A three year follow-up of chemotherapy with oxamniquine in a Brazilian community with endemic schistosomiasis mansoni*

A. C. SLEIGH,[1] K. E. MOTT,[1] J. T. FRANÇA SILVA,[2] T. M. MUNIZ,[2] E. A. MOTA,[3] M. L. BARRETO,[4] R. HOFF,[1] J. H. MAGUIRE,[1] J. S. LEHMAN[+] AND I. SHERLOCK[2]

[1]Dept. of Tropical Public Health, Harvard School of Public Health, Boston, MA, USA
[2]Centro de Pesquisas Gonçalo Muniz da Fundação Oswaldo Cruz, Salvador, Bahia, Brazil
[3]ICOMI Fellow, Federal University of Bahia, Brazil
[4]Dept. de Medicina Preventiva, Federal University of Bahia, Brazil
[+]Deceased.

Summary

Oral oxamniquine was tested as a control strategy for endemic schistosomiasis in a rural area of Bahia, Brazil. Adults were treated with a single dose (12·5 to 15 mg per kg) and children (<12 years old) with a total of 20 mg per kg in two doses. The 191 (infected) persons treated represented 69% of the infected population in the study area. Follow-up stool examinations (Kato-Katz method) at one, 3, 6, 13, 25 and 33 months showed the cure rate declining from 80% at three months to 46% at 33 months. Over one half of those not cured showed a decrease in egg counts throughout the follow-up which, after 33 months, remained 66% below the pre-treatment levels. Stool examinations conducted on all study area residents during three years before chemotherapy showed the prevalence and intensity of *Schistosoma mansoni* infection to be high and stable. 33 months after the chemotherapy the prevalence was 41% and for infected individuals the geometric mean egg count was 121 epg, a decline of respectively 35% and 40% from pre-treatment levels for each index. Chemotherapy of infected persons with oxamniquine protected the community as a whole from high worm burdens for almost three years, although at this point the prevalence began to rise towards pretreatment levels.

Introduction

Oral oxamniquine has been shown in Brazil to be an efficacious treatment for *Schistosoma mansoni* infection (KATZ, 1977). To test chemotherapy with oxamniquine as a control strategy we treated infected residents of a community in Brazil where schistosomiasis is endemic and evaluated the change in prevalence and intensity of schistosomal infection in the community (the study population) and the cure rate and reduction in egg excretion in those treated (the treated population) over the following three years.

Materials and Methods

The Study Design

The study population included all residents (mostly subsistence farmers) living in a 25 km² area within the Municipio of Castro Alves in the State of Bahia, Brazil. The characteristics of endemic schistosomiasis in this population had been defined by earlier studies; faecal examinations had been done in January, 1974, by a gravity sedimentation method, and in April, 1974, by a modification of the Bell method (LEHMAN et al., 1976). Another stool survey was performed in January 1977 (gravity sedimentation method). Treatment was then offered to all individuals shown to be passing schistosome eggs on one or more of the three previous examinations. Stools were collected a fourth time immediately before treatment (April 1977) and processed by the modified Bell method. This was to permit evaluation of the stability of schistosomal infection in the population between April, 1974, and April 1977 in terms of prevalence and intensity as revealed by the two Bell examinations.

Most evaluations of the effectiveness of oxamniquine therapy done in Brazil since 1974 have used the Katz-modified Kato faecal examination method (KATZ et al., 1972). To facilitate comparison we therefore also processed the April, 1977 pretreatment specimens by the Kato-Katz method, and thereafter used this technique exclusively for faecal examinations performed on treated individuals at one, 3, 6, 13, 25, and 33 months posttreatment and at 13, 25, and 33 months on the untreated population. A commercially available kit was employed (Kit a.k. A. K. Indústria e Comércio Ltda., Belo Horizonte, Brazil) which has a plastic template that delivers a mean weight of 42 mg of faeces. From 75 to 90% of the study population were represented in the pre-and postchemotherapy stool surveys (see Table I).

Table I—Proportion of the study population represented in the pre- and post-chemotherapy stool surveys[+]

Survey (method)	Study area population*	Number submitting stools	Response rate %
April 1974 (Bell)	445	360	81
April 1977 (Bell)	442	425	96
April 1977 (Kato-Katz)	442	330**	75
May 1978 (Kato-Katz)	420	340	81
May 1979 (Kato-Katz)	415	336	81
January 1980 (Kato-Katz)	402	330	82

[+]Results of the January 1974 and 1977 qualitative surveys (sedimentation method) are not shown.   Chemotherapy was administered immediately after the April 1977 survey.
*Based on the annual census preceding each stool survey.
**The Bell and Kato-Katz counts in April 1977 were performed on the same stools.   However, as some Kato slides were damaged, not all stools were examined by both methods.

Table II—Comparison of the post-treatment subgroups to the treated population

	Treated population	Post-treatment follow-up subgroups					
		one month	3 months	6 months	13 months	25 months	33 months
Number of subjects	135	112	82	61	102	96	80
Mean age (years)*	27	27	25	21	28	26	30
Geometric mean egg** count (epg) pre-treatment	224	248	225	184	245	241	220
Proportion of pre-treatment** egg counts > 100 epg (%)	73	75	70	64	73	72	69
Proportion of children < 12*** years old (%)	31	32	35	39	30	32	28

*Based on the October 1977 census
**Based on April 1977 pre-treatment Kato-Katz counts
***Age based on Oct. 1976 census.

Table III—Cure rates observed after oxamniquine therapy

	Months post-chemotherapy					
	1	3	6	13	25	33
% children* cured (N)**	56(36)	69(29)	50(24)	60(30)	39(31)	36(22)
% adults cured (N)	86(76)	87(53)	89(37)	71(72)	75(65)	50(58)
% cured over-all (N)	76(112)	80(82)	74(61)	68(102)	64(96)	46(80)

 * < 12 years old at October 1976 census
**N = denominator for the percentage calculation

Table IV—Egg count reduction in subjects not cured by oxamniquine

	Months post-chemotherapy					
	1	3	6	13	25	33
Number of subjects with egg counts higher than or equal to pre-treatment level	7	4	4	8	13	19
Number of subjects with egg counts lower than pre-treatment level	20	12	12	25	22	24
Arithmetic mean of the percentage egg count reductions ($\pm 95\%$ confidence interval)*	74 ± 10	63 ± 13	76 ± 13	76 ± 7	71 ± 10	66 ± 10

*Analysis included only the non-cured subjects with a post-treatment count lower than the pre-treatment count.   % egg reduction =

$$\frac{(\text{pre-treatment count—post-treatment count})}{\text{pre-treatment count}} \times 100$$

95% confidence limits calculated from the formula $\bar{x} \pm (t_{n-1,0.05}) (s/\sqrt{n})$.
$\bar{x}$ = mean; s = standard deviation; $t_{n-1,0.05}$ = one tail value for t at $0\cdot05$ probability level and n-1 degrees of freedom

Table V—Comparison of prevalence and intensity* of *Schistosoma mansoni* **infection in the total study population before and after selective chemotherapy with oxamniquine of a portion (191 persons) of the population**

	April 1977**	May 1978	May 1979	January 1980
Number of persons with stool examination	330	340	336	330
Prevalence of infection (percentage)	63	32	31	41
Geometric mean egg count of infected individuals (epg)	201	88	114	121
Arithmetic mean egg count of infected individuals (epg) $\pm$ SEM	514 ± 73	173 ± 26	353 ± 74	321 ± 46

*All examinations performed by the Kato-Katz method
**Pre-treatment examination

Administration of Oxamniquine

After verbal explanation of the purpose and risks, 191 persons were treated in the presence of a physician (J.F.S.). Oxamniquine was provided (Pfizer Ouimica Ltda., São Paulo) as a syrup containing 50 mg per ml (for children less than 12 years old) or as 250 mg capsules.   Each person was weighed.   Children less than 12 years old received 20mg per kg divided into two equal doses six to eight hours apart and older individuals received $12\cdot5$ to 15 mg per kg as a single oral dose.   Pregnancy, jaundice, ascites, liver failure or any overt illness were contraindications to therapy although actually only the few women known or suspected to be pregnant were excluded. All persons were requested to remain at the treatment post for two hours and to report symptoms to the physicians who remained in the area for 48 hours.

Results

1. *Complications of Therapy*

Only one person, a 21-year-old male, experienced a serious problem.   He had returned home within half an hour of ingesting the oxamniquine and soon felt dizzy, collapsed and developed rapid movements of his arms and legs.   The patient was observed by us and found to be drowsy and confused.   He had an enlarged liver, no palpable splenomegaly, a pre-treatment Bell count of 255 eggs per ml of stool and no prior history of convulsions.   Although he left the area shortly thereafter, his family reports that he has had no further problems.

2. *Effect of Oxamniquine Therapy*

a. *Impact on the treated population*: For analysis we defined the treated population as consisting of the 135 treated persons shown to be excreting eggs

on the April 1977 pre-treatment Kato-Katz examination. Of this group of 135 persons, post-treatment stool examinations were performed on 112 at one month, 82 at three months, 61 at six months, 102 at 13 months, 96 at 25 months, and 80 at 33 months. Each of these follow-up subgroups was compared to the total treated population for inadvertent bias with reference to age and intensity of infection that might influence the results (KATZ, 1977; McMAHON, 1978) (Table II). Only the six months' group was not representative.

Cure rates* declined from a high of 80% at 3 months to 46% at 33 months (Table III). Adult cure rates were substantially higher than those for children, especially noteworthy after 25 months (75% versus 39%). At the six follow-up examinations, between 24% and 46% of those not cured maintained egg counts at the original or higher levels. However in those non-cured individuals with a reduced egg output the decrease was significant and sustained (Table IV).

3. Impact on the study population

Comparison of the results of the two pre-chemotherapy Bell method stool surveys (April 1974 and 1977) showed that the prevalence rates changed only by 1% and that the geometric mean egg count for infected individuals changed by 12·6%. Thus schistosomal infection in the study population in the pre-treatment period was remarkably stable. The pre-treatment prevalence in the study area for the April 1977 Kato-Katz survey was 63%. Therefore the 191 persons treated represented 69% of those infected in the study population. As a consequence of treatment the crude potential contamination factor (arithmetic mean egg count for infected persons multiplied by the prevalence) was decreased 83% at 13 months, 66% at 25 months and 59% at 33 months after the chemotherapy (Table V). However, we could not demonstrate a decline in the over-all or age-stratified incidence rates, a variable probably influenced by the intermittent positivity of those with marginal egg count, as well as by the acquisition of new infections.

Discussion

Enthusiasm for oxamniquine in the treatment of S. mansoni infections stems from its effectiveness, its ease of administration, and its apparent innocuousness. However, there have now been 11 cases reported of transient behavioural disturbances following oxamniquine ingestion (KATZ et al., 1976; COURA, 1975; CAMPOS et al., 1976) and BINA et al. (1976) have reported a case of a 61-year-old alcoholic with a history of lapses of consciousness who suffered a generalized convulsion one hour after ingestion of the drug. We could not elicit a history of previous convulsions or psychic disturbances in the case of oxamniquine-associated epileptiform seizures that we report here. It would seem prudent to consider such a history a

contraindication to oxamniquine therapy and to observe all patients for two hours after the drug is ingested.

The cure rates reported here resemble those obtained in earlier trials (KATZ, 1977; BINA, 1977). The drug was less efficacious in children than adults, as previously noted for oxamniquine and other schistosomicidal compounds (McMAHON, 1978). However, schistosomal chemotherapy must be evaluated in broader terms for a reduction in the faecal egg count implies a concomitant decline in the worm burden and in the amount of environmental contamination, the dual goals of schistosomiasis control. Over one half of those not cured in this study maintained a decreased egg excretion throughout the 33 months of follow-up and these subjects, along with those who were cured, have benefited substantially from the chemotherapy. Treated persons not showing reduced egg counts may reflect the resistance of parasites to oxamniquine (GUIMARÃES et al., 1979).

Despite a reduction of 83% in the crude potential contamination factor, one year after treatment we could not demonstrate a decline in transmission. The decreasing cure rate over time, especially notable in children, may reflect reinfection (KATZ et al., 1978). However, we have shown that mass chemotherapy with oxamniquine, even with a coverage of only 69% of the infected individuals, can give the community as a whole a respite from high schistosomal burdens for at least three years, at which point mean egg counts were still almost 50% below pre-treatment levels. However at the three-year mark cure rates had fallen sharply and the community prevalence of infection was beginning to rise, implying that the protection afforded by the chemotherapy was waning. Probably the appropriate role for community based chemotherapy is to free the population from heavy infections while a definitive solution is developed, i.e., education of the population, improved sanitation, and the development of safe and convenient water supplies.

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*Cure rates are defined as the percentage of subjects at any particular follow-up examination with stools negative for schistosome eggs.

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