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Activity of Pyrazinamide in the Guinea Pig Model of Tuberculosis

Ordway et al. (8) have recently evaluated standard chemotherapy with a combination of rifampin, isoniazid, and pyrazinamide (PZA) in the guinea pig model of tuberculosis (TB) and described long-term bacterial persistence. Soon after the introduction of PZA in 1952, perhaps the most experienced group examining the activity of antituberculosis drugs in the guinea pig model reported that PZA had little or no activity (9). In the two guinea pig experiments they describe, established tuberculosis was treated, starting 21 or 30 days after infection with strain H37Rv, with about 150 mg PZA/kg of body weight twice daily by gavage for periods of 75 or 100 days. Deaths occurred in 3 of 22 untreated control animals and in 5 of 20 PZA-treated animals, with total organ macroscopic scores of 10.8 and 13.5 (controls) and 9.2 and 9.6 (PZA), while a group treated with isoniazid (5 mg/kg/day) intramuscularly (i.m.) had no deaths and a score of 3.5. From a search of the literature, no one has apparently reported similar observations in the guinea pig model using more modern methods of assessment. While PZA had such low activity in the guinea pig, it is almost as active in human lesions as rifampin. PZA and rifampin are together responsible for almost all of the sterilizing activity of the standard treatment of pulmonary tuberculosis (1, 7). PZA has high activity against persisters, particularly those that are rifampin tolerant (4). Clearly, valid assessments cannot be made of current standard therapy in pulmonary tuberculosis using the guinea pig model unless it can be shown that PZA has similar activities in both. It could be argued that PZA might be more active in combination than when given alone, so an assessment of its efficacy in monotherapy could be misleading. However, in the mouse model, treatment with PZA alone was highly bactericidal, although eventually limited by the emergence of resistance, and is equally active in combined treatment (2). In pulmonary TB, PZA given alone for the first 14 days was highly bactericidal (5). Thus, available evidence suggests that a good model for human combined treatment should show PZA to be demonstrably active both given alone and in combination. Human pulmonary lesions are thought to have a pH slightly on the acidic side, estimated between pH 5.5 and pH 6.0 (3, 6). Could inactivity in the guinea pig be due to lower acidity in the lesions because their degree of hypersensitivity to tuberculins is less than that in humans?

REFERENCES

1. **East African/British Medical Research Council.** 1972. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet **20:**1079–1085.
2. **Grumbach, F.** 1958. Experimental antituberculosis activity of pyrazinamide (PZA). Ann. Inst. Pasteur. **94:**694–708.
3. **Gumbo, T., C. S. W. W. Dona, C. Meek, and R. Leff.** 2009. Pharmacokinetics-pharmacodynamics of pyrazinamide in a novel in vitro model of tuberculosis for sterilizing effect: a paradigm for faster assessment of new antituberculosis drugs. Antimicrob. Agents Chemother. **53:**3197–3204.
4. **Hu, Y., A. R. Coates, and D. A. Mitchison.** 2006. Sterilising action of pyrazinamide in models of dormant and rifampicin-tolerant *Mycobacterium tuberculosis*. Int. J. Tuber. Lung Dis. **10:**317–322.
5. **Jindani, A., C. J. Doré, and D. A. Mitchison.** 2003. The bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. Am. J. Respir. Crit. Care Med. **167:**1348–1354.
6. **Kubendiran, G., C. N. Paramasivan, S. Sulochana, and D. A. Mitchison.** 2006. Moxifloxacin and gatifloxacin in an acid model of persistent *Mycobacterium tuberculosis*. J. Chemother. **18:**617–623.
7. **Mitchison, D. A.** 2004. Antimicrobial therapy of tuberculosis: justification for current recommended treatment regimens. Semin. Respir. Crit. Care Med. **25:**307–315.
8. **Ordway, D. J., C. A. Shanley, M. L. Caraway, E. A. Orme, D. S. Bucy, L. Hascall-Dove, M. Henao-Tamayo, M. R. Harton, S. Shang, D. Ackart, S. L. Kraft, A. J. Lenaerts, R. J. Basaraba, and I. M. Orme.** 2010. Evaluation of standard chemotherapy in the guinea pig model of tuberculosis. Antimicrob. Agents Chemother. **54:**1820–1833.
9. **Steenken, W., and E. Wolinsky.** 1954. The antituberculous activity of pyrazinamide in vitro and in the guinea pig. Am. Rev. Tuberc. **70:**367–369.

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