PYRAZINAMIDE

Varinder Singh
P. Choudhury
R.K. Puri

Pyrazinamide was first shown to be an effective antitubercular drug in the year 1952(1). However, it fell into disrepute subsequently due to the high incidence of hepatotoxicity associated with its use in doses as high as 3 g/day. The erstwhile second line drug has now regained its place in the frontline with reduced dosages and incidental minimal side effects. This metamorphosis also occurred because of its prime sterilizing capacity and important role in the short term chemotherapy of tuberculosis(2,3).

Physical Characteristics

It is a synthetic analog derivative of nicotinamide which is white in color, slightly bitter to taste and moderately lipid soluble(4).

From the Department of Pediatrics, Maulana Azad Medical College, New Delhi 110 002.
Reprint requests: Dr. P. Choudhury, Department of Pediatrics, Lok Nayak Jai Prakash Narain Hospital, New Delhi 110 002.
Accepted: December 1, 1992

Mechanism of Action

The exact mechanism of action of pyrazinamide is not known. In the monocytes, the pyrazinamide is hydrolysed to pyrazinoic acid by pyrazinamide deamidase which causes a fall in the intracellular pH making it slightly acidic. It is not clear whether it is the bactericidal activity of drug or its mocity or the unfavorably acidic conditions in the macrophage below the tolerance limits of bacilli or both which make the drug effective(5,6). Metabolically inactive tubercular bacilli are resistant to pyrazinamide thus rendering its utility as a sterilizing drug only in the initial phase of therapy(7).

Pharmacokinetics

Pyrazinamide is readily absorbed from the gut and gets widely distributed in all the body fluids. Its absorption is not significantly hindered by meals. A CSF : serum ratio of 0.74, 1.15 to 1.09 is achieved 2, 5 and 8 hours following an oral dose of 35-40 mg/kg. The excellant penetration of pyrazinamide across the blood brain barrier is expected due to its moderately lipophilic nature, unchanged at body pH and not bound to serum proteins(8). The tubercular bacteria is killed at a level of 12.5 μg/ml(4). It is metabolized in the liver and is hydrolysed to pyrazinoic acid and then further hydroxylated to 5-hydroxy pyrozinoic acid.

The unchanged drug (4%) and its metabolites are excreted almost completely by the kidney(1,4,9).

Formulations

Pyrazinamide is available as 500 mg and 750 mg tablets under various brand names, *e.g.*, PZA-CIBA (Ciba Giegy),

P-Zide (Cadilla), Lynamide (Lyka), Prialdina (Pharmed) and Pyzina (Lupin). The drug costs Rs. 13.39 to 17.12 per ten 500 mg tablets and Rs. 20.48 to 26.88 per ten 750 mg tablets. It is also available as a fixed dose combination with Rifampicin and INH (Tricox, Rifater).

Storage

The drug should be kept out of reach of children, away from direct heat, light or high moisture areas.

Therapeutic Uses

Pyrazinamide is a potent antitubercular drug which kills multiple intracellular organisms with 100% CSF penetration(9). In combination with other drugs it plays an important role in first two months of therapy. Inclusion of this drug in the treatment regimen can reduce the late relapse rate and allow shorter duration of antitubercular therapy(10). The bactericidal activity of a drug regimen is best indicated by the speed with which the bacilli are eliminated from the sputum and is assessed by achievement of negative cultures (conversion) within two months after initiation of therapy. This conversion is increased from 70-75% with isoniazid and rifampicin combination to 95% when four antitubercular drugs (streptomycin, isonex, rifampicin and pyrazinamide) are used(10,11). The drug is not effective against resistant strains of *Mycobacobacterium* and *Mycobacterium bovis* bacilli strains due to the lack of an enzyme pyrazinamidase, which converts pyrazinamide to pyrazinoic acid(12,13). The efficacy of 'the sterlizing' action of a drug regimen is the incidence of late relapses after completion of therapy. With inclusion of pyrazinamide in six month regimen with initial intensive therapy with 4 antitubercular drugs has proven to be highly successful with a relapse rate of less than 2%. This regimen is also successful in patients with initial isoniazide resistance. Such short course chemotherapy can also be made oral by substitution of ethambutol for streptomycin(14,15).

Dosage

Pyrazinamide is administered as 20-35 mg/kg/day in two to three divided doses for the initial 2 months of antitubercular therapy in conjunction with other drugs. In intermittent regimen, 40-50 mg/kg of pyrazinamide is given twice weekly.

In patients with uremia and end stage renal disease the recommendations are variable. Pyrazinamide can however be used at lower end of usual recommended dosage, *i.e.*, 15-20 mg/kg(16,17).

Side Effects

In proper dosage, pyrazinamide is well tolerated whether used alone or in combination(18,19). Fever, loss of appetite, unusual tiredness or weakness are frequently encountered side effects. Hepatotoxicity due to pyrazinamide being dose dependent is on the decline due to decrease in the dosages currently in use(20-22). The PZA hepatotoxicity is not a major risk in Indian patients(23,24),

Arthralgia and gout like arthritis is another dreaded side effect of pyrazinamide. It is due to the decreased uric acid excretion resultant hyperuricemia because of pyrazinoic acid(4). This toxicity though reported in 10% of adults treated with pyrazinamide is relatively rare in children(25). Arthralgia *per se* requires discontinuation of the drug and readily responds to analgesics(26). Nausea, vomiting, photosensitivity, pruritis and rash are less frequent side effects indicating medical attention only if bothersome.

Monitoring and Specific Precautions with the use of Pyrazinamide

Patients intolerant of ethionamide, isoniazide, niacin or other chemically related medications may not tolerate this drug. In patients concomitantly suffering from diabetes mellitus, gout or severe hepatic impairment, physician must assess the risk benefit before starting treatment with pyrazinamide(27).

AST (aspartate aminotransferase) and ALT (alanine amino transferase) should be monitored prior to and every 2-4 weeks during treatment. However, elevated serum enzymes alone may not be predictive of clinical hepatitis and may return to normal despite continued therapy(27). Serum uric acid levels should also be monitored.

Use in Pregnant and Nursing Mothers

Transplacental passage of pyrazinamide has been shown but its use in pregnancy is not contraindicated. No embryo fetotoxicity or teratogenicity has been observed(28). Pyrazinamide though detectable in human milk is far below the therapeutic range and considered safe for use in nursing mothers(29).

REFERENCES

1. Subbarao KE, Marks MT. Antituberculous therapy. *In:* Antimicrobial Therapy in Infants and Children. Eds Koren G, Prober CG, Gold R. New York. Marcel Decker Inc, 1988, pp 405-432.
2. Fox W. Whither short courses chemotherapy. Br J Dis Chest 1981, 75: 331-357.
3. Pretet S, Liard R, Perdrizet S. Pyrazinamide is a major antitubercular drug. Lancet 1982, 1: 399.
4. Mandell GL, Sande MA. Drugs used in the chemotherapy of tuberculosis and leprosy. *In:* Goodman and Gillman's The Pharmacological Basis of Therapeutics, Vol II. Eds Goodman Gilman A, Rall TW, Nies AW, Taylor P. 8th edn. New York, Maxwell MacMillan Publishing. pp 1154-1155.
5. Dickinson JM, Aber VR, Mitchinson DA. Bactericidal activity of streptomycin, Isoniazid, rifampin, ethambutol and pyrazinamide alone and in combination against *Mycobacterium tuberculosis.* Amer Rev Resp Dis 1977, 116: 627-635.
6. Heifets LB, Flory MA, Lindholm-Levy PJ. Does pyrazinoic acid as an active moeity of pyrazinamide have specific activity against *Mycobacterium tuberculosis.* Antimicrobial Agents Chemother 1989, 33: 1252-1254.
7. Stead WW, Dutt AK. Chemotherapy for tuberculosis today. Am Rev Resp Dis 1982, 125 (Suppl 3): 94-101.
8. Ellard GA, Humphries MJ, Gabriel M, Teon R. Penetration of pyrazinamide into CSF in tubercular meningitis. Br Med J 1987, 294: 284-285.
9. Rqbóz J, Suzuki R, Yu TA-F. Mass fragmentographic determination of pyrazinamide and its metabolites in serum and urine. J Chromatography 1978, 147: 337-347.
10. Singapore Tuberculosis Service/British Medical Research Council Study. Clinical trial of six month and four month regimens of chemotherapy for the durations in the treatment of pulmonary tuberculosis. Second report. Tubercle 1980, 61: 59-69.
11. Hongkong Chest Service/British Medical Research Council. Controlled trial of four thrice weekly and a daily regimen all given for six months for pulmonary tuberculosis. Lancet 1981, i: 171-174.
12. Trivedi SS. Pyrazinamidase activity of *Mycobacterium tuberculosis* – A test of sensitivity of pyrazinamide. Tubercle 1987, 68: 221-224.
13. Salfinger M, Crowle AJ, Reller LB. Pyrazinamide and pyrazinoic acid activity

against tubercle bacilli in cultured human macrophages and in the BACTEC system. J Infect Dis 1990, 162: 201-207.

14. Angel JH, Somer AR, Citreen KM. Six month regimens in pulmonary tuberculosis (Abstract). Am Rev Resp Dis 1982, 125 (Suppl): 171.
15. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second Report. Results during the 24 months after the end of chemotherapy. Am Rev Resp Dis 1982, 126: 460-462.
16. Friend JAR, Petrie JC. Respiratory diseases. *In:* Avery's Drug treatment, 3rd edn. Eds Speight TM. UK, Adis Press Ltd 1987, pp 840-845.
17. Des Prez RM, Heim CR. Mycobacterium tuberculosis. *In:* Principles and Practice of Infectious Diseases, 3rd edn. Eds Mandell GL, Douglas RG Jr, Bennet JE. New York, Churchill Livingstone 1990, pp 1877-1906.
18. Steale MA, Des Prez RM. The role of pyrazinamide in tuberculosis chemotherapy. Chest 1988, 54: 845-850.
19. Kumar L, Dhand R, Singhi PD, Rao KLN, Katariya S. A randomized trial of fully intermittent versus daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatr Inf Dis J 1990, 9: 802-806.
20. Singapore Tuberculosis Service/British Medical Research Council. Clinical trials of six months and four months regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am Rev Resp Dis 1979, 119: 579-585.
21. Biddulph J. Short course chemotherapy for childhood tuberculosis. Pediatr Inf Dis J 1990, 9: 794-801.
22. Donald PR, Shoeman JF, Okennedy A. Hepatic toxicity during chemotherapy for severe tuberculous meningitis. Amer J Dis Child 1987, 141: 741-743.
23. Pamra SP. Chemotherapy of pulmonary tuberculosis – Present state. Indian J Tuberc 1979, 26: 106-110.
24. Seth V. Antituberculous therapy in children. Indian J Pediatr 1986, 53: 179-198.
25. Starke JR. Modern approach to the diagnosis and management of tuberculosis in children. Pediatr Clin North Am 1988, 35: 441-464.
26. Horsfall PAZ, Plummer J, Allan WGL, Girling DJ, *et al.* Double blind controlled comparison of aspirin, allopurinol and placebo in the management of arthralgia during pyrazinamide administration. Tubercle 1979, 60: 13-24.
27. Drug Information for the Health Care Professional USPDI-Vol. IB, United State Pharmacopial Council, 1989, pp 2068-2069.
28. Onnis A, Grella P. *In:* The Biochemical Effects of Drugs in Pregnancy. Chichester, Ellis Horwood Ltd, 1984, p 106.
29. Holdiness MR. Antituberculous drugs and breast feeding. Arch Int Med 1984, 144: p 1888.