doi: 10.1111/j.1472-8206.2007.00490.x

ORIGINAL ARTICLE

Lack of association between rifampicin plasma concentration and treatment-related side effects in osteoarticular infections

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Keywords
gastrointestinal side effects,
hepatotoxicity,
rifampicin,
therapeutic drug
monitoring

Recevied 25 July 2006;
revised 6 November 2006;
accepted 19 February 2007

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Correction added after online publication 19 April 2007: Author names corrected (Choulet was changed to Choutet, Simorinard was changed to Simonnard and LeGuellec was changed to Le Guellec).

ABSTRACT

The aim of this study was to assess the frequency of gastrointestinal side effects (GSE) and hepatotoxicity in patients treated with rifampicin for an osteoarticular infection and to determine if there is an association between rifampicin plasma concentrations and side effects. Rifampicin plasma concentrations were prospectively measured before (trough concentration, C_0) and 2 ± 0.5 h (peak concentration, C_2) after drug intake. The presence of GSE, the alanine transferase (ALT) value, and concomitantly administered medications were recorded on the day rifampicin concentrations were measured. C_0 and C_2 were compared for differences regarding the presence or absence of side effects. Multivariate analysis was performed, with associated medications being taken into account. Seventy C_0 and 57 C_2 values were measured in 46 adults after a median treatment of 8 days (range, 1–179). Wide inter-individual variability was observed for C_0 and C_2. Thirteen (28%) patients reported GSE at least once. When GSE occurred, C_0 (median, 1 mg L^{-1}; range, 0.1–9.9 mg L^{-1}) and C_2 (median, 10.3 mg L^{-1}; range, 1.8–40.3 mg L^{-1}) were similar to C_0 (median, 0.6 mg L^{-1}; range, 0.1–10.3 mg L^{-1}) and C_2 (median, 10.9 mg L^{-1}; range, 2.9–29.0 mg L^{-1}) without GSE. The ALT value was more than normal in only three patients (6.5%) after rifampicin treatment began. The patients received no different associated medications whether or not GSE were present. Multivariate analysis showed no association between rifampicin plasma concentrations and GSE. GSE occur frequently in patients receiving rifampicin for osteoarticular infection but without an association with rifampicin plasma concentrations. Thus, therapeutic drug monitoring of rifampicin is irrelevant in the management of GSE.

INTRODUCTION

Antibiotherapy for osteoarticular infections is prolonged and frequently includes a combination of two or more antibiotics. Because of good rifampicin bioavailability, bone diffusion, and efficacy against staphylococci, rifampicin-based antibiotic combinations play an important role in the treatment of osteoarticular infections [1–4].

The clinical pharmacokinetics of rifampicin have been reported previously but were mainly assessed in healthy volunteers or patients treated for tuberculosis

[5–8]. Significant pharmacokinetic variability of rifampicin plasma concentrations and clearance has been reported [9,10]. Drug-related toxicity can be problematic, particularly in patients receiving rifampicin and isoniazid for tuberculosis. Adverse effects caused by rifampicin develop in <4% of patients receiving the standard daily dose for tuberculosis [6,11] and include gastrointestinal disturbance, hepatitis, and various immunoallergic side effects such as rash, 'flu-like syndrome', leukopenia, anemia, thrombocytopenia, or renal insufficiency [11–13]. Drug-induced hepatitis occurs in 1–2.5% of patients treated for tuberculosis with rifampicin-containing regimens; the incidence did not differ in patients treated with 400, 600, or 750 mg daily [7,11]. Hepatic toxicity associated with rifampicin-based antibiotic combinations for osteoarticular infections has not been studied extensively but seems moderate as an elevated transaminase level was noted in only one of 20 patients treated for osteoarticular infection [1]. However, rifampicin is perceived by clinicians as poorly tolerated when used to treat staphylococcal infections. Nausea, vomiting, and abdominal cramps could occur more frequently when 600 mg of rifampicin is administered twice daily, which is recommended for osteoarticular infections [14].

Therapeutic drug monitoring of rifampicin is currently recommended in patients treated for tuberculosis both to insure success in specific clinical settings and to avoid toxicity [10,15–17]. Patients who require therapeutic drug monitoring are those with multidrug-resistant tuberculosis, concomitant human immunodeficiency virus (HIV) infection, malnutrition, known malabsorption disease, hepatic or renal failure, and those who fail to respond to conventional therapy after 1–2 months [6,8,18]. Nevertheless, rifampicin concentrations have not been monitored in patients with non-tuberculous infections who are receiving higher dosages. Identifying a relationship between rifampicin plasma concentrations and toxicity in the presence of osteoarticular infections would provide the basis for individual dosage adjustment [10].

This pilot study was undertaken in patients treated with a rifampicin-based antibiotic combination for osteoarticular infections to assess the frequency of gastrointestinal side effects (GSE) and hepatotoxicity, examine the inter-individual variability in plasma concentrations of rifampicin, and compare rifampicin plasma concentrations in patients experiencing or not experiencing side effects.

PATIENTS AND METHODS

Description of patients

Patients 18 years or older treated in the orthopedic surgery unit with a rifampicin-based antibiotic combination for an osteoarticular infection were eligible to be included. No a priori calculation of the number of patients was made due to the exploratory nature of this study, which was conducted from May 1, 2004 to December 31, 2004. Forty-six patients (27 men, 19 women; mean age, 64.4 ± 19.5 years; median, 67 years; range, 19–93 years) were prospectively studied. No patients had a previously known hypersensitivity to rifampicin, malabsorption syndrome, or HIV infection. Patients with hepatic dysfunction [alanine transferase (ALT) levels increased by two more than normal] were not included. Patients were followed up for side effects from the day treatment started to hospital discharge.

Antibiotic treatment

All antibiotic combinations were allowed, according to the physician's prescriptions based on bacteriologic and clinical data. Rifampicin was administered parenterally on the day of surgery if patients were scheduled for surgery and then orally. Rifampicin was taken on an empty stomach, 2 h before breakfast and dinner.

All patients except two received oral therapy on the day of measurement. Forty-two patients (91%) received 600 mg twice daily, three patients received 600 mg three times daily, and one patient received 900 mg twice daily. Thirty (65%) patients underwent one measurement, eight (17.5%) underwent two measurements, and eight (17.5%) underwent three or more measurements.

Blood sampling for rifampicin measurement

Blood levels were determined during treatment, at least 24 h after rifampicin therapy began. All patients provided informed consent for these tests in compliance with the University Hospital of Tours Research Ethics Board. Blood samples were obtained to measure the trough concentration just before administration, i.e. 8 or 12 h after the previous dose. The peak concentration was measured $1\frac{1}{2}$ to $2\frac{1}{2}$ h after administration of oral rifampicin or immediately after completion of the 1-h rifampicin infusion [18].

Blood samples were collected in heparinized tubes and centrifuged within 2 h of sampling. Plasma then was supplemented with ascorbic acid and stored at −20 °C pending analysis. Rifampicin concentrations were measured by high-performance liquid chromatography

(HPLC) using the method described by Le Guellec et al. [19] without modification. The calibration curve for the assay was linear over the range of 0.1–10 mg L^{-1}. The limit of quantification (0.1 mg L^{-1}) was improved when compared with the original report because of a more sensitive UV-detector (WATERS 2487 variable wavelength absorbance detector; Waters SA, Saint Quentin-en-Yvelines, France). Intra-day reproducibility was 8.7%, 1.3%, and 0.8% at 0.1, 1, and 10 mg L^{-1}, respectively. Quality control specimens were analyzed within each run throughout the study period. The within-day coefficient of variation was 9.6% ($n = 21$), 6.5% ($n = 23$), and 5.7% ($n = 21$) at 0.1, 1, and 10 mg L^{-1}, respectively.

Clinical data

For each peak and trough level measurement, a predesigned request form was submitted to clinicians to collect patient demographic and clinical data that included age, sex, reason for treatment, underlying diseases, and related regular medications. On the day of the rifampicin peak and trough measurements, the presence of GSE, such as nausea, vomiting, diarrhea, or abdominal cramps, and/or the necessity for antiemetic medications were recorded.

Laboratory evaluations

The ALT value was obtained before rifampicin therapy started (baseline) and ±3 days around each rifampicin measurement. Rifampicin-induced hepatotoxicity would be considered if the ALT value was normal before rifampicin started and increased to exceed two times the normal during treatment.

Other treatments considered for side effect evaluation

Other medications introduced concomitantly with rifampicin were recorded. We first recorded all drugs taken by patients, especially antibiotics combined with rifampicin and analgesics including paracetamol-codeine, tramadol, and other morphine derivates, to compare their frequencies between patients with and without side effects. Using product information, we also identified those that might induce gastrointestinal disturbances, hepatotoxicity, or both, in order to include them in multivariate analysis of the risk of side effects.

Statistical analysis

The occurrence of GSE and an increase in the ALT value from a normal baseline value to greater than two times the normal were recorded if they occurred at least once in a patient. The percentage of patients who had side effects at least once was then determined. Median and range values of trough and peak rifampicin concentrations were derived from all drug measurements, whatever the sampling period. The intra-individual variability of rifampicin concentrations was evaluated on an individual basis to determine a trend according to the well-known metabolic auto-induction phenomenon.

Rifampicin plasma concentrations from patients in whom GSE were present were compared with those in whom GSE did not occur. Similarly, rifampicin levels were compared between measurements with and without abnormal ALT (>2 N) values. At this time, each measurement in an individual patient was considered independent of other measurements [unit of analysis, each rifampicin measurement (peak level and trough level)]. We also compared the frequency of each comedication between patients with and without side effects. The chi-squared test or Fisher's exact test was used for comparison between groups. Statistical significance was defined as $P < 0.05$.

Multivariate analysis of the risk of side effects was conducted using a marginal logistic model. This analysis allows taking into account the correlation between measurements from the same individual, which are not independent from each other, and adjusting for the presence or absence of coadministered drug(s) that also might induce side effects.

RESULTS

Rifampicin plasma concentrations

Seventy-five request forms were obtained after rifampicin treatment (range, 1–179 days; median, 8 days). Samples could not be obtained for five trough level and 18 peak level determinations. Seventy trough levels and 57 peak levels were ultimately determined (*Figure 1*). High inter-individual variability was observed, with a 100-fold range for trough concentrations and a 20-fold range for peak concentrations. The median trough level value was 1 mg L^{-1} (range, 0.1–10.3); ≤0.1 mg L^{-1} in 11 cases (16%); between 0.1 and 1 mg L^{-1} in 28 cases (40%); and >1 mg L^{-1} in 31 cases (44%). The median peak level value was 10.9 mg L^{-1} (range, 1.8–40.3); <5 mg L^{-1} in five cases (9%); between 5 and 10 mg L^{-1} in 22 cases (39%); and >10 mg L^{-1} in 30 cases (52%).

Analysis of rifampicin trough concentrations over time in those patients sampled more than once showed a trend to decrease with time during the first

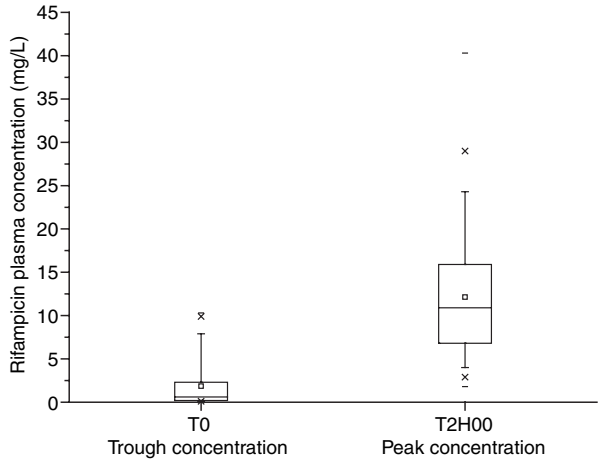

Figure 1 Trough and peak plasma concentrations of rifampicin from 127 measurements obtained from 46 patients during treatment. Subdivisions of the boxes and the top and bottom lines on the boxes represent median values and the 25th and 75th interquartiles, respectively. The squares (□) represent the mean value, the crosses (x) the 1st and 99th interquartiles, and the dashes (–) minimum and maximum concentrations observed.

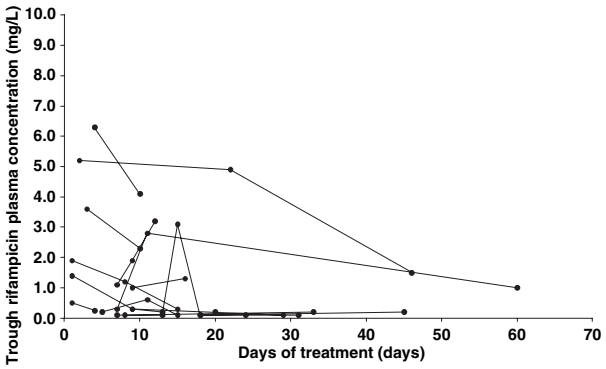

Figure 2 Evolution of rifampicin plasma trough concentrations over time for patients sampled more than once.

days of treatment (*Figure 2*). Concentrations fluctuated moderately in the majority of patients but were highly variable in others, without apparent explanation.

Side effects

Thirty-three patients (72%) had no side effects, and 13 (28%) reported GSE at least once and/or required antiemetic medications. The GSE consisted of nausea (70%), vomiting (12%), diarrhea (9%), or all of those, or the symptom was undetermined (9%). The median rifampicin treatment duration was similar whether or not patients presented with GSE. No differences were noted regarding rifampicin concentrations between patients who complained of GSE and those who did not (*Table I*).

Table I Peak and trough concentrations in patients with and without gastrointestinal side effects (GSE) and with and without ALT >1 N.

	GSE			ALT >1 N		
	Yes ($n = 13$)	No ($n = 53$)	P	Yes ($n = 8$)	No ($n = 38$)	P
Median C_0 (mg L^{-1})	1	0.6	0.94	0.8	0.7	0.43
Minimum C_0 (mg L^{-1})	0.1	0.1		0.2	0.1	
Maximum C_0 (mg L^{-1})	9.9	10.3		2.4	10.3	
	Yes ($n = 14$)	No ($n = 41$)		Yes ($n = 6$)	No ($n = 32$)	
Median C_2 (mg L^{-1})	10.3	10.9	0.96	12.5	11.2	0.43
Minimum C_2 (mg L^{-1})	1.8	2.9		6.1	3.6	
Maximum C_2 (mg L^{-1})	40.3	29		19.6	40.3	

Six (13%) patients had an ALT value greater than 1 N at least once. Among them, three already had a baseline ALT value greater than 1 N; only three patients (6.5%) had an ALT value greater than 1 N after the start of rifampicin treatment. None had an ALT value of 2 N or more. Trough and peak levels were similar between patients with an ALT value greater than 1 N and those with a normal ALT value (*Table I*).

Associated medications

Table II shows patients' treatment on the day of sampling for rifampicin values, according to the presence or absence of GSE. ALT were not considered at that stage because no patient experienced hepatotoxicity as defined in the study. Use of corticosteroids was statistically more frequent in patients with GSE. Tramadol also tended to have been administered more frequently to these patients, even though the difference did not reach significance. The statistical model that adjusted for administration of other drugs with potential GSE did not show an association between the rifampicin trough or peak levels and GSE.

DISCUSSION

The primary goals of this study were to assess the frequency of GSE and hepatotoxicity in patients treated with high-dose rifampicin and to determine a link between the occurrence of side effects and plasma concentrations. GSE appear to occur frequently in patients treated with a rifampicin-based antibiotic

Table II Rifampicin dosage and other medications administered on the day of measurement of rifampicin regarding the presence/absence of gastrointestinal side effects (GSE).

	Presence of GSE	Absence of GSE	P^a
Daily dose of rifampicin (mg)	1230 ± 236	1260 ± 194	0.58
Median (range) duration of treatment (days)	7.5 (1–60)	8.5 (1–179)	0.39
Associated medications (%)			
Morphine derivates	1 (5)	4 (7.3)	0.24
Tramadol	4 (20)	5 (9)	0.16
Paracetamol-codeine	5 (25)	20 (36)	0.52
Paracetamol-dextropropoxyphene	0	4 (7.3)	0.52
Paracetamol	6 (30)	19 (34.5)	0.93
Corticosteroids	7 (35)	1 (2)	0.0002
NSAID[b]	1 (5)	5 (9)	0.92
Antidepressant drugs	3 (15)	12 (22)	0.75
Bromazepam	6 (30)	10 (18.2)	0.39
Fluoroquinolones	13 (65)	47 (85)	0.05
Trimethoprim-sulfamethoxazole	4 (20)	5 (9)	0.24
Glycopeptide	2 (10)	5 (9)	0.61
Lactam	1 (5)	8 (15)	0.43
Others[b]	2 (10)	3 (5)	0.6

[a]Student's *t*-test or Mann–Whitney's test was used to compare continuous variables; the chi-square test or Fisher's exact test was used to compare caterogical variables.

[b]Non-steroidal anti-inflammatory drugs.

[c]Clindamycin ($n = 2$), metronidazole ($n = 2$), and fusidic acid ($n = 1$).

combination for osteoarticular infections. In contrast, hepatotoxicity, defined by an ALT value exceeding 2 N, was absent. GSE do not appear to be associated with plasma concentrations, which were highly variable.

Adverse reactions to rifampicin were reported during treatment of tuberculosis in <4% of patients [11–13,20,21]. In our study, 28% of patients reported GSE, which is much higher than that observed in a prospective study involving patients treated for staphylococcal infections, where gastrointestinal disturbance was reported in four (7%) of 58 patients receiving fleroxacin-rifampicin [22]. The high frequency of GSE in our study could not only be associated with the dose used in patients with osteoarticular infections, which was twice as high as that prescribed for tuberculosis, but could also be explained by the fact that patients were specifically questioned about gastrointestinal symptoms and received many other medications. There was no difference in the rifampicin dose or treatment duration between groups. Corticosteroids and tramadol were more frequently prescribed in patients with GSE, despite a frequency that did not reach significance for tramadol, suggesting a possible role of these drugs in the development of GSE. The role of rifampicin in inducing GSE by itself cannot thus be established. Nevertheless, GSE appear to occur more frequently in patients receiving a rifampicin-based treatment for osteoarticular infection than in those treated for tuberculosis.

Serious rifampicin-induced hepatitis has been reported in patients treated for tuberculosis, but who usually received a combination of isoniazid, rifampicin, and pyrazinamide [23]. In fact, rifampicin-induced hepatitis seems to be rare, and rifampicin might synergistically increase the risk of isoniazid or pyrazinamide-induced hepatitis in patients treated for tuberculosis [14,24]. In our study, elevated ALT values were rare, never reached critical levels, and were not clinically relevant. Similar results were found in previous studies in patients treated with rifampicin for staphylococcal infections [1,25,26]. These results confirm that the risk of rifampicin-induced hepatotoxicity is low even at higher dosages than that prescribed for tuberculosis, in patients who do not take isoniazid or pyrazinamide concomitantly. We found no relationship between rifampicin concentrations and ALT value even if we cannot exclude that hepatotoxicity could occur after a time lag.

The rifampicin plasma concentrations obtained in this study varied substantially, but were similar to those previously observed in healthy volunteers or in patients treated for tuberculosis [8–10,27]. Variability in rifampicin plasma concentrations is mainly attributed to varying intestinal absorption [8–10,15,17,18,28–30], the effect of food [31], or body size [8], and differences in hepatic metabolism [7]. In this study, all patients received rifampicin on an empty stomach and none of them had had a previously known malabsorption syndrome; thus, substantial variation in rifampicin plasma concentrations could not arise from variation in absorption due to food intake or accompanying diseases. As expected, plasma concentrations decreased with time, but the samples from the first week were not excluded from analysis because we aimed to explore a relationship between drug blood levels and side effects at the time they were observed.

In our study, the development of GSE was not linked to plasma concentrations, namely, to trough concentrations and to peak levels measured 2 h after drug intake. This does not mean that such a link does not exist but extensive analysis would have required the measurement of the area under the concentration–time curve to estimate total drug exposure, or of another sample at 6 h post-dose [17]. Obviously, a multiple sampling design

would have allowed more precise study of the concentration–effect relationships and also detection of patients with unusual absorption profiles and delayed C_{max}. However, the concentration–effect relationships of rifampicin had never been studied before in osteoarticular infections and a more complicated sampling scheme could not be envisaged for this exploratory study.

Despite the small sample size of this study, our results suggest that therapeutic drug monitoring of rifampicin is irrelevant for managing gastrointestinal toxicity in nontuberculous infections. If GSE occur in patients receiving rifampicin-based antibiotic treatment for osteoarticular infection, associated medications, particularly analgesics, should be first considered as causes and the treatment modified. Secondly, if we suspect the role of rifampicin, doses should be decreased, before stopping rifampicin, which is a highly powerful compound in the treatment of osteoarticular infections [2–4]. Even if our results do not show any dose–side effects relationship, we cannot conclude that one does not exist for a patient due to the high variability in the dose response. Therapeutic drug monitoring of rifampicin for efficacy has not been validated, but warrants further study because some patients can exhibit low rifampicin serum concentrations, which could theoretically lead to drug resistance.

ACKNOWLEDGEMENTS

The authors thank Lynda Charters for assistance in manuscript preparation.

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