Med. J. Cairo Univ., Vol. 62, No. 2, June : 275-282, 1994

The Effects of Treatment With Praziquantel on Hearing

M. SHAFIK KHALIFA, M.D.; NAGI M. ISKANDER, M.D.;
ADEL ABD EL MAKSOUD, M.D. and TAREK F. YOUSSEF, M.Sc.

The E.N.T. Departments, Faculties of Medicine, Cairo and Suez Canal Universities.

Abstract

Praziquantel is a commonly used broad spectrum antihelminthic drug, it has totally replaced the antimonial compounds in the treatment of schistosomiasis. In this study 109 patients were included to study the audiometric changes produced by the drug in the routine treatment regimen for schistosomiasis. Pre-treatment pure tone audiograms were obtained for all patients on air and bone conduction. They were then repeated after 24 hours of treatment, one week and one month after treatment. Eight patients out of 109 developed marked significant changes in their audiogram, defined as more than 15 dB from previous readings. Our results concluded that praziquantel treatment can cause mild audiometric changes mainly in the higher frequencies for a transient period which was followed by a return to normal hearing. Full audiological assessment to all patients undergoing treatment with praziquantel is highly recommended.

Introduction

PRAZIQUANTEL is a widely used broad spectrum antihelminthic drug that has totally replaced the antimonial compounds in the treatment of schistosomiasis and other round worms. Praziquantel has become accepted as the antischistosomal agent of choice for S. Mansoni, S. Hematobium, S. Japonicum, S. Mekong and S. Intercalatum [1].

Structurally, praziquantel is 2- cyclohexyl carbonyl (1, 2, 3, 6, 7, 11) hexa hydro-4 H- pyrazino (2, 1 -a) isoquinolin -4 one [2].

Praziquantel itself is the active antiparasitic agent, its hydroxylated and conjugated metabolites have little or no effect. The major antihelminthic activity of this asymmetric molecule is related to the pyrazino (2, 1-a) isoquinoline, while its broad spectrum appears to be dependent on an oxo group at position 4 and one acyl and thioacyl group on position 2 [3].

After oral administration, the drug is rapidly and efficiently absorbed from the intestine with a bioavailability of 80 to 100%. Although praziquantel binds reversibly to plasma proteins, a significant proportion of the drug is metabolized during the first pass through the liver, yielding in active metabolites that are excreted through the kidneys [1].

Side effects of praziquantel occurred in 10-15% of patients treated with the drug [4]. These side effects include abdominal discomfort, nausea, vomiting, anorexia and diarrhea. Neurologic symptoms include headache, vertigo and dizziness. It was noted that patients with schistosomiasis who have hepatic disease tolerated therapy well, although increased drug level in these patients have been associated with a higher incidence of symptomatic side effects [1].

In Egypt, praziquantel is reported as being the most effective antibilharzial treatment compared to metrifonate and oxaminoquine [5].

Our study has been triggered by a recent experimental study on the histopathological changes induced on the cochlea of guinea pigs reporting that one single therapeutic dose produced no significant effect on the organ of corti. Two therapeutic doses caused hydropic degeneration of Hensen's cells and some outer phalangeal cells. Four expirmental therapeutic doses of praziquantel produced hydropic degeneration in the outer and inner hair cells besides that in Hensen's cells [6].

Material and Methods

This study included 109 patients, those patients were infested with schistosoma mansoni and visiting El-Tal El-Kabir Central Hospital and El-Mahsamma Primary Care Unit for routine treatment with praziquantel.

Pure tone audiometry was performed to all patients before treatment, and then repeated after 24 hours, one week and one month after treatment. Pure tone measurments were at air conduction frequencies of 250, 500, 1000, 2000, 4000, 6000 and 8000 Hz. Bone conduction thresholds were also obtained, using masking, at 250, 5000, 1000, 2000, and 4000 Hz.

The following criteria had to be fulfilled before entering the study:

1. Age limited to 15-45 years old. This limitation aimed at ensuring good response to audiomteric procedure and eliminate the possible effects of aging on hearing found in older individuals.
2. Laboratory diagnosis of S. mansoni

based on microscopic examination of the stool.

3. The patient must have a normal range of blood pressure from 90 mmHg diastolic to not higher than 140 mmHg systolic, this to exclude the vascular changes that occur in the cochlear microvasculature with chronic hypertension.

4. The patient was not currently using a known ototoxic drug especially aminoglycosides, loop diuretics, antidepressants and non steroidal anti inflammatory drugs.

5. The patient has no symptoms of ear disease, has no history of hearing loss, had no history of previous ear surgery and shows normal drum on otoscopic examination.

6. The patient showed a normal hearing threshold on pure tone audiometry for air and bone conduction. The criteria used for normal was that no more than 25 dB loss on any test frequency.

Patients fulfilling the above criteria were given praziquantel tablets (Distocide 600 mg) in a dose of 40 mg/kg body wt as a single dose. Then followed by audiometric assessment 24 hours, 1 week and one month after treatment.

Results

The total studied sample was 109 patients, they were infested with S. mansoni and received praziquantel treatment in 40 mg/kg body wt. as a single oral dose. The sample included 69 males (63%) and 40 females (37%).

Seventy six patients developed post treatment side effects as shown in table (1).

Comparisons were made between pretreatment audiometric values versus posttreatment result on twenty four hours, one week and one month.

The results showed that air conduction values at 24 hours post-treatment showed no statistically significant decrease in thresholds on 250, 500, 1000, 2000, Hz for right ear $p > 0.05$ (Table 2).

It was also evident that no statistically significant decrease occurred in audiometeric thresholds on the left ear for frequencies of 250, 500 Hz, $p > 0.05$ when measured after 24 hours.

But significant decrease in audiometric thresholds occurred at the left ear on frequencies of 1000, 2000, 4000, 6000 and 8000 Hz, $p < 0.05$ (Table 3).

Table (1): Incidence and Type of Recorded Side Effects among the Studied Sample.

Side Effects	Number	%
Hearing loss	2	1.8
Tinnitus	22	20.1
Vertigo	16	14.6
Headache	36	33

Table (2): Mean Values, Standard Deviation (SD) and *t* Test of Pretreatment Audiometric Values on Air Conduction vs Post Treatment 24 hrs, One Week and One Month-Right Ear.

Frequency Hz	Pre-treatment		24 hrs Post-treatment			One week Post-treatment			One month Post-treatment		
	Mean	SD	Mean	SD	*t*	Mean	SD	*t*	Mean	SD	*t*
250	22.25	10.26	26.5	2.76	1	21.87	2.58	0.09	21.25	2.13	0.26
500	20	3.37	21.87	2.58	1.15	21.87	2.58	0.96	20.62	1.76	0.33
1000	19.37	3.20	20.62	4.17	0.67\	20	2.67	0.33	20.62	4.17	1.54
2000	17.50	3.78	21.87	2.58	1.71	25	3.78	23.24*	21.87	4.58	1.76
4000	16.87	5.30	24.37	6.23	2.59*	30	5.34	4.03*	24.37	4.17	2.45*
6000	16.87	2.58	28.12	10.32	2.98*	42.87	8.87	5.74*	25.5	2.67	6.65*
8000	19.87	3.20	28.75	8.34	2.96*	40.62	3.20	13.2*	29.37*	4.95	4.97*

* $p < 0.05$ significant.

Table (3): Mean Values, Standard Deviation (SD) and *t* Test of Pretreatment Audiometric Values on Air Conduction vs Pot Treatment 24 hrs, One Week and One Month-Left Ear.

Frequency Hz	Pre-treatment		24 hrs Post-treatment			One week Post-treatment			One month Post-treatment		
	Mean	SD	Mean	SD	*t*	Mean	SD	*t*	Mean	SD	*t*
250	21.25	3.53	21.12	5.53	0.0	22.5	3.67	0.69	22.5	3.78	0.68
500	20	3.78	21.25	2.31	0.79	21.87	2.58	1.15	22.5	3.78	1.32
1000	18.75	2.31	21.87	3.72	2.01*	22.523.	2.67	3*	21.5	2.31	2.38*
2000	18.12	3.72	23.12	2.58	2.40*	12	2.58	3.12*	21.25	4.43	1.53
4000	18.12	3.72	26.25	5.82	3.23*	31.87	3.72	7.39*	25.62	4.17	3.76*
6000	19.37	7.95	26.87	8.83	2.09*	36.87	5.93	6.40*	26.87	8.42	2.17*
8000	18.75	4.43	28.12	9.23	2.56*	42.5	3.34	12.1*	27.5	7.55	2.82*

* $p < 0.05$ significant.

Table (4): Mean Values, Standard Deviation (SD) and *t* Test of Pretreatment Audiometric Values on Air Bone Conduction vs Post Treatment 24 hrs, One Week and One Month-Right Ear.

Frequency Hz	Pre-treatment		24 hrs Post-treatment			One week Post-treatment			One month Post-treatment		
	Mean	SD	Mean	SD	*t*	Mean	SD	*t*	Mean	SD	*t*
250	14.37	3.20	15	3.68	0.35	15.62	5.20	0.57	15.62	1.76	0.97
500	14.37	4.17	16.87	3.72	0.62	15.62	3.20	0.67	14.37	3.20	0.0
1000	13.12	5.30	15.62	3.20	1.14	20	5.34	2.58*	15.62	3.20	1.41
2000	14.37	3.20	18.75	5.17	2.30*	25.62	3.20	7.03*	22.50	3.78	4.62*
4000	15	4.12	20.62	7.70	1.76	30.62	5.95	6.85*	23.75	3.53	4.56*

* $p < 0.05$ significant.

Table (5) Mean Values, Standard Deviation (SD) and *t* Test of Pretreatment Audiometric Values on Air Bone Conduction vs Post Treatment 24 hrs, One Week and One Month-Left Ear.

Frequency Hz	Pre-treatment		24 hrs Post-treatment			One week Post-treatment			One month Post-treatment		
	Mean	SD	Mean	SD	*t*	Mean	SD	*t*	Mean	SD	*t*
250	12.5	3.78	11.25	4.43	0.06	15.37	1.33	2.02*	15.62	4.17	1.56
500	14.37	4.17	13.75	3.53	0.32	16.87	4.58	1.14	16.25	5.17	0.08
1000	13.12	3.72	13.75	3.53	0.34	16.87	6.15	1.14	16.87	4.58	1.79
2000	15	4.62	14.5	3.78	0.23	23.75	5.82	2.62*	20.62	4.17	2.55*
4000	19.37	3.20	24.37	4.17	2.68*	33.75	5.82	6.12*	25	4.62	2.83*

* $p < 0.05$ significant.

Only statistically significant increase in thresholds occurred in the right ear after 24 hours at frequencies of 4000, 6000, and 8000 Hz, $p < 0.05$.

The mean bone conduction audiometric values at 24 hrs post-treatment were statistically insignificant at frequencies of 250, 500, 1000, 4000 Hz in the right ear compared to pretreatment mean values ($p < 0.05$).

It was statistically significant post-treatment bone conduction at 24 hours at frequencies of 2000 Hz on the right ear and 4000 Hz on the left ear, compared to pre-treatment mean values, $p < 0.05$ (Tables 4 & 5).

Discussion

Praziquantel is a commonly used broad spectrum antihelminthic drug marketed in Egypt under the brand Distocide. The drug has totally replaced older antimonial drugs in the treatment of schistosomiasis. In 1980s, the release of praziquantel provided significant inputs for the use of chemotherapy-based control of many trematode infections, including all forms of schistosomiasis, in endemic areas around the world [7].

The maximum serum concentrations are reached in 1-2 hours. The renal elimination half-life for praziquantel plus metabolites was 4-6 hours and the cumulative renal excretion of praziquantel within 4 days in excess of 80% of the dose. 90% of which was eliminated on the first day [8].

Post treatment side effects were found in 76 patients (69.7%) as in table (1). The incidence of side effects was up to 50% of patients treated with praziquantel [9]. Praziquantel produced much lower incidence of ototoxicity (7.33%) compared to gentamicin with reported incidence of 25% [10].

In our study, it is evident that praziquantel ototoxic effects occurred mainly on the higher frequencies on audiometric testing both in air and bone conduction. Eight patients out of 109 developed significant audiometric decrease in thresholds (more than 15 dB) at any test frequency when tested after 24 hours, 1 week and one month after treatment.

Although the changes occurring after 24 hours post-treatment are statistically significant they have a little value clinically since the maximum loss of hearing did not exceed 28 dB which is considered in the range of normal hearing.

The predominant ototoxic effect of praziquantel seemed to be related to high frequency 2000, 4000, 6000 and 8000 Hz on air conduction and 2000 and 4000 Hz on bone conduction.

The immediate effects caused by the ototoxic drugs are in the form of decrease in the resting endolymphatic potential, cochlear microphonics and action potential. Also, with reduction of ATPase with blocking of cation transport, interruption of cell respiration and interference with phospho-inositide metabolism [11].

Significant reversible changes occurred at one month post treatment as compared to pre-treatment results. These changes occurred at frequencies of 2, 4, 6, and 8 KHz on air conduction and 1 and 4 KHz on bone conduction. The reversible nature of this type of ototoxicity is similar to that of quinine, the oldest drug known for its ototoxic effects. Praziquantel being a quinine derivative bears similar pattern of ototoxicity.

Explanation of the transient and reversible nature of quinine ototoxicity was postulated as a transient state of contraction of smooth muscle of the vessels of stria vascularis and narrowing of these vessels by endothelial swelling [12]. Another proposed mechanism of quinine ototoxicity was demonstrated on the cochlea of guinea pigs. It was found that quinine affects the outer hair cells by formation of microtubule core in the cochlea and swelling of the surface cisternae in the outer hair cells [13].

We recommend full audiological examination to all patients undergoing praziquantel treatment. Also, their hearing should be closely monitored prior to and after the treatment.

Further work is needed for patients undergoing repeated courses of praziquantel treatment. Also the use of ultrahigh frequency audiometry is recommended. Electrocochleography and brain stem evoked response audiometry should also be used to determine the exact site of the lesion with continuing and increasing use of the drug in Egypt.

References

1. ANDREWS, P.; THOMAS, H.; POHLKE, R.; and SEUBERT, J.: Praziquantel. Med. Rev., 3: 147-200, 1983.

2. ANDREWS, P.: Praziquantel; mechanisms of antischistosomal activity. Pharmacol. Ther., 29:129-56, 1985.

3. CHARLES, H.; KING and MAHMOUD, A. A.: Drugs five years later: Praziquantel. Ann. Intern. Med., 110: 290-296, 1989.

4. COOK, J. A.: Strategies for control of human schistosomiasis. In Mahmoud A. A. ed. Bailliere's clinical tropical medicine and communicable disease Vol. (2) Philadelphia: Bailliere Tindall. 449-63, 1987.

5. HAWKINS, J. E. JR.: Drug ototoxicity. In Handbook of sensory physiology. Volume. Auditory system part 3: Clinical and special topics. Berlin and Heidelberg: Springer-Verlag, PP. 707-748. 1976.

6. KARLSSON, K. R. and PLOCK, B.: Ultrastructural changes in the outer hair cells of the guinea pigs cochlea on exposure to quinine. Acta Oto. Laryngol., 111: (3) p: 500-5, 1991.

7. LEOPOLD, G.; UNGETHUM, W.; GROLL, E.; DIEKMAN, H. W.; HOWAK, H.; and WEGNER, D. H. G.: Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes: an example of a complex

study covering both tolerance and pharmacokinetics. Eur. J. Clin. Pharmacol., 14: 281-91, 1978.

8. MAYER, R. D.: Amikacin therapy for gram negative bacillary infections. Ann. Intern. Med., 783-90, 1975.

9. POLDERMAN, A. M.; GEROLD, J. L.; MPAMILA, K. and MANSHANDE, J.P.: Side effects of praziquantel in the treatment of schistosoma mansoni in Maniema. Zaire. Trans. R. Soc. Top. Med. Hyg., 78: 752-4, 1984.

10. SALWA, S.; LAILA, H.; and HAILA, O.: Clinical Evaluation of the adverse effects of the recent oral Antibilharzial Drugs in children in Egypt. Med. J. Cairo Univ., 58 No. 2, P: 217-222, 1990.

11. SOMAYA, H.; WAGDY, T.; MOHAMED, N. and MOHAMED, S. K.: Histopathological changes induced by praziquantel on the cochlea of Guinea pigs. Med. J. Cairo Univ., 59, No. 3, P. 645-652, 1991.

12. SMITH, D.I.; LAWRENCE, M. and HAWKINS, J.A. : Effects of noise and quinine on the vessels of the stria vascularis, an image analysis study. Am. J. Otolaryngol. vol. 6 (4): P: 280-9. Praziquantel pharmacokinetics and side effects in Schistosoma Japonicum infected patients with liver disease. J. Infect Dis., 157:530-5, 1985.

13. WATT, G., WHITE, N. J.; and PADRE, L.: Praziquantel pharmacokinetics and side effects in Schistosoma Japonicum infected patients with liver disease. J. Infect. Dis., 157: 530-535, 1988.