

# Suicide and Neuropsychiatric side effects in patients taking Niridazole

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## SUMMARY

The suicide of a young woman who had just completed a course of niridazole prompted this review of 72 inpatients who had been treated with niridazole between January 1974 and June 1975 at the University Teaching Hospital, Lusaka (U.T.H.) There were seven instances of neuropsychiatric disturbances, including one other suicide. All seven patients with side-effects were suffering from a pathology in addition to Schistosomiasis. Six were among the 37 patients infested with Schistosoma Mansoni, an incidence of 17%. The dose of niridazole was significantly higher in the patients with neuropsychiatric side-effects. Phenobarbitone had no effect on the incidence of side-effects.

## INTRODUCTION

Niridazole, marketed by CIBA as Ambilhar, has been widely used in the treatment of Schistosomiasis since 1964. There have been several reports on its neuropsychiatric side effects. This retrospective study, prompted by the episode described in the case report (which is not included in the series), is of inpatients treated with niridazole at the University Teaching

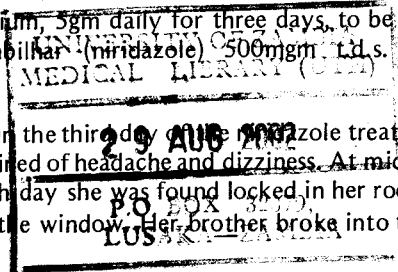
Hospital, Lusaka, between January 1974 and June 1975. One hundred and thirty files were examined, of which 58 were rejected due to early discharge without follow-up of the patient. This left 72 cases in the study.

## CASE REPORT

At 4 a.m. on 4/9/75 a 33 year old Zambian woman, married with three year old twins, was admitted to the University Teaching Hospital, Lusaka, with a short history of confusion, hallucination and attempted suicide.

She had been seen in the O.P.D. on the 26th August where she had given a three-month history of abdominal pain and malaise. She was found to have Hookworm ova in the stool and Shistosoma Haematobium ova in the urine. She was treated with Bephenium, 5gm daily for three days, to be followed by Ambilhar (niridazole) 500mgm t.i.d.s. for five days.

On the third day of niridazole treatment she complained of headache and dizziness. At midnight on the fifth day she was found locked in her room banging on the window. Her brother broke into the room



and brought her to the U.T.H.

She was a fit woman, not pale or jaundiced, and with no abnormal physical findings; there was no hepatosplenomegaly. There was no history of serious illness and no past or family history of psychiatric disorder. She was confused, not knowing where she was, and hallucinating, claiming to see her dead father. However, she was cooperative and allowed herself to be injected with 200mgm of chlorpromazine, although she was convinced that the hospital staff were in league with her brother in trying to kill her.

In the morning she pretended to be asleep and did not respond to questioning. When the other patient was taken out of the two-bedded ward she took the opportunity to jump at the closed window, breaking the glass and falling two floors. She sustained severe injuries and died four hours later. A post-mortem was not done.

### RETROSPECTIVE SURVEY

There were 72 patients in the series, of whom 42 were suffering from some pathology in addition to Schistosomiasis. Schistosomiasis was diagnosed by stool and urine microscopy in most cases, by rectal snip in 24 cases, by liver biopsy in 2 cases and by vulval biopsy in one case. In most cases the treatment for Schistosomiasis was started after the treatment of the accompanying disease. Niridazole was given in doses varying from 17.8 mgm/kgm to 37.5 mgm/kgm for periods of 5 to 10 days. Phenobarbitone was given concurrently to 53 patients.

Seven of the 72 patients suffered from Neuropsychiatric side-effects and the data on these seven is shown in Table 1.

TABLE 1

Case	Diagnosis	Sh.	L.	S.	Bil.	GOT	GPT	Side-effect	Day
1. F,55	Pyelonephritis	H	3	4	0.3	33	14	Psychosis	3
2. F,30	Anaemia	M	3	0	1.5	9	7	Psychosis	5
3. F,20	Anaemia	M	4	15	6	37	26	Psychosis	5
4. F,21	Cirrhosis	H+M	7	28	0.6	6	4	Psychosis	4
5. F,37	Anaemia+cirrhosis	M	0	0	0.9	3	20	Fits	1
6. M,65	Pneumonia	M	0	2	?	?	?	Confusion	5
7. M,18	Anaemia	M	0	1	?	?	?	Suicide	7

(L. and S. refer to size of liver and spleen in cms.)  
H = S. haematobium; M = S. Mansoni.

Case 1 absconded the day after the psychosis developed; cases 2,3,4 and 6 remained and recovered from their psychoses or confusion. Case 5 had no more fits.

Case 7, an eighteen year old boy, was admitted with iron-deficiency anaemia (Hb 3.2gm%) and was given two pints of blood and then put on oral iron therapy. A week after admission his Hb was 7.1gm% and at this stage he was given niridazole 500mgm

t.d.s. At that time he was in good health and weighed 40kgm. His spleen was just palpable. On the fourth day of treatment he complained that his guardian was treating him badly. On the sixth day, when his discharge was being considered, he said that if he went home he would be neglected. He was not confused and his behaviour was normal. On the seventh day he was found dead in the lavatory, having hanged himself with his pyjama cord from a handle three feet from the floor.

### RESULTS

Of the 72 patients with Schistosomiasis 42 suffered from an additional pathology and the seven patients with side-effects were found among these 42. Of the 72 patients 35 had *S. Haematobium* infestations, one of whom had neuropsychiatric side-effects, 26 had *S. Mansoni* infestations, five with side-effects, and 11 had mixed infestations, one with side-effects. Thus six out of 37 patients (17%) who had *S. Mansoni* and were treated with niridazole suffered from neuropsychiatric side-effects. Thirty-seven patients had no hepatosplenomegaly and of these two had side effects. Thirty-five had a palpable liver or spleen or both and of these five had side-effects. Fifty-three patients received phenobarbitone along with the niridazole and 19 were treated with niridazole alone. There were 5 side-effects in the former group and 2 in the latter. The weight of the patient and the dosage of niridazole were both known in 31 cases only (due to the fact that the treatment sheets or temperature charts were missing in half the files).

Statistical significance of results (B. Edwards)

The incidence of neuropsychiatric side-effects with *Haematobium* and *Mansoni* infestation, with and without other pathology, with and without hepatosplenomegaly and with and without phenobarbitone is shown in Table 2. Beneath the number of cases actually observed is shown the number expected to occur under the hypothesis that there is no association between the classifications. It is assumed for Table 2a that there could not be a higher incidence of side-effects with *Haematobium* than with *Mansoni* infestations, for Table 2b that other pathology in addition to Schistosomiasis would be unlikely to decrease the incidence of side effects, for table 2c that hepatosplenomegaly would increase the susceptibility to side-effects, and for table 2d that addition of phenobarbitone to the niridazole regimen would be unlikely to increase the incidence of side-effects. With these assumptions one-tailed tests of statistical significance are appropriate. Because the lowest expected numbers are less than 5 in all cases, the approximate Chi<sup>2</sup> test of significance could not be used, necessitating the exact test for 2x2 contingency tables. The sum of the probabilities of the occurrence of the observed tables and those less likely under the hypothesis of no association between classifications were calculated

according to Bailey (1959) and is shown under each table. The significance level, that is the probability of rejecting the hypothesis when it is true, was chosen to be 0.05.

TABLE II

		2a		2b	
		Infestation		Other pathology	
		Haem	Mans	Absent	Present
Side-effects:	Obs:	1	5	0	7
	Exp:	3.4	2.6	2.8	4.2
No side-effects:	Obs:	34	21	29	36
	Exp:	31.6	23.4	26.2	38.8
Hypothesis probability, p:		.0456		0.0219	

		2c		2d	
		Hepatosplen		Treatment	
		Present	Absent	Nir.	Nir+phenob.
Side-effects:	Obs:	5	2	2	5
	Exp:	2.3	3.7	1.8	5.2
No side-effects:	Obs:	30	35	17	48
	Exp:	11.7	19.3	17.2	47.8
Hypothesis probability, p:		.193		.598	

In each case the critical region for p is less than 0.05.

The table confirms that side-effects are significantly less likely in patients with Haematobium infestations than with Mansoni infestations, occurring in 2.9% of Haematobium cases compared to 23.8% of Mansoni. Cases with mixed infections are not included in table 2a. Table 2b shows that the incidence of side-effects when there is an additional pathology is 19.4% compared to Schistosomiasis alone when no side-effects occurred; this is statistically significant. Although table 2c shows side-effects in 16.7% of cases with hepatosplenomegaly compared to 5.7% cases without, there is no statistical indication that this is not due to chance. The incidence of side-effects when phenobarbitone was given with niridazole was 11.8% compared to 10.4% with niridazole alone implying that phenobarbitone is ineffective, as shown in table 2d.

In 31 cases the patients' weight and the niridazole dose were known. The doses per kilogram were calculated and compared in patients with and without side-effects. The results are shown in Table 3.

TABLE III

	Side-effects	No side-effects
No. of pat.	6	25
Mean dose mgm/kgm	33.9	27.3
Std. Dev.	3.6	4.5
F	2.30	
Fcr	6.28	
t	-3.34	
tcr	-2.76	

The mean dose (33.9mgm/kgm/day) given to patients who had side-effects was significantly higher than that given to patients without side-effects (27.3

mgm/kgm/day) implying that the dose is important in the likelihood of developing neuropsychiatric side-effects.

DISCUSSION

Since its introduction in 1964 the heterocyclic nitro-compound, 1-(5-Nitro-2-thiazolyl)-2-imidazolidinone (niridazole) has been widely and effectively used in the treatment of all types of Schistosomiasis in Africa, South America and the Far East, and has been particularly useful in the mass treatment of out-patients. Side-effects include headache, nausea, anorexia and malaise, and, more rarely, epistaxis and papular skin eruptions. Neuropsychiatric disturbances have been reported since 1965.

Jordan, from Tanzania, reported three instances of neuropsychiatric side-effects, two patients with hallucinations and one with mania, out of 76 adults with *S. Mansoni* treated with 25mgm/kgm niridazole. DaSilva, from Rio de Janeiro, reported two instances of psychosis and one of convulsions out of 48 adults with *S. Mansoni* treated with 20-40mgm/kgm. Pesigan et al, from Manila, treating 16 patients with *S. Japonicum* found that two developed convulsions and one psychosis. McMahon and Kilala, from Tanzania, reported on 92 male African adults with *S. Mansoni* treated with 25mgm/kgm. Five had CNS side-effects, two patients having convulsions, two confusion and one developing psychosis. Davidson, from Lusaka Central Hospital, reported on 20 patients, fifteen with *S. Haematobium* and five with *S. Mansoni*; there were EEG changes in eight patients treated with niridazole and there were CNS side-effects in four (coinciding with EEG changes in two cases). One of the patients attempted suicide. Abdallah and Saif, from Cairo, treated 859 cases with 25mgm/kgm niridazole and found neuropsychiatric side-effects, mainly confusion, hallucination and fitting, in 0.56% patients with *S. Haematobium* and 18.6% patients with *S. Mansoni*; 28.5% of patients with hepatosplenic schistosomiasis had side-effects. They recommended that patients with *S. Mansoni* should be admitted to hospital for treatment. Wolfe, treating 576 Tanzanians, aged 7 to 16, managed to follow up 83%, 13% of whom developed minor side-effects. There were no patients with serious CNS disturbances. Generally it has been found that side-effects occur on the third to fifth day of treatment, and that LFTs are not helpful in predicting which patients will develop them.

The results in this study are consistent with the findings of previous workers. Apart from case 5 all the symptoms of neuropsychiatric disturbances first occurred on day 3, 4 or 5. The bilirubin was raised in patient 3, otherwise the LFTs were normal in affected patients. Patients with *S. Mansoni* and those suffering from other pathologies were significantly more likely to develop side-effects and, although not significant, it seems, and it has been shown in previous studies,

that hepatosplenomegaly increases the likelihood of neuropsychiatric side-effects. Although a definite picture of the patient at risk emerges, it should be remembered that the woman in the opening report was infested with *S. Haematobium*, had no hepatosplenomegaly and apparently had no other illness.

On the positive side it should be noted that the dose of niridazole is clearly important and should not exceed 25mgm/kgm. In both the patients who took their lives there were some symptoms two days prior to their suicides so that, with more awareness of this possibility during niridazole therapy, future tragedies should be averted.

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