

EXPERIMENTAL CHEMOTHERAPY OF SCHISTOSOMIASIS

V — Laboratory trials with U.K. 3883, a 2-aminomethyltetrahydroquinoline derivative

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SUMMARY

U. K. 3883 (2-isopropylaminomethyl-6-methyl-7-nitro-1, 2, 3, 4 tetrahydroquinoline), a cyclic analogue of mirasan, is highly effective in mice experimentally infected with *Schistosoma mansoni* when administered by the oral, intraperitoneal and intramuscular routes. All mice treated with a single dose of 50 mg/kg and a single intramuscular injection of 25 mg/kg presented oograms changes. At these dose levels the hepatic shift of schistosomes and the percentage of dead worms in the liver were very pronounced. U. K. 3883 was found active in mice when incorporated in the diet at a concentration as low as 0.05%. This compound acts against maturing schistosomes and displays a high degree of chemoprophylactic activity in mice. Although the antischistosomal activity was rather low in hamsters (a single oral dose of 400 mg/kg was necessary to alter the oogram of all treated animals and to shift 100% of the worms towards the liver), U. K. 3883 was very effective in *Cebus* monkeys. Actually, interruption of egg-laying, was observed after a single oral administration of 50 mg/kg. U. K. 3883 was found devoid of a significant activity in mice infected with *S. japonicum*.

INTRODUCTION

U. K. 3883 (Pfizer Limited, Sandwich, England) is 2-isopropylamino-methyl-6-methyl-7-nitro-1, 2, 3, 4, - tetrahydroquinoline (Fig. 1). It has been shown that in members of the 2-aminomethyltetrahydroquinoline series, the antischistosomal activity is increased after the replacement of a diethylamino group by an isopropylamino group, the same occurring when a chlorine atom is replaced by a nitro group (RICHARDS & FOSTER¹⁴). CHEETAM & MESMER² demonstrated that U. K. 3883 exerts, in mice experimentally in-

fectured with an East African strain of *Schistosoma mansoni*, a very marked control regardless of the age of the infection when it is administered.

U. K. 3883, one of the most active compound of the 2-aminomethyl-tetrahydroquinoline series has been extensively studied in mice, hamsters and *Cebus* monkeys experimentally infected with *Schistosoma mansoni*. The results obtained in therapeutic as well as in protective tests are presented.

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MATERIALS AND METHODS

Laboratory trials in mice

Albino mice, weighing 18 to 20 g, were exposed to 120 ± 10 cercariae of *S. mansoni* (L. E. strain) by the tail immersion method (PELLEGRINO & KATZ⁸). The percutaneous route was used to infect mice with cercariae of *S. japonicum* shedded by naturally infected *Oncomelania nosophora* sent to Belo Horizonte, Brazil, from Kurume, Japan. Each animal was exposed to 25 to 35 cercariae.

In assessing the antischistosomal activity, U. K. 3883 was administered in a single dose or in a 5-day regimen, per os, intraperitoneally, intramuscularly (thigh muscular mass) or mixed in the diet. The therapeutic activity was evaluated by the following criteria: hepatic shift of schistosomes, dead worms in the liver, and oogram changes (PELLEGRINO & KATZ⁹). The animals were treated 6 weeks after exposure and killed and examined 7 days after dosing (single dose) or 3 days after completion of treatment (5-day regimen). In chemoprophylactic trials U. K. 3883 was administered per os (3 or 5 days) and the animals sacrificed 50 days after exposure.

Laboratory trials in hamsters

Adult hamsters (*Cricetus auratus*) were infected with 60 ± 10 cercariae (L. E. strain of *S. mansoni*) via the cheek pouch (PELLEGRINO et al.⁶).

U. K. 3883 was administered as a single dose per os, 6 weeks after exposure, at the levels of 400, 200, and 50 mg/kg. The animals were killed and examined 7 days after dosing. The criteria used for the assessment of therapeutic activity were the same as those mentioned for mice.

Laboratory trials in monkeys

The percutaneous route was used for exposing adult *Cebus apella macrocephalus* Spix, 1823 to $200 \pm$ cercariae (L. E. strain of *S. mansoni*). Rectal snips (20 to 40 mg) from *Cebus* monkeys were taken by mucosal curettage as described elsewhere (PELLEGRINO et al.¹⁰) the whole preparation being examined and all schistosome elements counted and classified. The number of

viable eggs per gram of rectal tissue was then calculated. U. K. 3883 was administered per os at the dose levels of 100, 50, 25 and 12.5 mg/kg (single dose). The results provided by serial mucosal curettages, before and after treatment, were used for the assessment of therapeutic activity. Effective schedules of treatment produce a gradual disappearance of immature and mature eggs in rectal snips thus decreasing the number of viable eggs per gram of rectal tissue (quantitative oogram).

Distribution of schistosomes and oogram in mice and hamsters

Mice and hamsters were killed by a blow on the neck. The schistosomes in the portal and mesenteric veins were recovered by perfusion using PELLEGRINO & SIQUEIRA'S¹² technique adapted to mice and hamsters. For oogram studies, press preparations of intestinal fragments (PELLEGRINO & FARRIA⁷) were microscopically examined and 200 to 300 viable eggs counted and classified according to their development stages (PRATA¹³; PELLEGRINO et al.¹¹). Changes in the oogram were considered significant when one or more stages of immature eggs were absent.

In mice and hamsters the number of dead worms in the liver was routinely determined by squashing the whole organ between two glass plates and examining the preparation with a dissecting microscope. The examination of the liver was performed after the organ had been perfused.

RESULTS

Therapeutic activity in mice

The results obtained after oral and parenteral administration of U. K. 3883 in mice are summarized in Table I. When administered for 5 consecutive days, a pronounced hepatic shift of schistosomes occurred at a dose level as low as 5 mg/kg/day, oogram changes being observed in 80% of mice. A comparable degree of activity was observed in animals which received a single oral dose of 25 mg/kg. All mice treated with a single oral dose of 50 mg/kg or 20 mg/kg for 5 consecutive days presented oogram changes.

TABLE I

Antischistosomal activity of U. K. 3883 in mice experimentally infected with *S. mansoni*. Oogram changes, distribution of schistosomes, and percentage of dead worms in the liver

Dose (mg/kg)	Number of mice	Animals dead	Mean worm burden	Distribution of schistosomes (%)			% of dead worms in the liver	% of mice with oogram changes
				Liver	Portal vein	Mesenteric vessels		
<i>Per os/day, 5 days</i>								
20	16	1	20.7	96.6	0.0	3.4	71.5	100.0
10	16	2	20.0	95.0	0.5	4.5	48.0	85.7
5	16	1	20.0	88.4	1.8	9.8	50.9	80.0
Control	10	2	21.8	18.9	18.9	62.2	0.0	0.0
<i>Per os/day, single dose</i>								
200	15	9	19.0	100.0	0.0	0.0	93.7	100.0
100	15	4	14.0	100.0	0.0	0.0	83.3	100.0
50	15	4	13.5	98.1	0.0	1.9	56.5	100.0
25	15	2	15.9	93.7	1.3	5.0	37.7	84.6
12.5	15	2	16.9	33.7	16.6	49.7	5.9	23.1
6.25	15	4	28.7	18.1	10.6	61.3	4.2	0.0
Control	20	2	16.3	16.0	22.7	61.3	0.0	0.0
<i>Per i.p./day, single dose</i>								
80	20	11	26.8	99.6	0.0	0.4	71.7	100.0
40	20	3	21.5	98.6	0.0	1.4	82.7	100.0
20	20	1	21.0	89.0	1.0	10.0	46.7	100.0
10	20	1	25.5	75.3	8.5	16.2	32.6	76.7
Control	10	1	26.8	18.3	21.5	60.2	0.0	0.0
<i>Per i.m./day, single dose</i>								
100	15	2	12.6	97.6	0.0	2.4	59.5	100.0
50	15	0	12.6	93.6	0.0	6.4	49.2	100.0
25	15	4	13.4	84.1	7.5	8.4	20.6	100.0
12.5	15	1	16.1	63.6	7.7	28.7	11.6	50.0
Control	15	0	19.0	14.0	18.1	57.9	0.0	0.0
<i>Percentages in diet (5 days)</i>								
0.1	24	3	17.0	97.4	0.2	2.4	44.0	100.0
0.05	10	1	12.0	98.2	0.0	1.8	44.0	100.0
0.025	15	2	10.5	82.4	4.4	13.2	20.6	20.6
0.01	15	5	13.4	22.4	26.1	51.5	3.7	10.0
Control	15	2	15.3	12.3	18.4	69.3	0.0	0.0

U. K. 3883 was also very effective when administered by intraperitoneal route or intramuscularly, especially in the latter case (Table I). Actually, a single i.m. injection of 25 mg/kg produced oogram changes in 100% of mice whereas by i.p. route a total

dose of 100 mg/kg (20 mg/kg/day x 5) was required to show a similar effect. It is interesting to remark that the degree of the hepatic shift and the percentage of dead worms in the liver was very pronounced.

It has been observed that incorporation of U. K. 3883 in the diet is very effective in producing oogram changes and hepatic shift of schistosomes in mice. In fact, when the diet contained as low as 0.05% of the drug, alterations of the oogram occurred in all animals and almost all worms were shifted towards the liver (Table I).

In mice infected with *S. japonicum* and dosed with U. K. 3883 per os, for 5 consecutive days, at the dose levels of 200, 100, 50, and 25 mg/kg/day, no oogram changes were observed. At the highest dosage schedule a slight hepatic shift (44.0%) occurred and 22.6% of schistosomes were found in the liver.

The chemoprophylactic activity of U. K. 3883 is clearly shown in Table II. When administered per os at the dose levels of

200 and 100 mg/kg, for 3 consecutive days, no schistosomes could be found in mice exposed to 120 cercariae (*S. mansoni*) on the second day of treatment, 2 hours after dosing. Only a few worms could be recovered from mice dosed with U. K. 3883 at the levels of 50, 25, and 12.5 mg/kg/day x 3 (Table II).

The activity of U. K. 3883 (200 mg/kg/day x 5, per os) on maturing schistosomes is shown in Table III. No schistosomes were found in groups of mice when treatment was started 2 days before and 2 and 7 days after exposure to *S. mansoni* cercariae. A few worms were collected by perfusion of the liver and mesenteric veins in the groups of mice (5, 6, 7, and 8) treated 14, 21, 28, and 35 days after exposure. It is interesting to remark that in these animals no eggs could be found in intestinal fragments although adult and paired schistosomes were present in mesenteric vessels. No protective activity was observed in group 1, when exposure to cercariae was performed 2 days after completion of treatment (Table III). In this group the distribution of schistosomes within the hepatic-portal system as well as the oogram were similar to the figures in the control animals.

Therapeutic activity in hamsters

The activity of U. K. 3883 in hamsters (Table IV) was relatively low when compared with the results obtained in mice (Table I) treated with a single oral dose. Alterations of the oogram in all animals and complete hepatic shift of worms occurred at the dose level of 400 mg/kg. No oogram changes were observed in the group treated with 50 mg/kg although the hepatic shift was still evident (65.8%) at this level (Table IV).

TABLE II

Chemoprophylactic activity of U.K. 3883 in mice. On the 2nd day of treatment, 2 hours, after the administration of U.K. 3883, the animals were exposed to 120 *S. mansoni* cercariae. Mice were killed and examined 50 days after exposure

Schedule of treatment (mg/kg/day x 3, per os)	Number of mice	Animals dead	Mean worm burden
200	11	1	0.0
100	11	2	0.0
50	11	1	2.0
25	11	3	5.6
12.5	11	1	6.9
Control	11	0	28.3

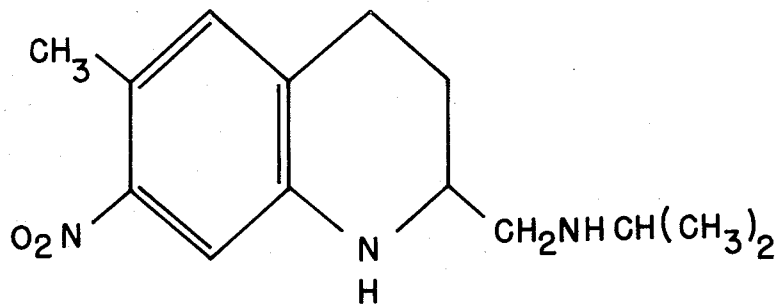


Fig. 1 — Chemical structure of U.K. 3883

TABLE III

Chemophylactic activity and effect of U. K. 3883 on maturing schistosomes (*S. mansoni*) in mice. The animals were killed and examined 50 days after exposure (120 cercariae per mouse)

Groups	Beginning of treatment (200 mg/kg/day x 5, per os) Days before (-) or after (+) exposure	Number of mice	Animals dead	Mean worm burden	Distribution of schistosomes (%)			% of dead worms in the liver	% of mice with oogram changes
					Liver	Portal vein	Mesenteric vessels		
1	- 6	20	4	18.4	28.3	22.9	48.8	0.0	0.0
2	- 2	20	4	0.0	0.0	0.0	0.0	0.0	No eggs
3	+ 2	20	5	0.0	0.0	0.0	0.0	0.0	No eggs
4	+ 7	20	8	0.0	0.0	0.0	0.0	0.0	No eggs
5	+ 14	20	6	0.8	50.0	0.0	50.0	33.3	No eggs
6	+ 21	20	1	3.2	60.3	17.3	22.4	6.9	No eggs
7	+ 28	20	4	1.5	33.3	0.0	66.7	0.0	No eggs
8	+ 35	20	4	2.2	93.5	0.0	6.5	80.6	No eggs
9	Control	20	3	17.7	25.6	29.6	44.8	0.0	0.0

TABLE IV

Antischistosomal activity of U.K. 3883 in hamsters experimentally infected with *S. mansoni*. Oogram changes, distribution of schistosomes, and percentage of dead worms in the liver. The animals were killed and examined 7 days after dosing

Schedule of treatment (mg/kg/day x 1, per os)	Number of hamsters	Animals dead	Mean worm burden	Distribution of schistosomes (%)			% of dead worms in the liver	% of hamsters with oogram changes
				Liver	Portal vein	Mesenteric vessels		
400	6	3	43.5	100.0	0.0	0.0	54.2	100.0
200	6	3	37.5	91.4	1.9	6.7	52.9	33.3
50	6	1	38.0	65.8	22.4	11.8	3.9	0.0
Control	6	0	42.7	20.2	15.4	64.4	0.0	0.0

TABLE V

Antischistosomal activity of U.K. 3883 in *Cebus* monkeys experimentally infected with *S. mansoni*. Parasitological follow up (quantitative oogram)

Monkeys	Duration of infection before treatment	Schedule of treatment	Days before (-) or after (+) dosing	Oogram from rectal snips					Dead eggs and shells	Number of viable eggs per gram of rectal tissue	Remarks
				Stages of viable eggs							
				1st	2nd	3rd	4th	Mature			
1	5 months	100 mg/kg per os (single dose)	- 7	25	18	51	18	124	58	9328	Interruption of egg-laying
			- 1	65	112	105	47	348	116	22566	
			+ 7	0	0	0	0	119	66	4917	
			+ 12	0	0	0	0	9	109	32	
			+ 14	0	0	0	0	3	25	120	
			+ 19	0	0	0	0	0	38	0	
			+ 29	0	0	0	0	0	7	0	
			+ 65	0	0	0	0	0	54	0	
			+ 77	0	0	0	0	0	3	0	
			+ 95	0	0	0	0	0	2	0	
+111	0	0	0	0	0	6	0				
+120	0	0	0	0	0	27	0				
2	5 months	50 mg/kg per os (single dose)	- 8	15	8	14	5	47	265	5855	Interruption of egg-laying
			- 1	66	33	87	4	378	500	30900	
			+ 7	0	0	0	0	123	244	5418	
			+ 12	0	0	0	0	17	267	821	
			+ 19	0	0	0	0	0	125	0	
			+ 29	0	0	0	0	0	254	0	
			+ 44	0	0	0	0	0	24	0	
			+ 65	0	0	0	0	0	51	0	
			+ 77	0	0	0	0	0	15	0	
			+ 95	0	0	0	0	0	20	0	
+111	0	0	0	0	0	24	0				
+120	0	0	0	0	0	36	0				
3	7 months	25 mg/kg per os (single dose)	- 41	63	105	174	99	638	343	41984	No antischistosomal activity
			- 2	54	34	62	33	250	231	27060	
			+ 5	132	46	120	40	640	915	37906	
			+ 9	107	104	180	50	906	382	63638	
			+ 20	130	76	128	148	552	217	43083	
			+ 30	318	124	136	116	794	691	60952	
+ 40	104	72	126	72	398	192	39793				
4	7 months	1st course:	- 41	19	1	8	4	165	54	10368	No antischistosomal activity
			- 2	5	12	1	1	294	64	14357	
			+ 5	36	8	3	1	72	55	5286	
			+ 9	64	9	25	9	162	113	13251	
			+ 20	71	10	14	14	99	58	10833	
			+ 56	28	27	73	26	71	51	10663	
	7 months	2nd course: 50 mg/kg	- 1	3	2	12	11	70	34	9782	Interruption of egg-laying
			+ 8	0	0	0	0	14	25	755	
			+ 18	0	0	0	0	0	2	0	
			+ 52	0	0	0	0	0	4	0	
			+ 76	0	0	0	0	0	3	0	
			+131	0	0	0	0	0	1	0	

Therapeutic activity in monkeys

Serial mucosal curettages in *Cebus* monkeys demonstrated that interruption of egg-laying occurred in monkeys treated with a single oral dose of 100, and 50 mg/kg (Monkeys 1 and 2, Table V). U. K. 3883 was completely ineffective at the levels of 25, and 12.5 mg/kg (Monkeys 3 and 4).

DISCUSSION

It has been shown that whereas compounds belonging to the mirasan series are inactive in primates (GÖNNERT⁵; STANDEN¹⁵), several of the 2-aminomethyltetrahydroquinolines are effective following intragastric administration to vervet monkeys (*Cercopithecus aethiops*) infected with *S. mansoni* (RICHARDS & FOSTER¹⁴). Actually, these Authors have found that a single dose of U. K. 3883 (50 mg/kg) is curative for vervet monkeys.

According to FOSTER¹⁴, U. K. 3883 is more active against male worms than against females, but removal of male worms from a host leads to an immediate cessation of egg-laying by the residual females. By a single oral administration to mice infected with an East African strain of *S. mansoni* the ED₉₉ value, as defined by mortality of male worms 14 days after the final treatment, was 87 mg/kg. This figure is reduced by 25% if living, phagocytized worms are assumed to have died eventually. Assessing mortality of male worms after 14 days, U. K. 3883 by a single oral dose had a superiority over hycanthon, lucanthon and ambilhar of approximately 2, 5, and 30 times respectively (FOSTER¹⁴). We have confirmed the finding that U. K. 3883 is more effective against male schistosomes than against females.

The results here reported demonstrate that U. K. 3883 is highly effective in mice when administered by different routes: oral, intraperitoneal, intramuscular. In addition, U. K. 3883 is active against *S. mansoni* infection in mice when incorporated in the diet at a concentration as low as 0.05%. One particular feature of U. K. 3883 is that it acts against maturing schistosomes and displays a high degree of chemoprophylactic activity in mice.

CHEETAM & MESMER² reported that treatment with U. K. 3883 (17.5 mg/kg given orally for 5 consecutive days) during the first week of infection led to a reduction of 95% of the worm burden in mice. Infections of 3 to 4 weeks of age were the most resistant to therapy, but treatment even at this stage resulted in a reduction of 51% in the ultimate worm load. Our data showed that no schistosomes could be recovered from mice when treatment as started 2 days before and 2 and 7 days after exposure. When treatment (5 days) was initiated 2 to 5 weeks after exposure, only a few worms could be recovered but no eggs were found in press preparations from intestinal fragments. A similar chemoprophylactic effect was described by CAMPBELL & CUCKLER¹ for a 2-phenyl quinoline compound.

Although the antischistosomal activity was rather low in hamsters, U. K. 3883 was very effective in *Cebus* monkeys. Interruption of egg-laying was observed after a single oral administration of 50 mg/kg.

The antischistosomal activity of U. K. 4271, a 6-hydromethyl derivative of U. K. 3883, reported by RICHARDS & FOSTER¹⁴ and FOSTER & RICHARDS⁴ was confirmed in our laboratories in *Cebus* monkeys.

Contrarily to what was observed in animals experimentally infected with *S. mansoni*, U. K. 3883 was found devoid of significant activity in mice infected with *S. japonicum*.

Further work with the novel series of 2-aminomethyltetrahydroquinoline, including different analogues of the parent compound U. K. 3883, is in progress.

RESUMO

Terapêutica experimental da esquistossomose V — Ensaios laboratoriais com o U. K. 3883, derivado da 2-aminometiltetrahidroquinolina

Foi demonstrado que o U. K. 3883 (2-isopropilamino-6-metil-7-nitro-1,2,3,4 tetrahidroquinolina), um análogo cíclico do mirasan, é altamente eficaz em camundongos experimentalmente infetados com o *Schistosoma mansoni* quando administrado por via oral, intraperitoneal e intramuscular. Alte-

rações do oograma foram observadas em todos animais tratados com uma única dose de 50 mg/kg (oral) e 25 mg/kg (intramuscular). Nestas doses, o deslocamento de esquistossomos para o fígado, bem como a percentagem de vermes mortos encontrados neste órgão foram muito elevados. O U. K. 3883 foi ativo quando incorporado na dieta de camundongos na proporção de 0,05%. Este composto atua contra esquistossomos ainda imaturos e possui um alto grau de atividade quimioprofilática em camundongos. Enquanto que a atividade esquistossomicida do U. K. 3883 foi relativamente baixa em hamsters (uma dose única de 400 mg/kg foi necessária para alterar o oograma de todos os animais tratados), em macacos *Cebus* foi muito elevada. De fato, interrupção da postura pôde ser observada após a administração de uma dose oral única de 50 mg/kg. O U. K. 3883 não foi eficaz em camundongos experimentalmente infetados com o *S. japonicum*.

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