

**TREND IN PRESCRIPTION RATES OF DRUGS  
SUSPECTED TO INDUCE HAEMATOPOIETIC DISORDERS  
IN A POPULATION IN NAGOYA**

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**ABSTRACT**

To clarify the frequencies of administration of the drugs possibly related to the haematopoietic disorders, three surveys were conducted in the periods of April–September 1972, October 1975–March 1976, and October 1977–March 1978 by reviewing the health insurance receipts for the civil servants in Nagoya, Japan.

Major findings are as follows.

- (1) Those who visited medical institutions at least once in the survey period of 6 months accounted for 71.9%, 62.2% and 70.1% among the total civil servants in the first, second and third survey, respectively. Among them, the relevant drugs were prescribed in 69.2%, 68.7% and 50.6%, correspondingly.
- (2) The prescription rates of chloramphenicols were 13.3%, 7.9% and 0.08% in the first, second and third survey. The corresponding figures were 1.2%, 9.3% and 2.2% for thiampenicols, 15.3%, 9.2% and 12.3% for sulfonamides, 40.0%, 51.5% and 40.9% for antipyretics, analgesics and sedatives.
- (3) The frequencies of a drug prescribed with other drugs in combination changed over years. Chloramphenicols were prescribed less frequently with sulfonamides and more frequently with penicillins, cephalosporins and thiampenicols. The prescription of thiampenicols with cephalosporins increased over years.
- (4) The prescription rates were different by age in individual drugs. The prescription rates were in general lower in the age group of 20–29 years than in the older age groups throughout three surveys.
- (5) Average durations of prescription tended to decrease between 1972 and 1977 in such drugs as sulfonamides, penicillins and cephalosporins.
- (6) The rates we surveyed are of prescription and not of actual ingestion; therefore, the rates should be deemed as the reference of the ingestion rates in a general population.

**INTRODUCTION**

A nation-wide survey (1) demonstrated that secondary aplastic anemia accounted for approximately 17% of all aplastic anemia cases in 1972 in Japan. Eighty per cent of these secondary cases are supposedly attributed to certain drugs. Among such drugs, chloramphenicols are most often incriminated in 45%; antibiotics and chemotherapeutics in 16.4%, antipyretics and analgesics in 13.5%, antiepileptics in 9.4%, antithyroid preparations in 2.3%, oral hypoglycemic agents in 1.2%, and the other drugs in 12.2%. (2)

In the U.S.A. (3,4), more than half of the patients with aplastic anemia are presumed to be drug induced, though aplastic anemia is a very rare disease there; the mortality rate being 2-5 per million.

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Since some of aplastic anemia cases have been attributed to certain drugs, it is of significance to clarify the frequencies of administration of the drugs possibly related to the subsequent haematopoietic disorders. This paper describes the pharmacoepidemiological findings of the three surveys conducted in a population in a defined area, Nagoya, Japan.

#### MATERIALS AND METHODS

The surveys were conducted in three 6-month periods of April–September 1972, October 1975–March 1976, and October 1977–March 1978 by reviewing the health insurance receipts for civil servants in Nagoya. The numbers of the subjects surveyed are presented in Table 1; being 17,245, 20,180 and 24,986 in 1972, 1975 and 1977, respectively.

Table 1.  
Age distributions of subjects whose monthly health  
insurance receipts are reviewed in three surveys

Age in years	First survey		Second survey		Third survey	
	April-September 1972	No. (%)	October 1975-March 1976	No. (%)	October 1977-March 1978	No. (%)
15-19	404 ( 2.3)		433 ( 2.1)		272 ( 1.1)	
20-24	3080 ( 17.9)		3413 ( 16.9)		2490 ( 10.1)	
25-29	2443 ( 14.2)		3200 ( 15.9)		4930 ( 19.7)	
30-34	2416 ( 14.0)		2912 ( 14.4)		3419 ( 13.7)	
35-39	2286 ( 13.3)		2432 ( 12.1)		3407 ( 13.6)	
40-44	2729 ( 15.8)		3017 ( 15.0)		3013 ( 12.1)	
45-49	1785 ( 10.4)		2307 ( 11.4)		3446 ( 13.8)	
50-54	1107 ( 6.4)		1319 ( 6.5)		2459 ( 9.8)	
55-	995 ( 5.8)		1147 ( 5.7)		1550 ( 6.2)	
Total	17245 (100.0)		20180 (100.0)		24986 (100.0)	

Male to female ratio of the subjects was 7:3 and unchanged over years. All monthly receipts were reviewed in the first and second survey, but 20% random samples in the third survey. Among all drugs prescribed by physicians (excluding dentists), those suspected to induce the haematopoietic disorders were surveyed. Such drugs were enumerated to be 1,274 kinds; being categorized into 15 major drugs (5); (1) chloramphenicols, (2) thiamphenicols, (3) sulfonamides, (4) cephalosporins, (5) penicillins, (6) antipyretics, analgesics and sedatives, (7) tranquilizers, (8) oral hypoglycemic drugs, (9) antithyroid preparations, (10) antiepileptics, (11) hypotensive diuretics, (12) alpha-methyldopa, (13) carbonic anhydrase inhibitors, (14) quinidine, and (15) quinine.

These drugs were prescribed in the forms of powder, granule, tablet, capsule, syrup and injection, and the episode of prescription was reviewed with its duration. There were a considerable number of drugs with different brand name, but with pharmacologically identical effect. All drugs with different brand names were listed according to the

Encyclopedia of Medical Drugs (6,7), and each drug prescribed was checked one by one by this list, when reviewing the receipts.

Among the total civil servants, those who visited medical institutions at least once in the survey period of 6 months were 71.9%, 62.2% and 70.1% in the first, second and third survey, respectively.

Among those who visited medical institutions, the frequencies of the prescription of the drugs specified above were 69.2%, 68.7% and 50.6%, correspondingly; being the lowest prescription in the third survey.

## RESULTS

Table 2 presents the prescription rates for the major drugs suspected to induce the haematopoietic disorders in the three surveys.

The prescription rates for chloramphenicols were 13.3%, 7.9% and 0.08% in the first, second and third survey, respectively; indicating the marked decrease in the five years. The corresponding rates for thiamphenicols were 1.2%, 9.3% and 2.2%; being the highest rate in the second survey. The prescription rates decreased to approximately one tenth, one ninth, and one fourth for sulfonamides, oral hypoglycemic drugs, and hypotensive diuretics (thiazid derivatives), respectively in these five years. In contrast, the prescription rate for

Table 2.  
Trends in prescription rates for major drugs suspected to induce  
haematopoietic disorders in three surveys

Major Drugs	First survey	Second survey	Third survey
	n=12407	n=12547	n=6096
Chloramphenicols	13.3 %	7.9 %	0.08%
Thiamphenicols	1.2	9.3	2.2
Sulfonamides	15.3	9.2	1.5
Cephalosporins	1.9	18.3	22.1
Penicillins	6.7	15.1	12.3
Antipyretics, analgesics and sedatives	40.0	51.5	40.9
Tranquilizers	16.0	11.6	6.1
Oral hypoglycaemic drugs	0.9	0.4	0.1
Antithyroid drugs	0.1	0.0	-
Anticonvulsants	0.2	0.1	0.1
Hypotensive diuretics	2.8	1.4	0.8
$\alpha$ -Methyldopa	0.2	0.4	0.3
Carbonic anhydrase inhibitors	0.1	0.0	0.0
Quinidine	-	-	0.0
Quinine	-	0.0	0.0

cephalosporins markedly increased from 1.9% in 1972 to 18.3% in 1975 and 22.5% in 1977. Penicillins were prescribed in 6.7%, 15.1% and 12.3% in the three surveys; antipyretics, analgesics and sedatives in 40.0%, 51.5% and 40.9%; indicating the highest prescription rates in the second survey.

Table 3 shows the frequencies of the drugs prescribed concomitantly with chloramphenicols in the first and second survey. By 'concomitantly', we mean the prescription of other drugs in combination with chloramphenicols at most one month apart. The frequencies of prescription in combination in the third survey are not shown since chloramphenicols were prescribed to only 5 among 6,096 patients. The prescription of chloramphenicols alone accounted for 27.1% in 1972 and 19.2% in 1975; indicating the decrease by 30% between two surveys. The drugs most frequently prescribed with chloramphenicols were antipyretics, analgesics and sedatives—57.2% in 1972 and 68.5% in 1975. In 1972, sulfonamides, penicillins, cephalosporins and thiampenicols were prescribed with chloramphenicols in 23.1%, 12.0%, 2.9% and 2.8%, respectively. The corresponding figures in 1975 were 14.2%, 20.2%, 21.8% and 16.1%; indicating the increased prescription with other antibiotics.

Table 4 details the prescription in combination for the other drugs. The frequencies of prescription without combination are presented in parenthesis. Thiampenicols were most frequently prescribed in combination with antipyretics, analgesics and sedatives (49.2%–71.5%), followed by chloramphenicols (13.6%–30.3%), sulfonamides (3.0%–27.1%), tranquilizers (8.3%–20.6%), cephalosporins (6.5%–25.5%) and penicillins (10.6%–18.4%). The combined prescription of thiampenicols with chloramphenicols, sulfonamides and tranquilizers decreased, but that with cephalosporins apparently increased over years.

Sulfonamides, cephalosporins and penicillins were also frequently prescribed in combination with antipyretics, analgesics and sedatives; being 63.7%–85.4%, 53.8%–70.7% and 56.1%–70.8%, respectively. Combined prescriptions with chloramphenicols were apparently decreased over years in all drugs surveyed, correspondingly to the decreased prescription of chloramphenicols as presented in Table 2.

Among those who were prescribed sulfonamides, both cephalosporins and penicillins were likely to be used more frequently, but among those who were prescribed cephalosporins, sulfonamides seemed to be less frequently prescribed over years. Among those who were prescribed penicillins, the combined use of sulfonamides also decreased over years; from 21.0% to 2.8%.

In 1977, cephalosporins and penicillins were used in combination with other antibiotics or sulfonamides with rather low rate; the rate being 1.9%–7.4% among those who were prescribed cephalosporins, and 0.0%–13.2% among those who were prescribed penicillins.

Antipyretics, analgesics and sedatives were most frequently prescribed with cephalosporins throughout three surveys. Tranquilizers were most frequently prescribed with antipyretics, analgesics and sedatives; 53.3%, 61.8% and 43.5% in the first, second and third survey. The frequency of the combined prescription of tranquilizers with antipyretics, analgesics and sedatives was much higher than that of single prescription in the first and the second survey; 53.5% vs 32.5% in 1972 and 61.3% vs 23.5% in 1975.

Figure 1 illustrates the age curves of the prescription rates for chloramphenicols, thiampenicols and sulfonamides in the three surveys. The prescription rate for chloramphenicols was approximately 20% in the age groups of less than 40 years and dropped to 15% with advancing ages. The rates for chloramphenicols in 1975 were

Table 3.  
Frequencies of drugs prescribed concomitantly with chloramphenicols  
in the first and second survey.

Major Drugs	First survey	Second survey
	(1972) n=1656	(1975) n=986
Chloramphenicols*	27.1%	19.2%
Thiamphenicols	2.8	16.1
Sulfonamides	23.1	14.2
Cephalosporins	2.9	21.8
Penicillins	12.0	20.2
Antipyretics, analgesics and sedatives	57.2	68.5
Tranquilizers	17.3	14.0
Oral hypoglycaemic drugs	0.6	0.4
Antithyroid drugs	0.2	-
Anticonvulsants	0.4	0.3
Hypotensive diuretics	2.1	1.1
α-Methyldopa	0.1	0.1
Carbonic anhydrase inhibitors	0.2	0.1
Quinidine	-	-
Quinine	-	-

\*prescribed without combination

Table 4.  
Frequencies of prescription in combination for major drugs  
suspected to induce haematopoietic disorders in three surveys

drugs prescribed in combination major drugs	Chloram- phenicols	TP	Sulf	CE	PC	AAS	TQ
Thiamphenicols (TP)	1972 (n=155) 30.3%	$\begin{pmatrix} 18.7 \\ 16.9 \\ 33.3 \end{pmatrix}$ *	27.1	6.5	12.3	64.5	20.6
	1975 (n=1168) 13.6		12.5	22.3	18.4	71.5	13.6
	1977 (n=132) -		3.0	25.0	10.6	49.2	8.3
Sulfonamides (Sulf)	1972 (n=1895) 20.2%	$\begin{pmatrix} 24.5 \\ 12.7 \\ 4.5 \end{pmatrix}$ *	2.6	9.2	63.7	18.1	
	1975 (n=1159) 12.1		24.2	20.2	80.4	13.8	
	1977 (n=89) -		27.0	23.6	85.4	14.6	
Cephalosporins (CE)	1972 (n=236) 20.3%	$\begin{pmatrix} 4.2 \\ 12.0 \\ 2.5 \end{pmatrix}$ *	20.8	$\begin{pmatrix} 23.7 \\ 18.7 \\ 39.8 \end{pmatrix}$ *	22.5	58.9	28.4
	1975 (n=2299) 9.4		10.9		21.3	70.7	14.9
	1977 (n=1344) -		1.9		7.4	53.8	5.2
Penicillins (PC)	1972 (n=834) 23.8%	$\begin{pmatrix} 2.3 \\ 11.2 \\ 1.8 \end{pmatrix}$	21.0	6.4	$\begin{pmatrix} 22.5 \\ 17.7 \\ 36.6 \end{pmatrix}$ *	61.5	17.6
	1975 (n=1900) 10.5		11.7	25.5		70.8	13.5
	1977 (n=749) 0.0		2.8	13.2		56.1	5.6
Antipyretics, analgesics and sedatives (AAS)	1972 (n=4967) 19.1%	$\begin{pmatrix} 2.0 \\ 13.7 \\ 1.6 \end{pmatrix}$	24.3	28.0	10.3	$\begin{pmatrix} 42.0 \\ 34.0 \\ 49.3 \end{pmatrix}$ *	21.3
	1975 (n=6460) 10.4		13.6	23.4	19.3		14.6
	1977 (n=2495) 0.0		3.0	29.0	16.8		6.5
Tranquilizers (TQ)	1972 (n=1981) 14.5%	$\begin{pmatrix} 1.6 \\ 9.6 \\ 3.0 \end{pmatrix}$	17.3	3.4	7.4	53.3	32.5
	1975 (n=1461) 9.5		10.6	20.1	16.9	61.3	
	1977 (n=372) 0.0		3.5	18.8	13.3	43.5	43.0

\* Frequencies of prescription without combination

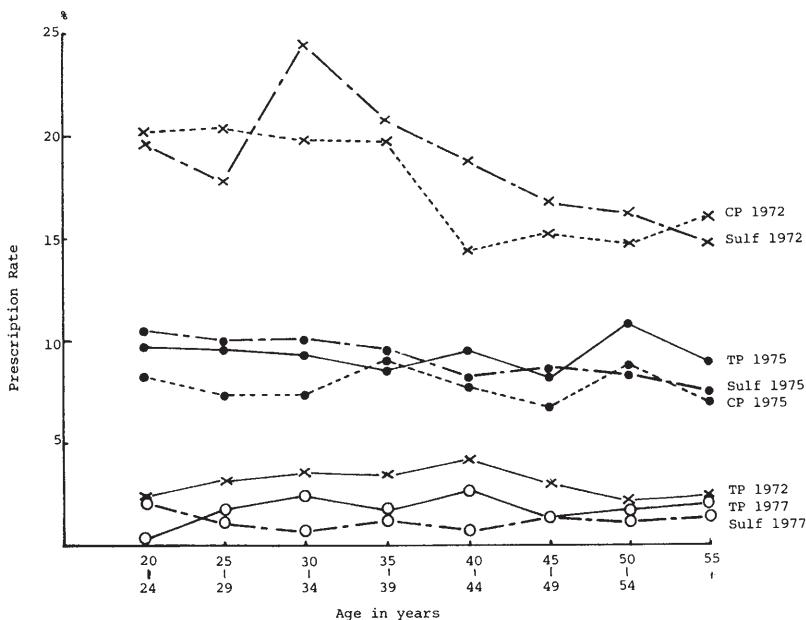


Figure 1. Age curves of prescription rates for chloramphenicols (CP) thiampenicols (TP) and sulfonamides (Sulf) in three surveys (1972, 1975 and 1977)

considerably lower than those in 1972 in every age group and were unaltered by age. Since chloramphenicols were prescribed to only 5 patients in 1977, the prescription rates by age were not shown.

The prescription rates for sulfonamides in 1972 were 20%–25% in the third and fourth decades, and decreased to 15% with advancing ages. The rates for sulfonamides in 1975 and 1977 were also considerably lower than those in 1972 in every age group and were unaltered by age.

The prescription rates for thiampenicols were virtually unchanged by age in three surveys, though the rates in 1975 were higher than those in 1972 and 1977 in every age group.

The average durations of drug prescription were 5.8 and 5.9 days for chloramphenicols in 1972 and 1975, and 6.8, 7.5 and 6.3 days for thiampenicols in 1972, 1975 and 1977, respectively.

The corresponding durations for sulfonamides were 10.7, 9.5 and 6.1 days; indicating the gradual decrease in the average days of prescription. In 1972, the average durations of prescription for sulfonamides were 8, 10 and 14 days in the age groups of 20–34, 35–49, and 50 years and over, respectively; indicating a gradual increase in the average days of prescription by age. In 1975 and 1977, however, the average durations of prescription of sulfonamides neither increased nor decreased by age.

The average durations of prescription of antipyretics, analgesics and sedatives were 17.4, 15.9 and 9.8 days in 1972, 1975 and 1977, respectively; showing the marked decrease in 1977. The prescription rates for tranquilizers were higher in 1972 and 1975 than those in

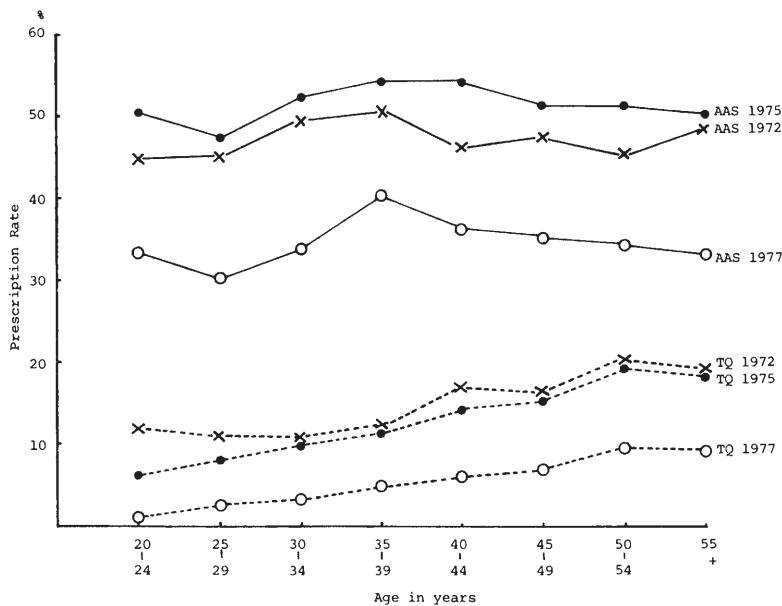


Figure 2. Age curves of prescription rates for antipyretics, analgesics and sedatives (AAS), and tranquilizers (TQ) in three surveys (1972, 1975 and 1977)

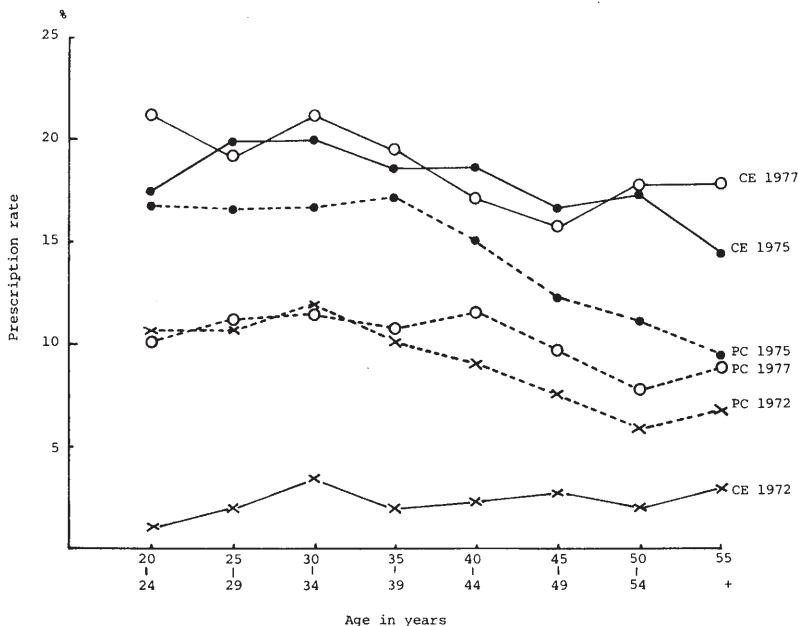


Figure 3. Age curves of prescription rates for cephalosporins (CE) and penicillins (PC) in three surveys (1972, 1975 and 1977)

1977 in every age group; showing the gradually increasing pattern of prescription rates by age. The increase gradient of the rates by age were quite similar in three surveys.

Figure 3 demonstrates the age curves of the prescription rates for cephalosporins and penicillins.

The prescription rates for cephalosporins were less than 5% in every age group in 1972, but markedly increased up to 15%–20% in 1975 and 1977. In 1975 and 1977, the prescription rates for cephalosporins were approximately 20% in the age groups of less than 40 years and 15%–18% in those of 40 years and over; indicating the slightly decreasing prescription rates by age.

The prescription rates for penicillins were higher in 1975 than those in the other two periods. In 1975, the rates for penicillins were 16%–17% in the age groups of less than 40 years, and dropped gradually with advancing ages; the rate being 10% in the age group of 55 years and over. In 1972 and 1977, the prescription rates for penicillins were 10%–12% in the age groups of 20–39 years and 5%–7% in the age groups of 45–54 years.

Penicillins were prescribed more frequently for the age groups of 40 years and more in 1977 than in 1972, as compared to the age groups of less than 40 years.

The average durations of prescription for cephalosporins were 9.9, 8.8 and 6.9 days, and those for penicillins 9.0, 8.8 and 6.9 days in 1972, 1975 and 1977, respectively; indicating the decreasing average days of prescription for these two antibiotics. The average durations of prescription of these two drugs tended to increase by age in 1972 and 1975, but virtually unchanged in 1977.

## DISCUSSION

Adverse reactions to drugs could be detected with relative ease, when they appear shortly after the ingestion. The mechanisms of adverse reactions could hardly be resolved, when the adverse reactions occur after a long latent period. A drug, in general, infrequently provokes the adverse reactions. This may also make the resolutions of the pharmacological and medical problems rather difficult.

Aplastic anemia occurs in approximately 1.5 per 100,000 population, and its etiological mechanisms are not fully known. The disease could not be successfully reproduced experimentally, when the healthy animals are used. (8)

Since the causal relationship between chloramphenicols or other drugs and aplastic anemia has strongly been suspected through the clinical observations, it is rather urgent to evaluate epidemiologically the causality or relative importance of this compound in aplastic anemia.

There seems to be only one survey in California (9), which reported how frequently and in what way the humans ingested the drugs in a defined area. Our surveys, which were conducted in a population of the defined area with approximately 20 million inhabitants, revealed the prescription rates and their trends for the drugs suspected to induce the subsequent haematopoietic disorders. Since the drug ingestion is closely related to the degrees of drug adherence among those prescribed, the prescription rates per se are not presumed to be the actual rates of ingestion.

The subjects examined as to their monthly health insurance receipts were 17,245, 20,180 and 24,986 in the first, second and third survey, respectively; indicating the gradual increase in the number of subjects. The subjects whose receipts were actually reviewed are not

always the same in each survey. In the third survey, 20% random samples of the monthly receipts were reviewed, since two previous surveys proved that 20% samples were sufficiently large enough to evaluate the trends in prescription rate for the relevant drugs. Male to female ratio of the subjects examined are 7:3 and unaltered over three periods, but those aged 20 to 49 years are the most part of the subjects in both sexes, and the highly aged persons are not included.

These are considered to be the main shortcomings in the present surveys Nevertheless, the present subjects may have the following epidemiological advantages; the unbiased distributions of their residence, social class and medical institution; since their residences were distributed throughout a large district of Metropolitan Nagoya (Nagoya city and its vicinities), since those with quite different educational levels were engaged in the variety of works as administratives, professionals, clerks, skilled and unskilled workers, and since the medical institutions they visited were not limited to major hospitals, but included other hospitals, clinics, dispensaries and other forms of institutions, which are distributed throughout Metropolitan area.

Chloramphenicols were prescribed in 13.3% in the first survey; this proportion of prescription yielding the estimated number of approximately 20 million prescriptions in 1972 in Japan.

In the previous communication (10), those who ingested chloramphenicols were estimated as 21–35 millions in Japan in 1971 with the assumption that the amount ingested by a person per one prescription is comparable between California (9) and Japan. This estimation is fairly close to the figure calculated by the prescription rate in our second survey (1975).

Chloramphenicols were prescribed with the average durations of 5.8 and 5.9 days in 1972 and 1975, but the majority of prescriptions were within 3 days and the amount per day was 1–2 grams; the amount ingested per person being 3–6 grams per prescription (9,11). This estimation is also very similar to the figure in California (9).

The trends between the production amounts (13) and the prescription rates appear to be well in parallel with each other in Japan and in the population we surveyed.

Annual production amounts of chloramphenicols were 173, 32, 2.2 and 4 tons in 1974, 1975, 1976 and 1977, respectively (12). The production amount remarkably decreased after 1975.

The prescription rates for chloramphenicols in the population we surveyed decreased remarkably from 13.3% in 1972 to 7.9% in 1975 and 0.08% in 1977, along with the decreased production amount.

In Japan, the regulation for indication of chloramphenicols was newly issued in December, 1975. To evaluate the probable effect of this regulation on the prescription rate, two assumptions were made. The first assumption was that chloramphenicols were prescribed in the same frequency as in 1972 for the period of October–December, 1975 and the prescription was strongly regulated in the subsequent three months of January–March, 1976. The second assumption was that the prescription rate for chloramphenicols was unchanged until September 1975 (before our second survey) and gradually decreased after October, 1975. Then, these two assumptions commonly yielded the estimated prescription rate of approximately 3% for March, 1976. The rate, as presented in Table 2, continuously decreased to 0.08% in October, 1977–March, 1978.

The prescription rate for thiامphenicols, whose chemical structure is quite similar to that of chloramphenicols, were 1.2%, 9.3% and 2.2% in 1972, 1975 and 1977, respectively. The

lower prescription rate in 1977 than in 1975 was observed in antipyretics, analgesics and sedatives and tranquilizers as well as thiامphenicol and chloramphenicol. The decreases in the prescription rates for antipyretics, analgesics and sedatives and tranquilizers were approximately by 20% between the second and the third survey.

In the population we surveyed, the rate of visiting physicians were 71.9%, 62.2% and 70.1% and 1972, 1975 and 1977, respectively; the rate being slightly lower in 1975. Overall prescription rate in this population for the drugs suspected to induce the subsequent haematopoietic disorders were 69.2%, 68.7% and 50.6%, correspondingly. Noteworthy is that the prescription rate in 1977 was lower by about 30% than that in 1975, while the rate of office visit was higher in 1977 than in 1975. This finding may suggest the possible decrease in the prescription rate from 1975 onwards.

The prescription rate for cephalosporins increased by 10 times in 1975, as compared to that in 1972, and then by about 20% in 1977. The rate for penicillins, on the other hand, decreased by 20% in 1977, as compared to the rate in 1975.

The average duration of prescription for antibiotics was apparently shortened between 1975 and 1977. This shortened duration of prescription was also observed in such drugs as antipyretics, analgesics and sedatives. The prescription of aminopyrin, for instance, remarkably decreased from 1972 onwards; the mortality rate from agranulocytosis (14) was seemingly reduced along with the decreased prescriptions. The prescription of drugs in combination was high in 1972 and 1975, but low in 1977.

These particular findings may possibly indicate that the amount of the drugs prescribed decreased in the population we surveyed.

Since the quality as well as the quantity of the drugs prescribed seem to be changed over years, then the future investigation should be undertaken focusing the qualitative aspects of the prescription. The more efforts should also be made for the examinations of the side effects of the drugs prescribed in this population.

In short, we conducted three surveys on the prescription of certain drugs in a population in a defined area, Nagoya. The population, however, was not a general, but limited one. The rate we surveyed and presented in this paper was not of ingestion, but of prescription. Accordingly, the rate presented should be deemed as the reference of the rate of ingestion in a general population.

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