An Essay on Safety of Drugs

Focusing on Adverse Drug Reaction Problems in Japan

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Introduction

In the long history of faighting against diseases, we had not had effective drugs for therapeutic practices, except for only a few drugs like morphine, digitalis, arsphenamine, liver extract(vitamin B_{12}), insulin, nicotinic acid(vitamin B_6), diphteria anti-toxin and so on, until the discovery of prontosil. In 1935, Gerhard Domagk reported his discovery that a sulfanilamide derivative, prontosil had an astonishing effect to treat patients for infectious diseases like sepsis. The strong effect of this life-saving drug was reported one after another, and many physicians felt that the new era in therapy had been opened and drugs had become to have important role in therapy[1]. Subsequent introduction of various life-saving drugs such as many sulfanil-amide derivatives, antibiotics represented by penicillin and so on, gave us too much confidence in drugs and dismissed from our minds the famous words described by Paracelsus, "All things can be poisons, for there is nothing without poisonus qualities. It is only the dose which makes a thing a poison.".

The first important therapeutic disaster which prompted us to remember the importance of the safety of drugs was thalidomide phocomelia in 1961. Subsequently, many adverse drug reactions (ADRs) and/or toxicities of drugs were pointed out, and distrust in drug was strongly implanted in our minds. Distrust seems to be gradually decreasing by stricter pre- and post-marketing tests during these two decades. The idea of Paracelsus' words is going to be

recognized by laymen as well by specialists in drugs. We meet, however, strong demand that drugs should be in higher level of safety than other products because drugs are materials to maintain our health and to cure diseases. On the other hand, we have problems related to the economics of new drug development which is apparent in the development of orphan drugs because of huge expenditures for safety tests.

Safety of drug has been one of the most important subjects in the pharmaceutical fields and also in the public, but the discussions between both areas have not been performed under a common background because of the complexity of its factors. It is important, I believe, that people in different fields must be able to discuss problems on drug safety under the common bases and to have the same recognition to drug safety. I would ,therefore, like to present here the outlines of ADR problems and an essay on safety of drugs as related to ADR to make common backgrounds among persons in various fields.

Outlines of Drug Safety Problems in Japan

In Japan, drugs like herb medicines were brought from China and had been used for more than 1,000 years. After the modern goverment was established in 1868, the medical systems were rapidly westernized, and western drugs became to be used widely. Health hazard problems accompanied with the

use of drugs were related with the intoxication by impurities and/or overdose of a powerful drug through the history of drugs before 1950. During the period, the supply of good quality drugs was rather the important problem on drugs.

Penicillin was introduced into Japan as a strong weapon against infective diseases in the confusing society after the second world war. It was available easily in the begining of the 1950's, and penicillin shock became gradually a subject in the medical community. In 1956, a famous proffessor died form the shock by penicillin in dental treatment. The press reports on this accident induced the flood of reports on similar penicillin shock cases in journalism. It is a typical pattern that potential ADR cases have been accumulated and a report on special cases set a fire on the ADR problem.

Outlines of drug safety problems after the penicillin shock issue are summerized in Table 1. The thalidomide disaster was found in Japan as well as

Table 1

in European countries after the warning by Dr Lentz in 1961. This prompted us to recognize the necessity of more and stricter toxicological tests of drug candidates and of ADR monitoring system. It was confirmed that there were 309 cases of thalidomide phocomelia, and 185 persons including victims and

their families brought civil actions against the goverment and six related pharmaceutical companies since 1963[2]. After the long debate in the court, the cases reached settlements through reconciliation. In Table 2 are summerized outlines of suit cases relating to ADR including thalidomide phocomelia.

Table 2

The next big issue was case of sudden death after takeing liquid medicine for cold contained in ampule(OTC). The cases appeared in 1965 though they had been reportedly occurring since 1959. The event threw light again on the importance of biological availability.

An unknown disease following the treatment of intestinal diseases appeared in Japan since 1955, and was named ,in 1964, "Subacute Myelo-Optic Neuropathy" or "SMON" after dysfunction of spinal cords, optic nerves, and of peripheral nerves such as dysesthesia and weakness in the lower extremities, numbness, optic atrophy, and disturbances of vision. SMON patients increased gradually and the goverment undertook the special studies to elucidate the cause of SMON. Some investigators proposed that SMON was caused by a virus. The communicable nature of viruses and the tragic symptoms of SMON invited the discrimination of SMON patients and their families in their community. The issue became a large social problem. The study eventually elucidated that the green material peculiar to urine, feces and tung of SMON patients

was a complex of chinoform with iron, and that most of SMON patients had took chinoform preparations for treatment of their intestinal diseases before catching SMON. Chinoform preparations were, therefore, withdrawn from the Japanese market in 1975, and new SMON cases decreased rapidly. It is estimated that more than 11,000 persons suffered SMON in Japan[3]. Chinoform was used for more than 70 years in Japan, and most of SMON cases were occuring during the last 15 years. This largest ADR disaster in Japan prompted us to bring the importance of the Paracelusus' words previously mentioned to our mind. SMON victims more than 6,000 and their families brought civil actions against the goverment and 22 pharmaceutical companies since 1971, as shown in the Table 2. The defendants lost many of the first traials and have appealed to the higher court by raising the point why the occurence of SMON could not be considered from the medical knowledge before the relation of chinoform with SMON was pointed out. Apart from the appeal, the reconciliation to relief SMON victims has been established between most of the victims and defendants through the courts. The disaster led, in 1979, to the amendments of the Pharmaceutical Affairs Law which reinforced the efforts for safety measures, and the establishment of a new law, that is, the Adverse Drug Reactions Sufferings Rilief Fund Law which provided that the Fund should pay some amount of money to the serious ADR victims and collect money from pharmaceutical companies in proportion to the selling amount and to the paying amount to the victims of a paticular drugs with ADR.

In the midst of disputing SMON issues, various ADR victims and their families brought civil actions as shown in Table 1 and 2. The ADR problems were liver damage by a coronary vasodilator(coralgil), hearing disorder by an antibiotic(streptomycin), vision dsiorder by an antiinflamatory and antiprozoal agent(chloroquine), blood doisorder by an antibiotic(chloramphenicol), muscle atrophy by intramusclar injections, and so on. Among these ADR problems, muscle atrophy seemed to be a problem worth writing here, as the problem was unique to Japan. In several areas, it was found that young children had difficulty to walk and had quadriceps contracture. It was, thereafter, pointed out that the quadriceps contracture was caused by the frequent intramusclar injections to the quadriceps when the children caught common cold or other diseases. Representatives of victims raised two points, that is, the negligence of physicians concerning the injuring properties of injections and the negligence of pharmaceutical manufacturers who had not informed on non-physiological properties of injection drugs to physicians. Victims and their families brought civil actions against goverment, prefectural offices, city offices, pharmaceutical companies, the Japan Medical Association, hospitals and physicians. The characteristic of this case was that people in medical field became defendants by the claim that they did malpractice. In some of the first trials, district courts ordered pharmaceutical companies and physicians to pay compensations. New cases of quadriceps contracture decreased

rapidly after the start of the suits.

I have presented here the outlines of some of ADR problems in Japan which were caused by negligence of medical people concerning essential qualities of drugs described by Paracelusus. The neglegence might be caused by the lack of scientific knowledge and the deficiency of ADR information systems. On the basis of these experiences, ADR information systems have been improved by the establishment of ADR monitoring systems, and by leagal obligations for pharmaceutical manufacturers to report ADR cases, to do postmarketing surveilances(PMS), and to promote the exchange of ADR information in the medical community. We have not had any large ADR problems scince 1975. However, we meet sometimes rare but serious ADR cases like shocks by iodocontrast media which are believed to be inevitable ADR on the use of the drug. We have esatblished the relief system for victims as mentioned above. Now, we should make efforts to know the present situation of ADR and to decrease such unhappy cases. In the next section, I will try to describe how often ADRs occurr.

Frequency of ADR found in the PMS in Japan

ADR frequency of a drug might be dependent on various factors such as the definition of ADR, the observers, the patient groups and the condition of diseases. It is, therefore, difficult to compare the results of PMS perform-

ed under different protocols and to interpret their meaning. But the results might give us the round figures of ADR frequency and help us to know how often drugs cause ADRs.

In Japan, several hundred to few thousand cases on a drug are investigated before approval, and several thousand to more than ten thousand cases on a drug are investigated in a PMS. PMS results of several groups of drugs are summerized in Table 3. The table shows that the drug for common disea-

Table 3

es like antipyretic-analgesic and antiinflammatory agents, minor tranquilizers, drugs acting circulatory systems or antibiotics causes ADR in several cases per a hundred while the drugs for more serious diseases such as malignant tumor, schizophrenia or parkinsonism cause ADR in the order of one tenth . The lists of ADR are shown on two drugs, that is, haloxazolam (minor-tranquilizer) and cefmetazole (antibiotics acting mainly on gram-positive and gram-negative bacteria) in Tables 4 and 5,respectively.

Table 4

Table 5

The frequent ADRs of haloxazolam (PMS on 21,822 cases) were the following:

- central and peripheral nervous disoreders including dizziness(296 cases, 1.4%), head ache(66cases, 0.3%) and 8 other ADRs.
- psychiatric disorders including somnolence(286 cases, 1.3%), rest-

less(11 cases, 0.1%) and 13 other ADRs.

- general systemic disorders including fatigue(76 cases, 0.3%), adynamia(36 cases, 0.2%) and 3 other cases.

These ADRs seems to be not serious although the terms needed for recovery from ADR was not reported. The frequent ADRs found in cefmetazole PMS (24, 283 cases) are the following:

- liver function disorders including GOT elevation(208 cases, 0.85%), GPT elevation(202 cases, 0.83%), jaundice(1 case, 0.004%) and 5 other ADRs.
- hypersensitiveness including eruption(196 cases,0.81%), itching(25 cases,0.10%), pyrexia(22 cases, 0.09%) and 3 other ADRs.
- stomach and intestinal disorders including nausea(27 cases,0.11%), diarrhea(25 cases, 0.10%), vomiting(12 cases, 0.05%),melena(4 cases, 0.02%), hemorrhagic colitis(1 case,0.004%), pseudomembranous colitis(1 case, 0.004%) and 5 other ADRs.
- blood disorders including agranulocytosis(42 cases, 0.17%), eosinophilia(18 cases, 0.07%), thrombocytopenia(9 cases, 0.04%) and oligocythemia(5 cases, 0.02%).

Most of these ADRs caused by cefmetazole seem to be not serious although a few cases like jaundice and colitises might be serious. The term needed for recovery from ADR is not described in the information.

As mentioned above, drugs caused ADRs in the order of one hundredth to one tenth depending on kinds of drugs. Those ADRs could be found in PMS and/or clinical tests before approval, and most of them seemed to be slight ADRs from which patients could easily recover by the discontenuation of the drug. Such slight ADRs have been generally accepted as unavoidable ones to recover from diseases. On the other hand, a few cases of death or incurable injuries caused by possible ADR may bring about a social problem and decide the destiny of the drug. This kinds of serious ADRs are generally difficult to be detected in the PMS and/or clinical tests before approval which are generally performed in the scale of cases less than hundred thousand.

The ADR Sufferings Relief Fund, however, has been recieving cases with serious injuries which were undeniably caused by ADRs. An unhappy example is the case where a 10 years old boy who was administered an antipyretic-analgesic and antiinflammatory agent, an antibiotic, a hemostatic agent and an antiemetic agent for acute pharyngitis, caught toxic epidermal necrolysis and eventually lost his sight. There are various unhappy cases such as deathes from malignant hyperthermia by general anesthetics and/or myorelaxants, from shock by antibiotics, antipyretic-analgesic and antiinflammatory agents and/or iodo-contrast media and so on. The lethality of intravenous pyelography with iodo-contrast media obtained form literatures are shown in Table 6 as an example of the frequency of such unhappy ADRs. It shows that few deathes occurred per hundred thousand cases in most investigation on

Table 6

intravenous pyelography with iodo-contrast media. Scince iodo-contrast media for intravenous pyelography have been changed to new ones, the lethality of present iodo-contrast media might be lower than that in Table 6. One of important problems concerning with the drug safety is to prevent the rare but fatal or disabling ADRs which may be caused by the interaction of drugs with the special physical constitution and/or physiological conditions of the patient.

In this section, I have outlined the frequency and the kinds of ADRs of the presently available drugs in Japan. I would like to describe outlines of the safety measures and my comments in the next section.

Safety Measures for Drugs

In Table 7 are listed the major problems on safety of the drugs and the safety measures which have been taken through the unhappy experiences in health hazards caused by drugs as mentioned previously.

Table 7

I would like to try to classify causes of ADRs to the following three groups:

(a) quality: health hazards caused by a drug of inferior quality like the drug contaminated by substance(s) out of the specification, for example, AIDS or hepatitis caused by a blood preparation contaminated by AIDS or hepatitis viruses.

(b) toxicity or ADR which appeared generally in people taking a drug: health hazards caused by the action of a drug which people in general take over a certain amount, for example, hypoglycemia caused by antidiabetics, and

(c) toxicity or ADR which appeared under special conditions: health hazards caused only under special condition by the concerted action of drug, state of disease, physiological condition and constitution of the patient, for example, shock or serious eruption caused by antibiotics.

In the cassification, the sequence of (a) to (c) seems to correspond to the decreasing order of the ADR frequency, to the increasing order of the difficulty to predict and/or detect the ADRs on the scientific basis of the preclinical toxicological data or the clinical and PMS data and to the order increasing the importance of experiences of individual cases of the ADR. It goes without saying that some of ADRs like delayed ADRs or ADRs caused by the accumulation of more than a tolerable amount of a drug are difficult to be detected even if the group of ADRs is in (a) or (b).

The following measures:

・the performance of various safety tests on the basis of the scientific knowledge in related fields such as medicine and pharmaceutical sciences,

・the observance of the guidelines like GLP and GCP(still in proposal)to insure the reliability of the data obtained in the safety tests,

・prudent evaluation for approval taken by the goverment,

・standardized production of drugs under the strict observances of GMP,

・surveilance and control of the production and marketing processes by the administration offices, and

・ADRs surveilances in various methods

have been taken effectively against ADRs of group (a) and (b). Futher safety measuers against these group of ADRs would be the followings:

(1) deepening understanding of diseases, dynamics and control mechanisms of various substances in a human body in conformity with the rapid advancements of related fundamental sciences,

(2) the establishment of more appropriate methods to test toxicity and/or ADRs and the development of the methods to use more effectively data obtained already or animal test data to investigate toxicity and/or ADRs of new substances, on the basis of (1),

(3) the developments of new drugs which have stronger efficacy and more limited ADRs than drugs available at present, and

(4) the consolidation of the education on the proper use of drugs and on ADRs for people in the medical field like physicians and pharmacists as well as laymen.

ADRs in the group (c) are related to rare but serious ADRs which are most important as the health hazards caused by current drugs in Japan as mentioned previously. These ADRs are difficult to take safety measures and give us complicated safety problems. A part of current safety measures as mentioned above have played an important part in the safety measures against ADRs in group (c) and the expected safety measures (1) to (4) should be indispensable to the matter. The scarcity and complexity of ADRs in group (c) bring us the following questions:

(5) what are the adequate methods to collect information for detecting the ADRs in the very early stage of their appearance ?

(6) will we be able to have any preliminary tests to prevent the outbreak of the ADRs ?

and in adddition to these scientific aspects, from the aspects of medical economics and bioethics

(7) what extent of safety measures should we take in view of the cost-effectiveness ratio ?

Concerning the data collection as mentioned in (5), various types of cohort surveies have been carried out but are limited only to some groups.

We expect to expand the sphare of this type of surveies since we are in good enviroments to do it by the use of the recent rapid advancement and propagation of electronic information processing and communication systems. In order to make a big progress in this field, methods for simple inputs of good quality data, way to obtain data compatibility and principles of data usage should be investigated in cooperation with the people in the related fields. In respect of information, we have another problem that informations on the frequency and quality of ADRs in simple and intelligible forms will be required for the purpose of (4) when patients will have a choice on their own medical treatments in the future. It will be possible to lead us to re-examination of ADRs information and to the request of quantitative ADRs data. Long time has passed since we started the collection, evaluation and circulation of ADRs information. These were important to ensure the safety of drugs, but we still have many problems which should be improved in this field. Answer to question (6) will be found of itself by the fruit of studies described in (1) and (2), and by the development of ADR data collection system as mentioned above.

As regards to question (7), the expenditure to detect or prevent ADRs has been calculated as the function of ADR occurrence probability, spontaneous appearance rate of the disease similar to the ADR and the cost of survey or test. It shows that huge expenditure is required to detect or prevent a case of quite rare ADR. At present, a general opinion on life and

health of human is that life and health should be kept in the highest level of medicine, and does not contain the idea on cost-effectiveness ratio. Social consensus on cost-effectiveness ratio in medical field, however, will become necessary as the expensive treatment will increase with the advancements of medical technology. The pursing limit of drug safety measures also will be discussed from the view of cost-effectiveness ratio, and it will be necessary to make efforts for establishing social consensus on drug safety. We, therefore, should endivor to make consensus on the evaluation of life and health, and accumulate more quantitative data on drug safety which is rather qualitative at the present.

As the conclusion of the discussion as described above, I consider that the pursit of the measures and questions (1) to (7) is important subjects to improve the drug safety in the future. The followings:

- that the rapid advancements of biological sciences will be used swiftly to evaluate and/or test the drug safety,
- that the recent rapid advancement and propagation of electronic information processing and communication systems will be used to establish the collection and circulation systems of ADRs information in improved quality, and,
- that the practical limit of the drug safety measures will be discussed by the people in more various field,

may be especially important.

Summary

People in general take an interest in the safety of drugs but limited people in the medical and pharmaceutical fields only take part in debates on drug safety except for some special cases which became journalistic topics. Aiming at the way to improve the safety of drugs in cooporation with the experts in various safety problems, I have introduced thefollowing topics:

1. health injuries related with drugs which became objects of public concern,
2. frequency and quality of ADRs observed in PMS on some currently available drugs, and
3. outlines of current safety measures for drugs,

focusing on experiences in Japan.

I have also pointed out that rare but serious health injureies are an important problem on the drug safety although they were caused by the complicated combination of the drug action, physiological condition and/or pysical constitution of a patient. Concerning about rare but serious ADRs, I have suggested that important measures are the followings:

1. investigations on the detection and/or evaluation methods in swift response to the rapid advancement of related sciences,
2. consolidation of the system collecting and distributing ADRs

information by use of rapid advancements and propagation of electronic information processing and comunication systems,

3. enrichment of ADRs information to debate the cost-effectiveness ratio on drug safety and to make the consensus on the pursing limit of drug safety measures.

Acknowledgements

I am grateful to Prof. S. Fujiwara and Dr. T. Yamada of Kanagawa University for their valuable suggestions and encouragements on this essay.

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Table 1 Outlines of Drug Safety Problems in Japan

Year	Drug Safety Problems
1956	Penicillin shock became a social problem through the death of a famous professor.
1961	Warning about thalidomide in relation with the birth of phocomelia babies.
1965	Sudden deathes after taking ample prepareations of medicenes for cold.
1970	Warning that SMON might be caused by chinoform.
	Liver disorder by coralgil was pointed out.
1971	SMON cases were presented to the civil courts.
	Coralgil cases were presented to the civil court.
	Streptomycin cases were presented to the civil court.
	Vision disorder by chloroquine became a social issue and the cases were presented to the court.
1975	Muscle atrophy caused by intramusclar injections was warned by a group of physicians and the cases were presented to the civil court.
	Ministry of Health and Welfare(MHW) esatblished a working group to investigate a relief system for the ADR sufferings.
1976	Report for the relief system was presented by the group.
1977	The first reconciliation in SMON cases was established in the Tokyo district court.
	Draft of ADR Sufferings Relief Law was published by MHW.
1978	Draft of the amendments of Pharmaceutical Affairs Law was publised by MHW.
1979	Amendment Law of Pharmaceutical Affairs Law and Adverse Drug Reaction Sufferings Relief Fund Law were adopted in the National Diet and enforced.

Table 2 Principal Suit Cases Concerning with ADR Problems

Case Name	Date of Action	Number of Courts	Number of Plaintiff	Defendants	Amount Claimed
thalidomide	1963.6.17. to 1971.9.2.	District 8 (Tokyo etc)	185 (patients 63)	goverment 5 pharm. companies	3,275 (million ¥)
chinoform	1971.5.28. to 1985.12.6.	District 32 Higher 7 (Tokyo etc)	7,635 (patients 6,455)	goverment 22 pharm. companies	284,992
chloram-phenicol	1975.7.31. to 1978.10.3.	District 1 (Tokyo)	12 (patients 5)	goverment 3 pharm. companies 11 physicians	411
muscle atrophy	1975.7.31. to 1980.10.20.	District 3 Higher 3 (Tokyo etc)	944 (patients 318)	goverment prefecture 2 cities 31 pharm. companies Jap. Med.A. 6 hospital 20 physicians	12,036
chloroquine	1975.12.22. to 1985.11.29.	District 2 Higher 1 (Tokyo etc)	282 (patients 95)	goverment 6 pharm. companies 14 hospital ・physicians	18,882
chlotaone	1976.2.6.	District 1 (Tokyo)	14 (patient 1)	goverment 1 pharm. company 1 hospital ・physician	112
strepto-mycin	1971.9.16.	District 1 (Tokyo)	4 (patient 1)	goverment 4 pharm. companies 1 physician	28
coralgil	1971.11.20. to 1980.5.20.	District 8 (Tokyo etc)	56 (patients 29)	goverment 1 company	864

This table was quoted from "Recent Administration on Pharmaceutical Affairs 61year version" edited by Pharmaceutical Affairs Beureau, Ministry of Health and Welfares, 1986, Yakumu-Koho-sha, Tokyo

Table 3 ADR Frequency found in some of PMS in Japan

Group	Drug Name	Date of Approval	Number of PMS cases	Frequency of ADR
Antipyretic-Analgesic and Antiinflammatory Agents	acetaminophen(suppository)	1979.08.03.	6,024	0.08%
	tolmetin sodium	1978.08.01.	15,894	4.3 %
	diclofenac sodium	1975.12.08.	17,518	8.0 %
	fenbufen	1979.05.22.	18,184	2.8 %
	tinoridine HCl	1971.05.10.	19,495	2.1 %
Psycotropic Agents	haloxazoram	1980.06.10.	21,822	3.7 %
	fludiazepam	1980.06.10.	8,752	2.6 %
	flurazepapm HCl	1978.08.01.	7,005	3.6 %
	sulpiride	1979.03.13.	15,104	15.1 %
	levodopa-benserazide HCl	1979.08.27.	2,875	13.9 %
Drugs Acting on Circulatory System	isosorbide nitrate (slow reliesing agent)	1981.05.01.	9,502	3.8 %
	indenolol HCl	1978.05.18.	5,941	4.0 %
	trapidil	1978.05.01.	11,856	2.6 %
	clofibrate aluminum	1978.01.24.	5,524	4.7 %
	ifenprodil tartarate	1978.05.18.	9,386	2.1 %
Antibiotics	piperacillin sodium	1979.05.22.	18,905	2.0 %
	talampicillin HCl	1977.03.05.	22,219	5.7 %
	cefmetazole sodium	1978.08.01.	24,283	2.9 %
	ampicillin-dicloxacillin sodium	1978.08.01.	4,569	1.9 %
	doxycycline HCl	1979.08.07.	5,997	6.0 %
Antineoplastic Agents	tegaful(suppository)	1977.08.10.	5,233	21.7 %
	tegaful(enterics)	1979.05.22.	9,047	14.2 %
	fluorouracil	1980.10.25.	6,929	32.4 %
	nimustine HCl	1979.05.22.	1,007	56.9 %
	mepitiostane	1978.08.01.	1,968	43.6 %

* These data were collected from "ADR Informations"(No55 - No76) edited by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

Table 4 ADRs of Haloxazolam*

Kinds of ADR	Number of ADR Cases	Frequency
central and peripheral nervous disorders	362	1.7 %
psychiatric disorders	310	1.4 %
general systemic disorders	115	0.5 %
autonomic nervours disorders	39	0.2 %
liver and bile duct disorders	49	0.2 %
stomach and intestinal disorders	20	0.1 %
metabolic and nutrient disorders	18	0.1 %
blood disorders	17	0.1 %
urinary disorders	7	0.0 %

* The data was cited from "ADR informations" edited by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

Table 5 ADRs of Cefmetazole Sodium*

Kinds of ADRs	Number of ADR Cases	Frequency
liver function disorders	482	1.9 %
hypersensitiveness	275	1.1 %
stomach and intestinal disorders	90	0.4 %
blood disoreders	74	0.3 %
renal function disorders	38	0.2 %
injected site disorders	40	0.2 %
shock and shock like reactions	21	0.1 %
vitamin deficiency	2	0.0 %
other ADRs	14	0.1 %

* This data was cited from "ADR Informations" edited by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare.

Table 6 Lethality of Intravenous Pyelography by Iodo-Contrast Media

Investigators(Country)	Year	Number of cases	Cases of Death	Lethality
Jungmichel(Germany)[1]	-1940	81,000	2	0.0025 %
De Becker(Bergy)[2]	-1949	60,000	1	0.0017 %
Pfeiffer(Germany)[3]	-1949	650,000	35	0.0055 %
Coliez(France)[4]	-1954	300,000	9	0.003 %
Burkhardt(Germany)[5]	-1954	1,000,000	7	0.0007 %
Pendergrass(US)[6]	1942-1958	11,546,000	99	0.00086%
Nesbit(US)[7]	-1959	144,500	1	0.0007 %
Wolfrom(France)[8]	1955/1965	912,300	15	0.0016 %
Toniolo(Italy)[9]	-1966	1,200,000	14	0.0012 %
Klumair(Austria)[10]	1955-1967	24,050	0	0.00000%
Ansell(UK)[11]	1966-1969	318,500	8	0.0025 %
Fisher(US)[12]	1960/1969	3,837,695	74	0.0019 %
Ochsner(US)[13]	1955-1968	41,308	1	0.0024 %
Shedai(US)[14]	-1973	47,678	5	0.01 %

* This table was quoted from "ADR Informations" edited by the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

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Table 7 Problems and Measuers Concerning the Safety of Drugs

Safety Problems	Safety Measuers		
	Resarch and Development	Approval	Manufacturing and Marketing
Quality: · products out of specification · change in quality · counterfeit drugs · contamination of impurity or poisonus substances (e.g. AIDS or hepatitis by blood preparation) · criminal addition of poisonus substance in marketing process Approval: · forgery of documents for approval application Toxicity and ADRs · ADRs · accidents by misuse (overdose, to take packaged drug, etc) · accidents under drug effects · drug addiction	Quality: · specification(purity, contents,solubility) · stability test · package Toxicity and ADRs · good laboratory practices(GLP) · genral toxicity test (acute, subacute, chronic) · special toxicity test effect on reproduction mutagenicity carcinogenicity local irritation antigenicity dependence · absorption,metabolism, excretion bioabailability metabolic activation distribution,storage · good clinical practice (GCP) · clinical tests · establishment of indication, dose, dosage, and direction for use	prudent evaluation by experts of various fields	Quality: · Good Manufactureing practices (GMP) · surveilances by adminstration offices Toxicity and ADRs · contenuous survey of literatures · re-evaluation of old drugs · ADRs monitoring · post-marketing surveilances(PMS) · reporting duty of new and/or serious ADRs for pharmaceutical manufactuerer · special studies on ADRs such as epidemiological saurvey · surveilances of advertisements by administration office · reversion of labeling by administration office · supply of ADRs information to medical proffesion · administerative orders(special test ,change of dose, dosage and indication, withdrawal)