 2170 (90.6 per cent) in group B, 2539 (87.4 per cent) in group C, and 1771 (67.4 per cent) in group D, respectively. All those answering the questionnaire were then interviewed and their descriptions regarding past histories of bronchial asthma and of drug hypersensitivities were critically reviewed. When an episode of drug hypersensitivity was ascertained, the causative drug and the type of reaction were also recorded. Evaluation was done solely on a clinical basis, i.e., no diagnostic examinations were attempted to confirm the drug hypersensitivity.

The criteria for positive histories were urticaria and/or angioedema, skin rashes, dyspnea, shock and other symptoms generally accepted as allergic manifestations following the administration of a drug. An episode suspected as drug fever was not included unless there was additional information to strongly support it.

RESULTS

Table 1 shows the distributions of sex and age of individuals interviewed. Age of the subjects in years ranged from 17 to 72. The mean ages were 31 in group A, 30 in B, 31 in C and 29 in D.

Individuals judged to have histories of drug hypersensitivities were 194 (3.23 per cent) in group A, 96 (4.42 per cent) in B, 169 (6.66 per cent) in C, and 119 (6.72 per cent) in D, respectively (Table 2). Statistically significant differences were proved between group A and group B, between A and C, between A and D, between B and C, and between B and D ($p < 0.01$). Throughout the 4 groups, 252 (4.2 per cent) out of 6003 males and 326 (5.0 per cent) out of 6474 females were considered to have drug hypersensitivities. Of 578 indi-

viduals with histories of drug hypersensitivities, 33 (5.7 per cent) were ascertained as having sensitivities to two or more of suspected drugs.

TABLE 2
Number of Cases with Drug Hypersensitivities.

Group	Year	No. of subjects	No. of cases with drug hypersensitivities			Per cent
			Male	Female	Total	
A	1962	5997	108 (17)*	86 (13)	194 (30)	3.23
B	1965	2170	35 (6)	61 (7)	96 (13)	4.42
C	1968	2539	66 (6)	103 (8)	169 (14)	6.66
D	1971	1771	43 (1)	76 (9)	119 (10)	6.72

* Figures in parentheses show cases with severe reactions.

TABLE 3
Ages at the Time of the Primary Drug Reaction.

Group	Ages at the time of the primary drug reaction (years)						Un- known
	-9	10-19	20-29	30-39	40-49	50-	
A	2	40	79	27	16	7	23
B	3	28	42	14	5	1	3
C	1	26	78	43	17	1	3
D	4	22	52	19	11	2	9

The age at which the first reaction to a drug occurred is listed in Table 3. Eighty-one per cent of the subjects had their first episode between the second and the fourth decade of life.

As shown in Table 4, drug hypersensitivities were mainly due to pyrazolones and/or barbiturates*, penicillins, aspirin, and sulfonamides. Numbers of individuals who had received

* In Japan, pyrazolones are often used in combination with barbiturates and, in many cases, it was difficult to determine which of the components was responsible for the hypersensitivity reaction. Therefore, these cases are dealt with en bloc as 'sensitive to pyrazolones and/or barbiturates'.

the principal causative drugs on one or more occasions are listed in Table 5. Over 90 per cent of the subjects in each group had received pyrazolones and/or barbiturates.

TABLE 4
Drugs Responsible for the Hypersensitivity Reactions.

Drug	No. of cases			
	A	B	C	D
Pyrazolones and/or barbiturates	88 (1)*	43 (4)	98 (0)	72 (1)
Penicillins	52 (23)	21 (7)	27 (7)	16 (4)
Sulfonamides	31 (3)	8 (0)	33 (2)	19 (0)
Aspirin	17 (0)	11 (1)	10 (1)	4 (1)
Lokal anesthetics	0	2 (1)	3 (3)	1 (1)
Streptomycine	0	1 (0)	0	1 (1)
Tetracyclines	1 (0)	1 (0)	3 (0)	1 (0)
Chloramphenicol	0	3 (0)	3 (0)	1 (0)
Other drugs	8 (4)	7 (2)	5 (1)	8 (2)
Unknown	7 (0)	7 (0)	2 (0)	3 (0)

* Figures in parentheses show cases with severe reactions.

Incidence of the hypersensitivity reaction to pyrazolones and/or barbiturates was significantly higher in group C (3.9 per cent), or in group D (4.1 per cent) than in group A (1.5 per cent) or in group B (2.0 per cent) ($p < 0.01$) (Table 4). Incidence of sulfonamide hypersensitivity was also higher in group C (1.3 per cent), or in group D (1.1 per cent) than in group A (0.5 per cent) or in group B (0.4 per cent) ($p < 0.05$). On the other hand, the incidence of penicillin hypersensitivity had not increased, i.e., 0.9 per cent in group A, 1.0 per cent in group B, 1.1 per cent in group C, and 0.9 per cent in group D.

Clinical manifestations of the drug hypersensitivity reactions are summarized in Table 6. Five hundred and seventy (90 per cent) of the 618 reactions involved the skin. Forty-one

TABLE 5
Number of Subjects Who Had Received the Principal Allergy-Inducing Drugs.

Group	Pyrazolones and/or barbiturates			Penicillins			Drug			Sulfonamides			Aspirin		
	Male		Total	Male		Total	Male		Total	Male		Total	Male		Total
	Female	Male		Female	Male		Female	Male		Female	Male		Female	Male	
A	3129	2460	5589	2193	1457	3650	1245	610	1865	1939	1218	3157			
B	797	1246	2043	540	696	1236	336	317	653	454	525	979			
C	1197	1199	2396	798	631	1429	509	372	881	727	542	1269			
D	474	1188	1662	319	553	872	191	266	457	266	314	580			

(59 per cent) of the 70 life-threatening reactions were due to penicillins (Table 4). Clinical manifestations were analysed on 550 reactions produced by the 4 major causative drugs (Table 7). Two hundred and thirty-eight (79 per cent) of the 301 hypersensitivity reactions related to pyrazolones and/or barbiturates and 75 (82 per cent) of the 91 reactions related to sulfonamides developed skin rashes including fixed eruptions, exanthematic eruptions, erythema multiforme-like eruptions, and exfoliative dermatitis. Twenty-six (22 per cent) of the 116 reactions produced by penicillins caused shock, and 29 (69 per cent) of the 42 reactions due to aspirin developed urticaria and/or angioedema.

TABLE 6
Clinical Manifestations of Drug Reactions.

Group	Clinical manifestations				
	Shock	Dyspnea	Urticaria and/or angioedema	Skin rashes	Drug fever
A	20	5	54	133	0
B	12	3	26	65	0
C	6	3	44	132	1
D	6	4	27	89	0

TABLE 7
Types of Hypersensitivity Reactions Produced by the 4 Principal Causative Drugs.

Clinical manifestation	Drug			
	Pyrazolones and/or barbiturates	Penicillin	Sulfon- amides	Aspirin
Shock	3	26	3	0
Dyspnea	2	8	1	3
Urticaria and/or angioedema	61	44	12	29
Skin rash	238	40	75	11
Drug fever	0	0	0	0

TABLE 8

Incidences of Drug Hypersensitivities Among Individuals With and Without Histories of Bronchial Asthma.

		Drug hypersensitivity		Total
		+	—	
Asthma	+	18	131	149
	—	560	11768	12328
	Total	578	11899	12477

Of the 578 drug hypersensitive persons, 18 (3.1 per cent) had histories of bronchial asthma, whereas 131 (1.1 per cent) of the 11899 non-drug hypersensitive persons had similar histories. Incidences of drug hypersensitivities among individuals with and without histories of bronchial asthma were 12.1 per cent (18 of 149) and 4.5 per cent (560 of 12328), respectively. The difference was statistically significant ($p < 0.01$) (Table 8).

DISCUSSION

This study was supported by the consulting doctors of each company. It was possible, through the use of medical records, to check the medications used and to retrospectively study the reactions given as drug hypersensitivities.

Any population study that relies entirely upon the histories of the subjects is always exposed to error. Although we believe that mistaking negative for positive was minimized by the interview, there might be persons with drug hypersensitivities who replied erroneously in the negative. In fact, of the 12477 individuals examined, no one answered as having had a history of liver damage or disturbances of the haematopoietic system attributable to a drug. Regarding episodes suspected of drug fever, it was often difficult to determine whether it was really caused by a drug or not. Since doubtful cases were excluded, it was possible that the rate of drug fever was underestimated.

TABLE 9
The Annual Production of the Principal Causative Drugs in Japan.

Drug	1953-1955	1956-1958	1959-1961	1962-1964	1965-1967	1968-1970
Procain penicillin G in aqueous suspension (100,000 unit)	109,779,915	112,536,717	155,601,696	118,702,173	75,968,400	56,874,700*
Phenoxymethyl penicillin (tablet) (100,000 unit)	0	3,403,684§	6,485,690	31,233,476	93,841,366	76,415,350*
Sulpyrine (Kg)	18,969	74,386	138,686	357,209	449,385	757,767
Barbital (Kg)	9,243	4,592	4,280	2,832	20,703	26,941
Aspirin (Kg)	145,243	194,055	201,897	156,195	216,400	343,339
Sulfaisomidine (Kg)	39,359†	148,505	237,136	206,935	176,641	178,647
Sulfadimethoxine (Kg)	0	0	0	89,970	124,336	184,678

* Average annual production in 1968 and 1969.

§ Average annual production in 1957 and 1958.

† Average annual production in 1954 and 1955.

Despite these limitations, it is thought that the clinical history is one of the important aids for the study of hypersensitivity reactions to drugs.

Incidences of drug hypersensitivities in the recent two surveys were significantly higher than those in the earlier two surveys. This suggests that drug hypersensitivities have been increasing in the urban population of Tokyo, which is perhaps attributable to increases in sensitivities to pyrazolones and/or barbiturates and to sulfonamides.

As shown in Table 9, the annual production of sulpyrine (dipyrene), one of the common pyrazolone derivatives, has expanded enormously in Japan within the past 15 years (7). Since almost all of the drug manufactured in Japan is consumed within the country, the increased incidence of drug hypersensitivity may be a reflection of the increased production of the drug. Sulfonamides commonly used in Japan have changed from the short-acting to the long-acting ones. It was difficult in this study to determine whether the increased incidences of sulfonamide hypersensitivities might be related to the prevalent use of the long-acting ones or not. The production of oral penicillins has also increased, while that of penicillins for parenteral use has decreased in recent years. Among 40 individuals with histories of hypersensitivity reactions produced by penicillins in group C and group D, 4 were due to the oral forms. The production of aspirin in 1969 was about twice that in 1962. The increase is less remarkable and the incidence of aspirin hypersensitivity remained almost unchanged.

Smith and associates reported that males were more likely to develop penicillin reactions than females (2, 6). In our study, no evidence was obtained in regard to the influence of sex on susceptibility to drugs. It was suggested by several reports that allergic reactions to drugs occur more frequently in atopic persons than in non-atopic ones (1, 3, 5, 6). Miller reported that 17 per cent of the 740 patients with atopic respiratory diseases had positive histories of drug allergies, but controls were not studied (4). In our study, the differences in the incidences of drug hypersensitivities between the groups

with and without histories of bronchial asthma were significant.

Present data are not sufficient to analyse any differences in causative drugs and types of hypersensitive reactions between asthmatics and controls. An unanswered question is whether the atopics differ from non-atopics in their drug hypersensitivity reactions.

SUMMARY

Twelve thousand four hundred and seventy-seven white collar workers in Tokyo were subjected to population studies on drug hypersensitivity reactions. These surveys were made on four different occasions in the last 10 years.

Histories of drug hypersensitivities were ascertained in 194 (3.23 per cent) of the 5997 individuals in 1962, 96 (4.42 per cent) of the 2170 in 1965, 169 (6.66 per cent) of the 2539 in 1968, and 119 (6.72 per cent) of the 1771 in 1971. Incidences of hypersensitivities in the two recent surveys were significantly higher than those in the earlier two ($p < 0.01$). This suggests that drug hypersensitivities have been increasing in the urban population of Tokyo, which is perhaps attributable to increased incidences of hypersensitivities to pyrazolones and/or barbiturates, and to sulfonamides.

Pyrazolones and/or barbiturates, penicillins, aspirin, and sulfonamides were suspected as principal causative drugs. Possible relationship between the increased incidences of some drug hypersensitivities in recent years and the annual production of drugs in Japan was discussed.

Incidences of drug hypersensitivities in individuals with histories of bronchial asthma were significantly higher than in those without such histories ($p < 0.01$).

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