The Pharmacokinetics of Oral Rifampicin in AIDS Patients

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Abstract

Previous studies in AIDS patients have shown that the peak serum concentration of rifampicin at 2 hours after administration are below normal ranges. These may be due to malabsorption of the drug resulting in therapeutic failure. However, there is no published data to demonstrate the pharmacokinetics of rifampicin in these AIDS patients. Therefore, the aim of this study was to provide such data. Eight AIDS patients with tuberculosis participated in this study. All patients were scheduled to receive oral rifampicin 600 mg once daily in the morning on an empty stomach. Rifampicin pharmacokinetics were studied on day 14. The mean C_{max} was 9.81±4.41 ug/ml. The mean T_{max} was 2.25±0.71 h. The mean AUC_{0-24} was 60.25±36.88 ug. h/ml. The results of our study did not confirm the previous studies. The absorption of rifampicin in most of our AIDS patients were not reduced and delayed. Therefore, rifampicin dosage adjustment for Thai patients may not be necessary.

The incidence of tuberculosis in developed and developing countries has increased dramatically in the past decade. One of the important reasons is the epidemic of human immunodeficiency virus (HIV) infection, in which people with progressive reduction in cell-mediated immunity become more vulnerable to the development of tuberculosis[1,2]. It is estimated that 5-10 per cent of asymptomatic HIV-seropositive and purified protein derivative (PPD) skin test positive individuals may develop active tuberculosis within a year of their HIV serodiagnosis[3]. Therefore, the world wide incidence of tuberculosis, particularly in HIV-positive individuals, is a serious and growing public health concern.

Rifampicin, a semisynthetic derivative of rifamycin, is still one of the most valuable agents for the treatment of tuberculosis[4]. This drug combined with other antituberculous drugs including isoniazid, ethambutal, pyrazinamide are well established as the standard treatment of tuberculosis[4]. Previous studies in AIDS patients

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have shown that the peak serum concentration of rifampicin at 2 hours after administration are below normal ranges[5-7]. These may be due to malabsorption of the drug resulting in therapeutic failure. However, there is no published data to demonstrate the pharmacokinetic study of rifampicin in these AIDS patients. Therefore, the aim of this study was to provide such data.

MATERIAL AND METHOD

Subjects and drugs

Eight AIDS patients with tuberculosis, six pulmonary tuberculosis and two tuberculous lymphadenopathy, participated in this study. All were male. Their mean age was 34.38 ± 6.44 years (range 25-47) and their mean weight was 52.93 ± 6.72 kg (range 43-59.4). Their CD_4 cell count was more than 200 cell/mm^3. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each patient. Patients were excluded from the study if they were considered unlikely to survive for more than 2 weeks. They were also excluded if they had evidence of liver dysfunction, creatinine clearance rate of less than 50 ml/min., vomiting or diarrhea, or a history of rifampicin intolerance.

Rifampicin was purchased from Lederle (Thailand).

Drug administration and samples collection

All patients were scheduled to receive oral rifampicin 600 mg once daily in the morning on an empty stomach. On day 14 of rifampicin treatment, blood samples (approximately 5 ml each) were obtained by direct venepuncture at the following times : immediately before rifampicin administration (time 0) and every 1 hour for 8 hours, then 10, 15, 18 and 24 hours after rifampicin dose. The serum obtained was stored at -80°C until analysis

Rifampicin assay

The concentration of rifampicin was determined by reversed phase HPLC. Papaverine HCl (50 ug/ml) was used as the internal standard and the samples were extracted by the method of Darouiche et al[8]. An aliquot of the extracted sample (50 ul) was injected, using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA), onto a BONDAPAK C18 column (Waters Associates). The mobile phase was 50 mMol/l potassium dihydrogen phosphate, acetonitrile (62:38,v/v) *p*H 4.7, at a flow rate of 1 ml/min. The column effluent was monitored by UV detection (Waters 486, Waters Associates) at 340 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates, Milford, MA). The limit of detection of rifampicin was 2.5 ng per injection.

Pharmacokinetic parameters

The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were determined by visual inspection of the individual plasma concentration-time profiles. AUC_{0-24} were the areas under the concentration *versus* time between 0 and 24 h calculated using the trapezoidal rule. Results were expressed as mean±S.D. and statistical comparisons were made using the Student's *t*-test for paired data.

RESULTS

The mean serum rifampicin concentration-time data are depicted in Fig. 1. The mean C_{max} was 9.81±4.41 ug/ml. The mean T_{max} was 2.25± 0.71 h. The mean AUC_{0-24} was 60.25±36.88 ug.h/ml.

DISCUSSION

A study in patients with advanced AIDS demonstrated that most of these patients have diffuse mucosal abnormalities of the small intestine resulting in malabsorption of several drugs[9]. Previous studies in AIDS patients coinfected with *Mycobacterium tuberculosis* showed that the 2-hour peak serum concentration of antituberculous drugs were below normal[5-7]. In particular, 19 of 20 measurements of rifampicin concentrations in the dosage of 600 mg were lower than normal ranges which were established on the basis of values of 8-24 ug/ml[5]. In addition, a study in 20 human immunodeficiency virus-infected patients with disseminated Mycobacterium avium complex disease also showed that the 2-hour peak serum concentration of antimycobacterium including rifampicin, ciprofloxacin, ethambutal and clofazimine were below normal ranges[10]. Therefore, these studies conclude that the low serum concentrations of antimycobacterial drugs in AIDS patients may be due to impaired drug absorption and these patients should be screened for drug malabsorption before treatment failure.

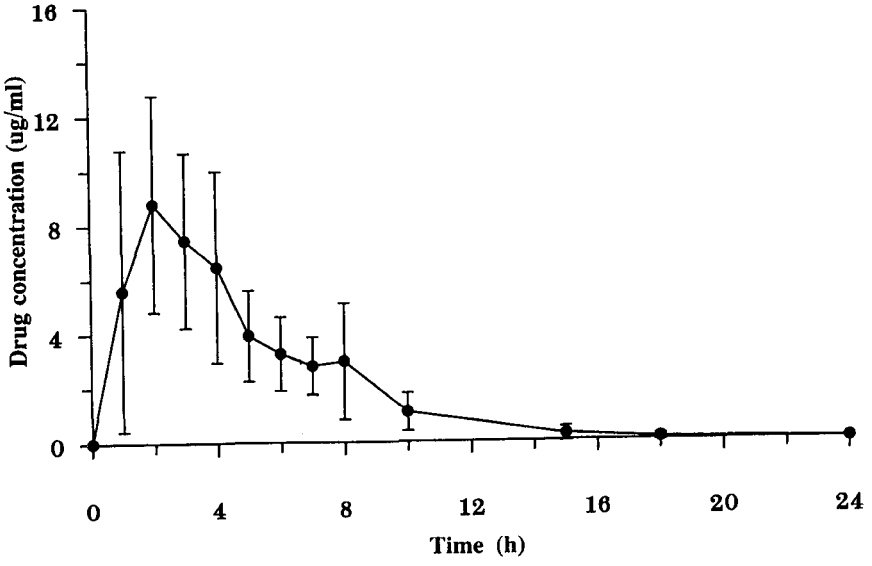

Fig. 1. Mean serum concentrations of rifampicin in eight AIDS patients following administration of a 600 mg of oral rifampicin once daily for 14 days.

The results of our study did not confirm the previous studies. Rifampicin kinetics studies in AIDS patients showed that the mean C_{max} of rifampicin were within normal ranges. The absorption of rifampicin in most of our AIDS patients were not reduced and delayed except for two patients. This may be due to 1) the low body weight of our Thai patients when compared with patients in previous studies 2) high CD_4 cell count of our Thai patients. Therefore, rifampicin dosage adjustment for Thai patients may not be necessary. However, drug monitoring should be required in advanced AIDS patients to prevent treatment failure.

SUMMARY

The absorption of rifampicin in most of our AIDS patients was not reduced and delayed. Therefore, rifampicin dosage adjustment for Thai patients may not be necessary.

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REFERENCES

1. Cohn DL. Treatment and prevention of tuberculosis in HIV-infected persons. Infect Dis Clin North Am 1994; 8: 399-412.
2. Sathe SS, Reichman LB. Mycobacterial disease in patients infected with the human immunodeficiency virus. Clin Chest Med 1989; 10: 445-63.
3. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries : epidemiology and strategies for prevention. Tuber Lung Dis 1992; 73: 311-21.
4. Mandell GF, Sande MA. Antimicrobial agents : drugs used in the chemotherapy of tuberculosis and leprosy. In : Gillman AG, Rall TW, Nies AS, Taylor P, eds. Goodman & Gillman's the Pharmacological Basis of Therapeutics. 8th ed. New York: Pergamon Press, 1991: 1146-64.
5. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications. N Engl J Med 1993; 329: 1122-3.
6. Patei KB, Belmonte R, Crowe HM. Drug malabsorption and resistant tuberculosis in HIV-infected patients. N Engl J Med 1995; 332: 336-7.
7. Berning SE, Huitt GA, Iseman MD, et al. Malabsorption of antituberculosis medications by a patient with AIDS. N Engl J Med 1992; 327: 1817-8.
8. Darouiche R, Perkins B, Musher D, et al. Levels of rifampin and ciprofloxacin in nasal secretions : correlation with MIC90 and eradication of nasopharyngeal carriage of bacteria. J Infect Dis 1990; 162: 1124-7.
9. Gillin JS, Shike M, Alcock N, et al. Malabsorption and mucosal abnormalities of the small intestine in the acquired immunodeficiency syndrome. Ann Intern Med 1985; 102: 619-22.
10. Gordon SM, Horsburgh Jr CR, Peloquin CA, et al. Low serum levels of oral antimicrobacterial agents in patients with disseminated Mycobacterium avium complex disease. J Infect Dis 1993; 168: 1559-62.

เภสัชจลนศาสตร์ของยาไรแฟมปิซินชนิดกินในผู้ป่วยเอดส์

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จากการศึกษาในผู้ป่วยเอดส์พบว่าความเข้มข้นสูงสุดของ rifampicin ในซีรั่มที่เวลา 2 ชั่วโมง หลังการบริหารยาจะต่ำกว่าค่าปกติ ซึ่งเชื่อว่ามีสาเหตุมาจากการดูดซึมที่ผิดปกติของยาอันจะนำไปสู่ความล้มเหลวในการรักษา อย่างไรก็ตามจนถึงปัจจุบันยังไม่มีข้อมูลที่แสดงให้เห็นถึงเภสัชจลนศาสตร์ของ rifampicin ในผู้ป่วยเหล่านี้ ดังนั้นวัตถุประสงค์ของการศึกษาครั้งนี้ก็เพื่อแสดงให้เห็นถึงข้อมูลเหล่านี้ ผู้ป่วยเอดส์ที่เป็นวัณโรคจำนวน 8 ราย จะได้รับ rifampicin ในขนาด 600 มก/วัน ในตอนเช้าขณะท้องว่าง ในวันที่ 14 ของการได้รับยา ผู้ป่วยจะถูกเจาะเลือดเพื่อศึกษาทางด้านเภสัชจลนศาสตร์ของยา ผลการศึกษาพบว่าค่าเฉลี่ยของความเข้มของยาสูงสุดในซีรั่มเท่ากับ 9.81±4.41 ไมโครกรัม/มล ค่าเฉลี่ยของเวลาที่จะได้ความเข้มข้นของยาสูงสุดในซีรั่มเท่ากับ 2.25±0.71 ชั่วโมง และค่าเฉลี่ยของพื้นที่ภายใต้กราฟของความเข้มข้นของยาในเวลา 24 ชั่วโมงเท่ากับ 60.25±36.88 ไมโครกรัม-ชั่วโมง/มล ผลจากการศึกษาครั้งนี้แตกต่างจากการศึกษาก่อนหน้านี้ การดูดซึมของยา rifampicin ในผู้ป่วยเอดส์ไม่ได้ลดลงหรือล่าช้า ดังนั้นขนาดของยานี้ที่ใช้ในคนไทยจึงไม่มีความจำเป็นต้องเปลี่ยนแปลง

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