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ALTERATION IN THE LEVELS OF PYRAZINAMIDE IN PLEURAL FLUID FOLLOWING SIMULTANEOUS ADMINISTRATION OF PREDNISOLINE IN PATIENTS OF TUBERCULAR PLEURAL EFFUSION

A. R. WAGAY, K. C. SINGHAL* AND R. BHARGAVA

Departments of Pharmacology and Medicine,
J.N. Medical College,
A.M.U., Aligarh — 202 002

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Abstract : 20 Patients of tuberculous pleural effusion were administered a combination of pyrazinamide (30 mg/kg) + isoniazid (300 mg) orally for 7 consecutive days and pyrazinamide was estimated by spectrophotometric method in serum and pleural fluid. Prednisolone was added to the above regimen for next 7 consecutive days and pyrazinamide was again estimated. The level of pyrazinamide in pleural fluid was 23.4 ± 1.2 (μg/ml). Following addition of prednisolone the level increased (27.6 ± 1.3) significantly ($P < 0.001$). The serum pyrazinamide level was not influenced by simultaneous administration of prednisolone. The pleural fluid/serum pyrazinamide ratio was increased from 0.465 to 0.542 by the addition of prednisolone to therapeutic regimen.

Key words : pyrazinamide prednisolone pleural effusion tuberculosis pharmacokinetic

INTRODUCTION

Tubercular pleural effusion is the result of delayed hypersensitivity reaction to tubercle bacilli protein (1), which enters the pleural space. Further higher adenosine deaminase (ADA) levels observed in serum and pleural fluid of patients of tubercular pleural effusion (2-5) suggest the stimulation of cellular immunity (6). Several antitubercular drugs including isoniazid (INH), rifampicin, pyrazinamide (PZA), ethambutol, paraaminosalicylic acid, ethionamide and cycloserine attain good therapeutic concentrations in pleural fluid especially when the pleura is inflamed (7,8). Corticosteroids facilitate the absorption and prevent the effusion formation by controlling the hypersensitive state (9). The steroids also prevent the formation of mediators of inflammation (10).

The present study was designed to determine whether the concentration of PZA in pleural fluid is changed following oral administration of prednisolone.

METHODS

Patients of tubercular pleural effusion of either sex (male 13; female 7) in the age group of 15 to 65 years, were selected from tuberculosis and Chest Outpatient Department, J.N. Medical College Hospital, Aligarh. Written consent of the patients under study was obtained. Diagnosis of tubercular pleural effusion was confirmed by chest skiagram, biochemical and bacteriological examination of pleural fluid. Exclusion criteria included previous exposure to antitubercular therapy, associated hepatic or renal dysfunction, marked nutritional deficiency and pregnancy. Patients were administered a combination of PZA (30 mg/kg) and isoniazid (300 mg) daily in the morning on an empty stomach. On 7th day pleural fluid and venous blood samples were collected in separate sterilized vials for estimation of PZA, 2 hr after drug administration. From 8th day prednisolone 20 mg/day orally was added to the therapeutic regimen. Pleural fluid and venous samples were collected in a similar manner on 14th day.

*Corresponding Author

PZA estimation was done within 24 hr of sample collection as described by Caccia (11). The sensitivity of test approaches 0.5 to 2 μg/ml. The results were analysed by paired students' t-test.

RESULTS

The mean serum concentration of 50.4 ± 2.0 (range 40-65) μg/ml was achieved 2 hr after the ingestion of pyrazinamide. The levels of pyrazinamide were not different in relation to age or sex. Simultaneous administration of prednisolone for 7 consecutive days did not alter its serum levels (Fig. 1, Table I).

The mean PZA level in pleural fluid was 23.4 ± 1.2 μg/ml (range 15-32). The level was not different according to age or sex. However, simultaneous administration of prednisolone significantly increased pyrazinamide level in pleural fluid ($P < 0.001$). This increase was irrespective of age or sex (Fig. 1, Table I).

Ratio of pleural fluid to serum concentration was 0.465 which was raised to 0.542 by concomitant administration of prednisolone (Table II).

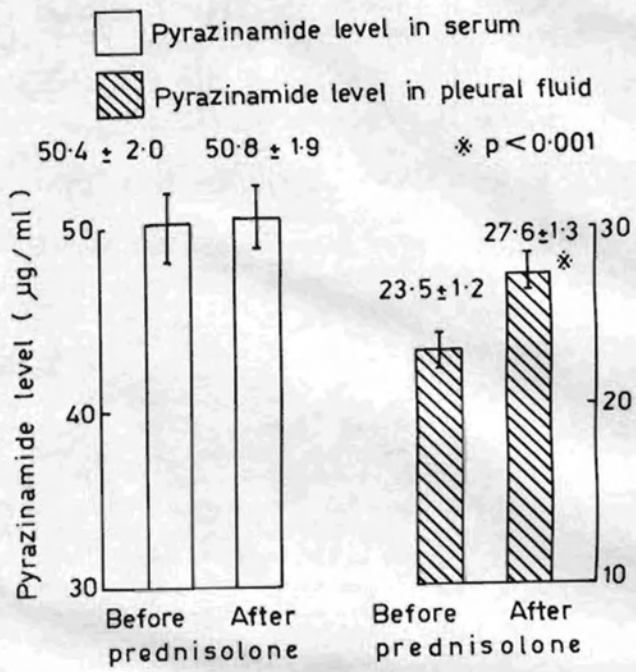

Fig. 1

TABLE I : Pyrazinamide levels (μg/ml, mean ± SEM) in serum and pleural fluid of patients of tubercular pleural effusion before and after prednisolone administration according to age and sex.

	SERUM		*PLEURAL FLUID*	
	Before Prednisolone	*After Prednisolone*	*Before Prednisolone*	*After Prednisolone*
Upto 30 Years n = 13	49.9 ± 2.5	50.2 ± 2.5	23.2 ± 1.5	27.0 ± 1.5*
Above 30 years n = 7	51.4 ± 3.7	51.7 ± 3.4	24.0 ± 2.0	28.6 ± 2.0*
Male n = 13	50.4 ± 2.6	50.6 ± 2.3	22.9 ± 1.2	27.2 ± 1.4*
Female n = 7	50.4 ± 3.6	50.9 ± 3.8	24.4 ± 2.5	28.1 ± 2.8*

*P< 0.001

TABLE II : Concentration of pyrazinamide (PZA, Mean ± SEM) in serum and pleural fluid in patients of tubercular pleural effusion before and after prednisolone administration.

Drug	*Hours after* dosage	*Concentration* μg/ml		Ratio of fluid to serum PZA
		Serum	Pleural fluid	
Pyrazinamide + INH	.2	50.4 ± 2.3	23.5 ± 1.2	0.465
Pyrazinamide + INH + Prednisolone	2	50.8 ± 2.0	27.6 ± 1.3	0.542

DISCUSSION

It has recently been shown (12) that simultaneous prednisolone administration facilitates the entry of rifampicin in pleural fluid thereby increasing its concentration. However, there was no effect on serum rifampicin level. Similar results have been obtained with the combination of prednisolone and PZA.

The inclusion of corticosteroids in the therapy of tubercular pleural effusion is beneficial in many ways. It prevents fluid formation, facilitates absorption of pleural fluid, prevents thickening of pleura and increases the concentration of antitubercular drugs (12-15).

PZA is widely distributed throughout the body water being very weak base (8). The minimum inhibitory concentration (MIC) against mycobacterium tuberculosis has been reported to vary from 12.5-25 μg/ml (16-18). Addition of prednisolone increased the concentration of PZA in pleural fluid to level higher than MIC.

The increased levels of PZA in pleural fluid when administered in combination with prednisolone can be attributed to its antiinflammatory and antiallergic effects. Pleural cavity contains minimal amount of fluid for lubrication. During inflammation the fluid starts increasing in amount carrying with it proteins, macrophages and other cells. PZA has affinity for acidic environment provided by macrophages and inflammatory pleural surface (19-20). Thus PZA gains entry into macrophages and pleural cavity. With the inhibition in the process of inflammation and hypersensitivity by prednisolone, the movement of macrophages stops, but the reabsorption of fluid continues and the drug may not get reabsorbed with the same rate it had entered thus leading to an increase in the concentration of PZA in pleural fluid.

REFERENCES

1. Light RW. Diseases of the Pleura. Chest Medicine by Ronald, BG., Light RW, Matthay RA. 1983; Churchill Livingstone 520-25.
2. Piras MA, Gakis C, Bulroni M, Andreoni G. Adenosine deaminase activity in pleural effusion. An aid to differential diagnosis. *Br Med J* 1978; 2: 1751-52.
3. Petterson T, Ojala K, Weber TH. Adenosine deaminase in the diagnosis of pleural effusions. *Acta Med Scand* 1984; 215: 299-301.
4. Niwa Y, Kishimotu H, Simokata K. Carcinomatous and tuberculous pleural effusion: Comparison of tumour markers. *Chest* 1985; 87: 351-52.
5. Chopra RK, Singh V, Lal H, Saini AS, Chawla RK, Raj B. Adenosine deaminase and T. lymphocyte levels in patients with pleural effusions. *Ind J Tub* 1988; 35: 22-24.
6. Ocana I, Mattinez, Vazquez JM, Segura BM, Fernandez De-sevilla T, Capdevila, JA. Adenosine deaminase in pleural fluids. Tests for diagnosis of tubercular pleural effusions. *Chest* 1983; 84: 51-53.
7. Mandell GL, Sande MA. Antimicrobial agents. IN: Goodman AG, Goodman LS, Rall WT, Murad F eds. The Pharmacological Basis of Therapeutics. Macmillan Publishing Company, New York 1985: 1150-1218.
8. Yu TF, Berger L, Stone DJ, Wolf J, Gutman AB. Effect of pyrazinamide and pyrazinoic acid on urate clearance and other discrete renal functions. *Proc Soc Exp Biol Med* 1957; 96: 264-67.
9. Aspin J, O'Hara H. Steroid treated tuberculous pleural effusion. *Br J Tube and Dis Chest* 1958; 52: 81-83.
10. Laurens DR, Bennett PM. Endocrinology I. Clinical Pharmacology. 6th Ed. Churchill Livingstone 1988; 652.
11. Caccia PA. Spectrophotometric determination of pyrazinamide blood concentrations and excretion through the kidneys. *Am Rev Tuberc* 1957; 75: 105-10.
12. Wagay AR, Singhal KC, Malik A, Bhargava R. Alteration in the levels of rifampicin in pleural fluid following simultaneous administration of prednisolone in patients of tubercular pleural effusion. *Ind J Pharm* 1990; 22: 133-37.
13. Menon NK. Steroid therapy in tuberculous pleural effusion. *Tubercle* 1964; 45: 17-20.
14. Onadeko BO. Tuberculous pleural effusion: Clinical pattern

and management in Nigerian. *Tubercle* 1978; 59: 269-75.

15. Weatherall DJ, Ledingham JAC, Warrell DA. Tuberculosis. Oxford Textbook of Medicine. 2nd Ed OUP 1987; 5.279-89.

16. Mackaness GB. The intracellular activation of pyrazinamide and nicotinamide. *Am Rev Tuberc Pulm Dis* 1956; 74: 718-28.

17. Stottmeier KD, Beam RE, Kubica GP. The absorption and excretion of pyrazinamide. *Am Rev Resp Dis* 1968; 98: 70-74.

18. Kulshrestha S. A study of chronopharmacokinetics of pyrazinamide in tuberculosis patients. *Ind J Tub* 1986; 33: 66-76.

19. Grosset J. The efficacy of short-course chemotherapy for tuberculosis. *Bull Pan Am Health Organ* 1980; 14: 139-49.

20. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 1984; 65: 1-4.