MANAGEMENT AND UTILIZATION OF ORPHAN DRUGS AGAINST PARASITIC INFECTIONS IN RECENT 7 YEARS IN JAPAN

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Abstract: Since many important antiparasitic drugs are not registered in Japan, a research group, for the past 7 years, has managed the use of non-registered orphan drugs. Initially there were 16 orphan drugs under control of the group, these were as follows; chloroquine, Fansidar, Fansimef, quinine (iv), primaquine, mebendazole, praziquantel, thiabendazole, quinacrine, dehydroemetine (iv), pentamidine, Pentostam, suramin, stibophen, nifurtimox and pyrimethamine. Of these drugs, Fansidar, thiabendazole, mebendazole and praziquantel were recently registered. The number of cases treated with these drugs was nearly one thousand (920). The number of malaria cases treated in this group was 201, corresponding to 22% of the total cases treated with orphan drugs. Mebendazole was used in 210 cases, praziquantel in 163, thiabendazole in 120, quinacrine in 125, pentamidine in 67, dehydroemetin in 28, Pentostam in 5 and suramin in 1. Most drugs were evaluated as effective in their antiparasitic actions but severe adverse reactions occurred at relatively high incidences.

INTRODUCTION

Tropical diseases are not endemic in Japan because of its geographical location in the temperate zone. In addition, helminthic diseases, which prevailed in Japan for 2 decades after World War II, have reduced incidence due to a change from use of night soil to chemical fertilizer in agriculture, and due to improvements of public health and environmental hygiene. Recent economical growth in Japan has created an urbanized life style for most people. On the other hand, an increase of international relations has caused an importation of parasitic diseases. In connection with the latter problem, effective antiparasitic drugs are necessary.

At the start of the present study, only a limited number of drugs effective against parasitic infections were available on the market. Those were pyrantel pamoate, pyrvinium

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pamoate, metronidazole, tinidazole, diethylcarbamazine, bithionol and quinine chloride (po, powder), paromomycin and so on. Other drugs were not registered in Pharmacopoeia Japonica, so-called "orphan drugs". Although many antiparasitic drugs have been developed in recent years and used widely in the world, pharmaceutical companies were not willing to register the drugs in Japan, on account of the cost in application for approval, limited business benefits and the occurrence of adverse reactions to these drugs. In order to collect clinical data on the orphan drugs, the Ministry of Health and Welfare in Japan (MOHW) set up a research group for orphan drugs in 1980 and the members stored, managed and studied 16 different drugs. The clinical trials began in 1981 and the orphan drugs have been supplied for use for 7 years. The present study deals with the results of the clinical trials and the present management of orphan drugs against parasitic diseases in Japan.

METHODS

Our research group managed non-registered drugs and advertised the drug list. Each member of the group stored a set of drugs for distribution in accordance with the legal responsibility of the member. An individual physician who wishes to use a particular drug, contacts any member of the research group by telephone. The member sends out the requested drug along with prepared forms and guidelines for use of the drug. The doctor sends back a form of official request and an informed consent signed by the patient. The doctor is obligated to make a report of the results of the trial. All drugs used in this study were purchased from pharmaceutical companies in foreign countries.

The following drugs have been managed in stock: antimalarial drugs; (1) chloroquine phosphate (Aralen, Resochin), (2) sulfadoxine-pyrimethamine (Fansidar), (3) mefloquine hydrochloride in Fansidar (Fansimef), (4) quinine dihydrochloride (parenteral, Quinimax), (5) primaquine phosphate (Primaquine); and other antiparasitic drugs, (6) mebendazole (Vermox), (7) praziquantel (Biltricide), (8) thiabendazole (Mintezol), (9) quinacrine hydrochloride (Atabrine), (10) dehydroemetine dihydrochloride (Dehydroemetine), (11) pentamidine isothionate, pentamidine methanesulfonate (Lomidine), (12) sodium stibogluconate (Pentostam), (13) suramin (Germanin), (14) stibophen (Fouadin or Neo-Antimosan), (15) nifurtimox (Lampit) and (16) pyrimethamine (Daraprim).

RESULTS

Clinical data on the use of orphan drugs have been collected for 7 years from April, 1981 to March, 1988, and are shown in Table 1 for malaria cases, in Table 2 for cases treated with mebendazole, praziquantel and thiabendazole and in Table 3 for parasitic infections treated with other anthelmintics.

Antimalarial drugs

Clinical trials of antimalarial drugs were carried out in 189 cases, out of which 158 cases were reported to this group as shown in Table 1. 106/158 (67%) cases were *Plasmodium vivax* infections, 50 (32%) were *P. falciparum*, 2 (1%) were *P. malariae*, and in the other 26 cases malaria species were not identified. The relationships of the species and antimalarial drugs are shown in Table 1.

Table 1 The number of clinical trials in malaria cases by use of chloroquine, Fansidar and quinine in 7 years

Species of plasmodium	Antimalarial drugs				Total
	Ch ^a	Fa ^b	Ch & Fa	Qu ^c & others ^d	
<i>Plasmodium falciparum</i>	16	7	9	18	50
<i>Plasmodium vivax</i>	61 (53) ^e	36 (32)	9 (7)		106 (92)
<i>Plasmodium malariae</i>	1	1 (1)			2 (1)
unable to identify	31 (12)	11 (4)	1 (1)		43 (17)
Total	109 (65)	55 (37)	19 (8)	18	201 (110)

a : chloroquine phosphate.

b : Fansidar (pyrimethamine-sulfadoxine).

c : quinine (parenteral, quinine dihydrochloride).

d : other antimalarial drugs including chloroquine (6 cases), Fansidar (6 cases) and both drugs (2 cases).

e : ( ) indicates the number of cases in which primaquine was used.

Primaquine was used in 92 cases (90%) of vivax malaria to prevent recurrence, and as a result the recurrence occurred in 3 cases originating from Southeast Asia (Thailand). Relapse was also seen in 2 patients with falciparum malaria. They had been treated with chloroquine or/and Fansidar, then quinine was given orally based on clinical evidence of drug-resistant malaria. One fatal case of falciparum malaria occurred due to delayed initiation of malaria therapy.

Adverse reactions were suspected in 3/42 cases (7%) treated with chloroquine (skin eruption, photophobia and liver injury) but no adverse reactions were reported with Fansidar.

Mebendazole

Mebendazole was administered in 210 cases in which 126 (60%) were *Trichuris trichiura* (whipworm) infection (Table 2). In most patients with trichuriasis, counts of eggs per gram (EPG) were at low levels except for one individual with a high EPG over 5,000. In 53/55 (96%) cases, EPG decreased after treatment. Adverse reactions were suspected in 5/75 (7%) cases. Abdominal pain and skin eruption were the reported reactions.

This drug was also used for treatment of trichinosis during an epidemic in 1981 in which about 60 persons were suspected of infecting the disease. The outbreak occurred in patrons of a restaurant in Yokkaichi in Mie Prefecture, where raw bear meat, possibly imported, was served to about 400 persons (Yamaguchi, 1983). There were two other epidemics in Japan; 15 out of 20 hunters in Aomori Prefecture in 1974 (Yamaguchi *et al.*, 1975) and 12 out of 94 persons who were served raw bear meat of local origin in Sapporo, Hokkaido in 1979 (Ozawa *et al.*, 1981; Tebayashi *et al.*, 1981).

Gnathostomiasis caused by *Gnathostoma spinigerum* and *G. hispidum* from raw fish sometimes occurs in Japan. The source of a recent infection with *G. hispidum* was imported

Table 2 Parasitic diseases and effects of mebendazole, praziquantel and thiabendazole

Drugs and illness	No. of cases	Collected cards	Effect (%)	Prognosis*				Side effect		
				C	R	D	U	Yes	No	
Mebendazole										
trichuriasis	126	96	85 (89%)	73	1		22	5		70
trichinellasis	55	4	2 (50%)	3			1			4
gnathostomiasis	13	4	3 (75%)	3			1	1		3
multi. echinococcus ^a	11	2	0 (0%)	1			1			2
others ^b	5	2	2 (100%)		1		1			2
Total	210	108 (51%)	92 (85%)	80	2	0	26	6 (7%)		81
Praziquantel										
clonorchiasis	87	40	36 (90%)	38	2			11		25
paragonimiasis										
westermani	17	11	8 (73%)	7	2		2	2		6
miyazakii	4	1	1 (100%)				1			1
fasciolasis	6	1	1 (100%)	1						1
schistosomiasis										
japonica	29	9	3 (33%)	4		2	3	2		1
haematobia	4	1	0 (0%)				1			
tape worm ^c	8	7	6 (86%)	6			1			6
others ^d	8									
Total	163	70 (45%)	55 (79%)	56	4	2	8	15 (27%)		40
Thiabendazole										
strongyloidiasis	106	75	65 (78%)	53	5	1	16	20		55
<i>Toxocara canis</i>	7	2	2 (100%)	1			1	2		
gnathostomiasis	5	3	1 (33%)	2			1	2		1
others ^e	2	1	1 (100%)	1				1		
Total	120	81 (68%)	69 (85%)	57	5	1	18	25 (31%)		56

a : *Echinococcus multilocularis*

b : others include *Angiostrongylus* (2 cases), *Toxocara canis* (1 case), larval migrans (1 case) and *Capillaria philippinensis* (1 case).

c : *Diphyllobothrium latum* (fish tapeworm, 7 cases), *Taenia solum* (pork tapeworm, 2 cases) and *Taenia saginata* (beef tapeworm, 1 case).

d : others include *Metagonium yokokawai* (5 cases) and *Sparganum mansoni* (3 cases).

e : others include *Capillaria philippii*. (1 case) and *Hymenolepis nana* (1 case).

* : C; cured; R; recurrent; D; died; U; unknown.

loaches from a neighboring Asian country (Ishii, 1983). Mebendazole was effective in reducing complaints due to subcutaneous or visceral larval migration.

Mebendazole was examined for treatment of *Echinococcus multilocularis* infection, alveolar hydatid disease (AHD). Clinical cases were reported from endemic regions in the Japanese island of Hokkaido.

Praziquantel

Praziquantel was used in 163 cases, of which clonorchiasis (liver fluke) made up 87

Table 3 Parasitic diseases and drug effects (continued)

Drugs and illness	No. of cases	Collected cards	Effect (%)	Prognosis*				Side effect	
				C	R	D	U	Yes	No
Quinacrine									
giardiasis	42	26	25 (96%)	17			8	3	16
tapeworm									
fish ^a	34	30	21 (70%)	11			10	17	12
beef ^b	9	7	6 (86%)	5			2	4	2
type unknown	40	18	4 (22%)	4			16	4	9
Total	125	81 (65%)	56 (69%)	37			36	28 (42%)	39
Pentamidine									
<i>P. carinii</i> ^c pneumonia 67	67	41 (61%)	20 (49%)	5		29	7	12 (38%)	20
Dehydroemetine									
hepatic amebiasis	28	14 (50%)	8 (57%)	9		1	4	3 (25%)	9
Pentostam									
Kala-Azar	3	2	2 (100%)	1		1		1 (50%)	1
leishmaniasis	2	0							
Suramin									
trypanosomiasis	1	1	1 (100%)	1					

a : *Diphyllobothrium latum*.

b : *Taenia saginata*.

c : *Pneumocystis carinii*.

* : C; cured, R; recurrent, D; died, U; unknown.

(53%) (Table 2). In clonorchiasis, the cure rate was 90% at a dosage of 25 mg/kg, given three times a day for 2 days.

In paragonimiasis (lung fluke) caused by *Paragonium westermani* and *P. miyazakii* (rare), praziquantel was shown to be effective with about a 70% cure rate.

The effect of praziquantel on *Schistosoma japonicum* infections could not be evaluated properly because new infections have ceased to occur in Japan since 1976 and all cases in this study were at chronic stages. Four cases of *S. haematobium* (Japan Overseas Cooperation Volunteers) originated from Egypt.

Adverse reactions to praziquantel were suspected in 15/54 cases (27%); including eruption (5 cases), drowsiness (4), abdominal pain (4) and diarrhea (2).

Thiabendazole

Thiabendazole was used in 120 cases, mainly for strongyloidiasis (Table 2). Infections with *S. stercoralis* occur regionally in the Southwest Islands including Okinawa Island. The cure rate was 87% but recurrence of the illness was often observed. Adverse reactions reported with thiabendazole were abdominal discomfort (13 cases), drowsiness (5) and eruption (2).

Other drugs

Quinacrine was used for the treatment of giardiasis (42 cases) and it provided a high rate

of cure. The drug was effective in recurrent cases after treatment with metronidazole. In one case of giardiasis, toxic reactions including liver damage and eruption occurred after treatment with quinacrine. Quinacrine was also used as an anthelmintic drug in 83 cases of tape worm infection.

Cases of hepatic amebiasis and *Pneumocystis carinii* pneumonia are increasing in number in Japan, resulting in increased uses of dehydroemetine and pentamidine, respectively.

A Japanese woman was infected with African trypanosoma, *Trypanosoma rhodesiense* and fortunately cured by administration of suramin (Negishi *et al.*, 1984).

Newly registered drugs

The present study describes the success of this first step toward effective administration of orphan drugs in this country. Among 16 orphan drugs listed previously, 4 drugs, thiabendazole, Fansidar, mebendazole and praziquantel were subsequently registered and are now available on the market. Two other drugs, chloroquine and pentamidine, are under consideration by the Central Pharmaceutical Affairs Council (CPAC) in MOHW. The data collected by this research group were widely utilized during evaluation for registration of these drugs.

DISCUSSION

Adverse reactions of the drugs studied by our group occurred often in this country, partly on account of metabolic differences of Asian races including Japanese from other races. In other instances, intoxication with chloroquine, chionoform and salidomide occurred by the result of prolonged treatment or large dosages. The pharmaceutical bureau in MOHW and pharmaceutical companies were legally accused of fostering intoxication with these drugs. The court trials concerning chionoform and salidomide were resolved by a compromise between plaintiffs and the supplying companies, however, court trials regarding chloroquine are still pending.

The reason why MOHW is also in litigation together with the supplying companies is because in Japan the approving organizations or review committees are charged with the same responsibilities as the accused when untoward effects result from the approved products. Because of the above legal liabilities and on-going court trials, CPAC recently has been careful in reviewing and approving new drugs. The same issues exist for decisions by ethical review committees in Japan for new medical trials on human subjects.

Due to careful attention to discussion and approval of drugs by CPAC, only data from preclinical studies strictly following the standardized methods defined by CPAC and carried out in Japan were the subject of consideration in the past. Nevertheless, data from preclinical studies conducted in foreign countries by methods, essentially equal to the Japanese standards, were recently considered valid by the Japanese CPAC.

Phase 1 and 2 clinical trials were conducted in normal and infected Japanese, respectively, by our research group. With the possibility of using preclinical studies from foreign countries and the data from clinical trials conducted by our group, pharmaceutical companies were encouraged and decided to apply for registration of a few orphan drugs and to offer these drugs for commercial sale as an action of social contribution, even though commercial merits would not be expected. Because of the above stated difficulties, 12 drugs still remain as orphan drugs in Japan.

In the USA, the Centers for Disease Control (CDC) Drug Service presently manages 9 drugs: diloxanide furoate (Furamide), dehydroemetine, nifurtimox (Lampit), sodium stibogluconate (Pentostam), melarsoprol (Mel B), suramin, bithionol, ansamycin, and quinine dihydrochloride (parenteral) as orphan drugs. Out of these 9 drugs, 5 are common to our orphan drugs. Our supply system for these drugs is incidentally the same as that in the USA, although our organization is composed of researchers without assigned staffs.

There are few reports dealing with clinical trials using newly developed antiparasitic drugs in Japan (Tanabe and Tanaka, 1986; Tanabe *et al.*, 1987). Data in the present study may reflect a new trend in parasitic infections in Japan because it is difficult for individual physicians to obtain antiparasitic orphan drugs from any other source by themselves.

In the present study, the total number of cases is not as large as that seen in tropical countries. However, in accordance with the increase in international travelers, parasitic diseases have become an important problem even in developed countries. From this point of view, the present study demonstrated an effective way for our country to provide orphan drugs needed to treat parasitic diseases.

Many problems have remained unsolved regarding parasitic diseases in our country. *Echinococcus multilocularis* infection occurs locally in Hokkaido and about 260 cases have been detected by clinical and pathological observations. According to recent reports based on serological surveys, echinococcus infections have been increasing in number (Takahashi, 1986). Amebiasis, giardiasis, strongyloidiasis and *Pneumocystis carinii* pneumonia are also increasing in number in association with STD or as opportunistic infections. Treatment of these diseases remains a problem and should be solved by developing new types of drug.

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寄生虫病薬の7年間の治験成績の検討 —稀用薬の入手緩和を求めて—

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昭和55(1980)年に発足した厚生省「輸入熱帯病の治療薬に関する研究」班では、寄生虫病の治療に稀用される薬剤の入手緩和を計ることを検討してきた。わが国の薬事で承認されていない寄生虫薬で、海外においては一部で既に使用されている16種の薬剤、すなわちファンシダール、クロロキン、プリマキン、キニーネ(注射液)、ファンシメフの抗マラリア薬とそれ以外のミンテゾール、メベンダゾール、ブラジカンテル、ペンダミジン(注射液)、アテプリン、デヒドロエメチン(注射液)、ペントスタム(注射液)、スラミン、スチィボフェン、ランピット、ピリメタミンを選定して輸入し、治験用に供給して臨床試験を実施してきた。昭和56(1981)から62(1987)年までの7年間に、920症例(マラリア患者では2種以上の治験薬が投与されても1症例として集計した)に薬剤を配布してきた。症例の内訳は201例(22%)がマラリア患者で、マラリア以外の投薬症例数はメベンダゾールが210例、ブラジカンテル163例、アテプリン125例、ミンテゾール120例、ペンタミジン67例、デヒドロエメチン28例、ペントスタム5例、スラミン1例である。このうち治療カードの回収できた症例について、有効性と副作用を検討して概略をまとめた。なお、今日ではファンシダール、ミンテゾール、メベンダゾール、ブラジカンテル、ペンタニジンの承認が済んでいる。

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