GAVIN PUBLISHERS

Applied Clinical Pharmacology and Toxicology

Research Article

Dupouey J, et al. Appl Clin Pharmacol Toxicol 3: 122.

DOI: 10.29011/2577-0225.100022

Plasma Rifampicin Concentrations in Patient Treated for Osteoarticular Infections and Impact on Clinical Outcomes

J Dupouey[1], C Muziotti[1], A Marsot[2], E Jouve[1], J Micallef[1], O Blin[1], A Ménard[3], R Guilhaumou[1*]

[1]Department of Clinical Pharmacology and Pharmacovigilance, CIC-CPCET, Hôpital de la Timone, Marseille.

[2]Laboratoire de Suivi Thérapeutique Pharmacologique et Pharmacocinétique, Faculté de Pharmacie, Université de Montréal, Montréal H3T 1J4, Canada (QC)

[3] Pôle des Maladies Infectieuses et Tropicales, Fondation IHU Méditerranée Infection, AP-HM, Marseille cedex 05, France.

[*]**Corresponding Author:** Romain Guilhaumou, Department of Clinical Pharmacology and Pharmacovigilance, Hôpital de la Timone, Marseille, Telephone: +330610270117; E-mail: romain.guilhaumou@ap-hm.fr, romain.guilhamou@hotmail.fr

Citation: Dupouey J, Muziotti C, Marsot A, Jouve E, Micallef J, et al. (2019) Plasma Rifampicin Concentrations in Patient Treated for Osteoarticular Infections and Impact on Clinical Outcomes. Appl Clin Pharmacol Toxicol 3: 122. DOI: 10.29011/2577-0225.100022

Received Date: 08 August, 2019; **Accepted Date:** 25 October, 2019; **Published Date:** 30 October, 2019

Abstract

Rifampicin (RIF) is the key antibiotic treatment in Osteoarticular Infections (OAI) due to gram positive cocci. In tuberculosis patients, RIF pharmacokinetics studies reveal an important inter individual variability and therapeutic drug monitoring appears as an essential tool. However, data are lacking regarding RIF concentrations variability in OAI and impact on infection management. The aim of this descriptive study was to characterize RIF concentrations and variability in patient treated for OAI. Association with clinical evolution and side effects was also evaluated. We retrospectively analyzed RIF plasma concentrations observed in patients hospitalized for OAI and treated with 300 mg three times daily. Observed concentrations were described by median and range. Relationship with demographic (age, sex, body weight) and clinical data (material type, antibiotic comedication, side effects, clinical course) was also evaluated. Plasma concentrations were collected in thirty six patients. Median peak RIF concentration was 3.9 µg/ml with a wide variability (0.6 - 16.1 µg/ml). RIF median concentration (range) was significantly lower in patients presented a poor clinical course (n=11): 3.4 (0.7-10.5) µg/ml vs 4.3 (0.6-16.1) µg/ml (p=0.027). RIF median concentration was not significantly different in patients presented gastrointestinal disorders or not (3.85 µg/ml vs 4.25 µg/ml, respectively, p=0.788). This study points out the large inter-individual variability of rifampicin plasma concentrations in OAI. Prospective studies seem essential to confirm the impact of this pharmacokinetic variability on patient outcome and define the specific therapeutic range of RIF in these indications.

Keywords: MRSA; Osteoarticular Infection; Plasma Concentration; Rifampicin

Introduction

Osteoarticular Infections (OAI) remain currently serious diseases, notably due to orthopedic material associated complications [1,2]. According to French and American recommendations, Rifampicin (RIF) still represents the key antibiotic in staphylococcal OAI treatment, always in association to prevent the emergence of bacterial resistance [3,4]. Indeed, RIF fulfills main criteria for OAI treatment, with an important bactericidal activity for susceptible strains as *Staphylococcus aureus* or Coagulase-Negative Staphylococci (CNS) [5,6], a good oral bioavailability, an excellent diffusion in bone tissue and biofilm [7,8] and a limited toxicity as hepatotoxicity and gastrointestinal side effects [9-12]. RIF Therapeutic Drug Monitoring (TDM) is routinely performed in tuberculosis patients, especially in high risk populations (suspected malabsorption, HIV infection, diabetes mellitus, drug-drug interactions) [13].

In IAO, several arguments seem to be relevant to support RIF TDM: necessity to obtain adequate concentrations in the bone compartment (superior to MIC); a higher risk of potential toxicity due to a high dose (20mg/kg compared to 10 mg/kg classically used in tuberculosis) and long treatment duration (3 to 6 months) [3]. Moreover, an important Pharmacokinetic (PK) variability and an impact of comedication on PK parameters has been recently observed in this population [14]. However, in order to consider TDM RIF in IOA, data are lacking on observed rifampicin peak concentrations, variability and impact on clinical evolution/ side effects. In the present study, we described RIF observed concentrations and variability after a therapeutic schedule of 300 mg three times daily in patient treated for OAI. Association

with clinical course and side effects was also evaluated.

Patients and Method

Description of patients

Patients hospitalized in Infectious Diseases Unit (La Conception hospital, Marseille) for OAI were retrospectively included from August 2012 to October 2014. Inclusion criteria were an oral antibiotherapy including RIF 300 mg three times daily for three or six months (without/with material infection, respectively) and one determination of RIF peak concentration. Therapeutic schedule of 300 mg three times daily was chosen historically by clinicians regarding to a feeling of a better tolerance of RIF, with less hepatotoxicity or gastrointestinal side effects reported by patients. RIF concentrations were determined to confirm compliance, detect absorption impairment and in case of suspected toxicity. The same day rifampicin concentration has been determined, demographic (age, sex, body weight) and clinical data (material type, antibiotic comedications, side effects, clinical course) were collected from medical files. Compliance and side effects were reported by patients, using a questionnaire with a "yes/no" item for "compliance", "nausea", "vomiting", "diarrhea", "abdominal pain" or "other side effects". Clinical course was determined as "poor" or "good" by clinicians based on a complete or partial resolution of leukocytosis, temperature (<38.5°C) and signs of infection (clinical, radiological or microbial evidence of infection). Biological data as RIF plasma concentration, plasma creatinine, hepatic enzyme blood levels (ALT, AST and GGT) and bacteriological results were collected from the hospital laboratory database.

Determination of RIF Blood Concentration

Samplings were performed at least two weeks after the introduction of antibiotic therapy (steady state condition) and two to three hours after drug intake (peak concentration) [13]. Blood sample was dispatched within 5 hours to the laboratory. Plasma was separated and frozen at -80°C until analysis. RIF plasma concentration was quantified in plasma using a high performance liquid chromatography assay with UV detection, validated according EMA guidelines [Guideline on bioanalytical method validation. European Medicines Agency. 2011]. Briefly, extraction procedure was carried out using acetonitrile, with diazepam as internal standard. Chromatography was performed on a C18 column. Elution was achieved isocratically with potassium buffer/acetonitrile at a flow rate of 1.0 ml/min. Method was linear in the 0.5-20 µg/mL range [14].

Statistical Analysis

RIF plasma concentrations distribution was described by median and range. Relationship between concentration and dosage (in mg/kg/day), age and body weight was investigated using Pearson coefficient correlation. The median test was used for analyzing the impact of sex, comedications and infection type (materiel or not) on RIF observed concentrations and compare RIF concentrations according to clinical course and associated side effects. Proportions were compared using Fisher's exact test. A p-value of <0.05 was considered statistically significant. Analyses were performed using the software SPSS version 17.

Results

Between August 2012 and October 2014, 36 patients were included, with a sex ratio of 2.6. In most case, patients presented material infection with prosthesis (n=16) or osteosynthesis equipment (n=12). The most incriminated pathogen was *Staphyloccocus aureus* (n=22) followed by CNS (n=16), mainly in monomicrobial infection (n=31). Patient characteristics are summarized in (Table I). All patients ensured good compliance to treatment.

One blood sample per patient was collected and all of the observed concentrations were over the limit of quantification.

Demographical data	Total
Total patient	36
Sex ratio (M/W)	2.6 (26/10)
Age (years)	54.0 (20 to 82)
Body weight (kg)	73.0 (46 to 119)
Dosage (mg/kg/d)	12.3 (7.6 to 19.6)
Infection type Prosthesis infection (knee/hip/elbow)	16 (8/7/1)
Osteosynthesis material infection	12
Knee arthritis	3
Spondilitis	3
Brodie abcess	1
Elbow arthritis	1
Antibiotic Comedication Fluoroquinolone (ofloxacin/ciprofloxacin)	18 (15/3)
Fucidic acid	9
Clindamycin	5
Glycopeptides (vancomycin/teicoplanin)	6 (4/2)
Beta-Lactams	5
Cotrimoxazole	1

Table I: Demographical and clinical description of the studied population. Data are median (minimum to maximum) or frequency.

Median RIF peak concentration was 3.9 µg/ml, with minimal and maximal observed concentrations of 0.6 µg/ml and 16.1 µg/ml (Figure 1). No correlation was observed between RIF concentrations and dosage, age and body weight (Figure 2). Patients with fusidic acid coadministration presented higher median RIF concentrations (range): 8.9 (2.1-16.1) µg/ml vs 3.6 µg/ml (0.6 -11.5) (p=0.012). No influence of sex, infection type and others coadministrated antibiotics was observed.

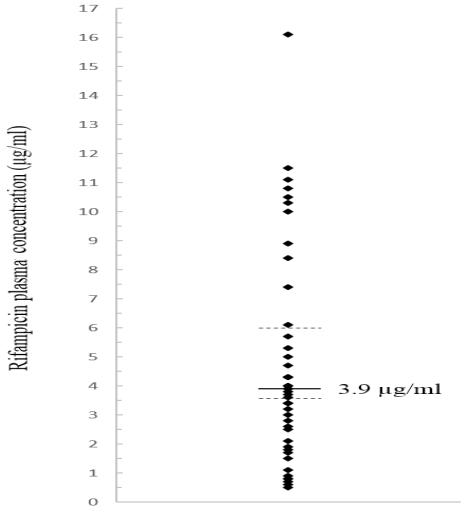


Figure 1: Observed rifampicin plasma concentrations (µg/ml). Horizontal bars depict median value (solid line) and IC95% (dotted line).

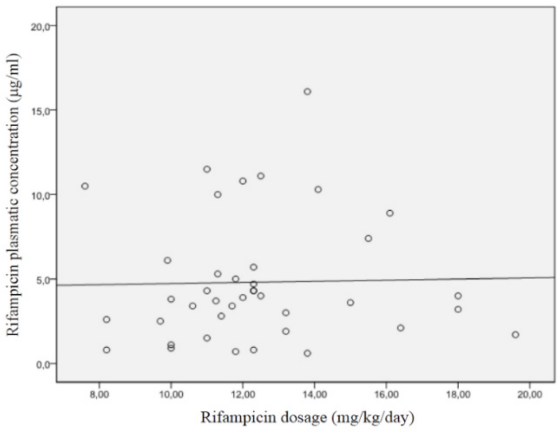
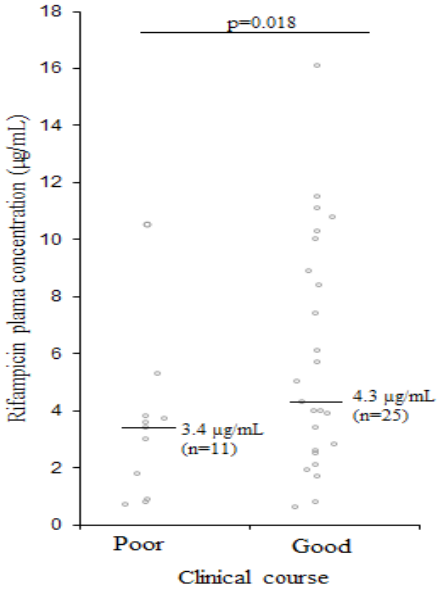


Figure 2: Rifampicin maximal plasmatic concentrations and dosage correlation.

RIF median concentration (range) was significantly lower in patients presented a poor clinical course (n=11): 3.4 (0.7-10.5) µg/ml vs 4.3 (0.6-16.1) µg/ml (p=0.027) (Figure 3). Proportion of good clinical course was lower in patients with material infection compared to non-material infection (69.4% versus 87.5%, respectively, p<0.05).

(a)



(b)

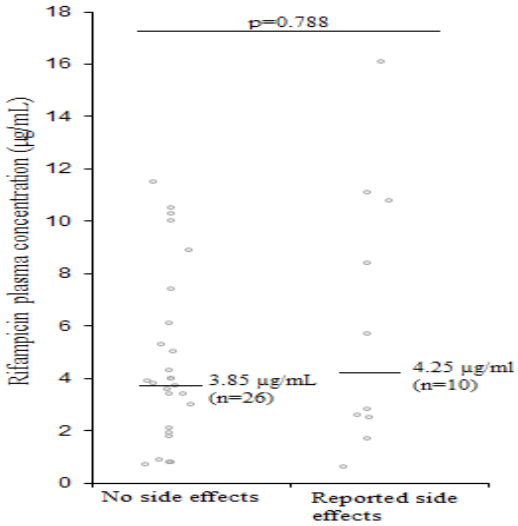


Figure 3: Comparison of rifampicin median plasma concentrations and clinical course **(a)** or reported side effects **(b)** evaluated during consultation. Horizontal bars depict median values.

Analyzing plasma creatinine and hepatic enzyme blood levels, all patients presented normal liver and renal function, without biological abnormalities. Ten patients reported gastrointestinal disorders. RIF median concentration was not significantly different to patients presenting a safer profile: 3.85 µg/ml vs 4.25 µg/ml, respectively (p=0.788) (Figure 3). Median dosage in mg/kg was not different between patients presented gastrointestinal disorders or not (12.6 mg/kg vs 12.4 mg/kg respectively, p=0.622).

Discussion

If the legitimacy of RIF is undeniable in the management of staphylococcal OAI [2,4], there is a lack of published data concerning observed concentrations and variability in this indication. In our study, we described RIF plasma concentrations observed in patients treated for OAI with 300mg three times daily. We observed a wide inter-individual variability, with a 25-fold range for RIF peak concentration (0.50 µg/ml to 16.10 µg/ml). These results are consistent with data from Roblot et al, reporting that a same dose regimen could result in an important range of plasma RIF concentrations [15]. Moreover, other studies confirmed the important inter-individual variability of RIF pharmacokinetic in tuberculosis patients or in healthy subjects, notably due to a variable absorption rate [16-18]. No correlation was observed in our study between dosage (in mg/kg/day) and plasma maximal concentration (p=0.884), in accordance with results from Guillaume et al [19]. The "take-home message" from these observations is that an identical dose of RIF will not lead to a predictable plasma concentration, correlated to a potential variability in antibiotic activity. In OAI, low plasma concentrations could lead to low concentrations in bone tissue, potentially associated with an antibiotic inefficiency and acquisition of drug resistance [20]. Consequently, the important variability observed in RIF concentrations is in accordance with a usefulness of RIF TDM in this population, as in patients treated for TB. This argument is supported by the observation in our study of lower RIF concentrations in patients with a poor clinical course. This is especially crucial in material infection that is well-known to have a poorer clinical outcome [1]. Indeed, we observed in our study a lower ratio of good clinical course in this population. However, studies are still lacking concerning the PK/PD target and the therapeutic range of RIF concentrations in OAI. In a murine model studying Staphylococcal pulmonary infection, Hirai et al. [21] showed that rifampicin demonstrated concentration-dependent killing. Cmax was a good predictive PK/PD index, but was impacted by dosing schedule, so they conclude that the AUC/MIC was a more pertinent predictive PK/PD index. The AUC/CMI target was defined as 952 for *Staphyloccocus aureus*. However this target was not confirmed in infected patients and future studies are required to determine specific therapeutic range of RIF in OAI.

No relationship between occurrence of side effects and RIF plasma concentrations was observed in our study. In a comparable study, Roblot et al. failed to identify a relationship between RIF plasma concentrations and toxicity in patient treated for OAI. In absence of any concentration-side effects relationship, they concluded that TDM of RIF was irrelevant for managing gastrointestinal toxicity in this population [14]. Our results seem consistent with their conclusion. However, in presented study, hepatotoxicity or gastrointestinal side effects were reported by patients and not based on any biomarkers or physician's diagnosis. Less side effects were reported, probably due to the difficulty for patients to precisely self-diagnose symptoms that are good indicators of hepatotoxicity or gastrointestinal side effects. Consequently, furthers studies are required to investigate the relation between rifampicin concentration and sides effects, especially in high dose regimen. Current issues remain debated for the ideal dose to be used in OAI. Indeed, studies and recommendations are not consensual. According to IDSA recommendations, medical treatment for a patient with Staphylococcal OAI is RIF 300–450 mg orally twice daily [2,22]. The recommended dose according to French recommendations is 20 mg/kg/day, divided into two or three doses [3]. Other studies report successful treatment with a dose of 20 mg/kg/d, without specifying the schedule [17,23], or recommend different dose, such as 300 mg or 450 mg in two intakes [2,24]. Thus, additional data on RIF PK/PD target in IOA infection are require to determine the ideal daily dosage and frequency of administration of RIF.

Our study presents some limits. First, only a cohort of 36 subjects could be included and a larger sample size would provide a better estimate of RIF concentrations and variability. Moreover, owing to the retrospective design of the studies, the compliance was assessed as patient self-assessment which is not the best tool of evaluation. A DOT - directly observed treatment – methodology would have been more appropriate. Likewise, impact of several covariates on RIF concentrations were not tested due to the retrospective nature of the study. A prospective study including non antibiotic comedications, eating habits or body mass index, should improve the description of RIF concentrations variability. In the same way, some confounding factors affecting postoperative course of OAI have to be included in a future study (comorbidities, smoking habits). In conclusion, presented results showed an important inter-individual variability of RIF plasma concentrations in patient treated in OAI, in favor of RIF TDM. Prospective studies seem essential to confirm the impact of this pharmacokinetic variability on patient outcome and determine specific therapeutic range of RIF in OAI.

Acknowledgements:

The authors would like to thank Laurence Delaunay, Bérengère Lambert and Laurent Allanioux for their excellent technical assistance and Amina Mendjel for collecting clinical and biological data in medical files.

Ethical issues: Ethical approval was granted by the local ethics committee AMU (n° 2016-06-07-06).

Funding: This study was supported by internal funding.

Conflict of interest statement: The authors have no conflict of interest to declare.

Author's contributions: JD and CM performed the experiments. JD, AM[1], EJ and RG analyzed the data. AM[1] and EJ performed statistical analysis. AM[2] included patient. JD, CM, JM, AM[2] and RG wrote the manuscript. OB validated the manuscript. RG conceived and designed the study and supervised the work. All authors read and approved the final manuscript.

Meeting presentation: Part of these data was presented as an oral presentation at the "16èmes Journées Nationales d'Infectiologie", June 12 2014, Bordeaux, France.

Reference

1. Leone S, Borrè S, Monforte A, Mordente G, Petrosillo N, et al. (2010) Consensus document on controversial issues in the diagnosis and treatment of prosthetic joint infections. Int J Infect Dis l 4: S67-77.

2. Zimmerli W, Trampuz A, Ochsner PE (2004) Prosthetic-joint infections. N Engl J Med 351: 1645-1654.

3. Recommendations for clinical practice. Osteo-articular infection therapy according to materials used (prosthesis, implants, osteosynthesis). Med Mal Infect 39: 745-774.

4. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, et al. (2013) Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 56: 1-10.

5. EUCAST 2015: http://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=242&Specium=-1

6. Murphy CK, Karginova E, Sahm D, Rothstein DM (2007) In vitro activity of novel rifamycins against gram-positive clinical isolates. J Antibiot 60: 572-576.

7. LaPlante KL, Woodmansee S (2009) Activities of daptomycin and vancomycin alone and in combination with rifampin and gentamicin against biofilm-forming methicillin-resistant *Staphylococcus aureus* isolates in an experimental model of endocarditis. Antimicrob Agents Chemother 53: 3880-3886.

8. Saginur R, St Denis M, Ferris W, Aaron SD, Chan F, et al. (2006) Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. Antimicrob Agents Chemother 50: 55-61.

9. Darley ES, MacGowan PA (2004) Antibiotic treatment of Gram-positive bone and joint infections. J Antimicrob Chemother 53: 928-935.

10. Forrest GN, Tamura K (2010) Rifampin Combination Therapy for Nonmycobacterial Infections. Clin Microbiol Rev 23: 14-34.

11. Grosset J, Leventis S (1983) Adverse effects of rifampicin. Rev Infect Dis 3: S440-450.

12. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE (1998) Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 279: 1537-1541.

13. Alsultan A, Peloquin CA (2014) Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs 74: 893-954.

14. Marsot A, Ménard A, Dupouey J, Muziotti C, Guilhaumou R, et al. (2017) Population pharmacokinetics of rifampicin in adult patients with osteoarticular infections: interaction with fusidic acid. Br J Clin Pharmacol 83: 1039-1047.

15. Roblot F, Besnier JM, Giraudeau B, Simonnard N, Jonville-Bera AP, et al. (2007) Lack of association between rifampicin plasma concentration and treatment-related side effects in osteoarticular infections. Fundam Clin Pharmacol 21: 363-369.

16. Acocella G (1978) Clinical pharmacokinetics of rifampicin. Clin Pharmacokinet 3: 108-127.

17. Acocella G, Pagani V, Marchetti M, Baroni GC, Nicolis FB (1971) Kinetic studies on rifampicin. I. Serum concentration analysis in subjects treated with different oral doses over a period of two weeks. Chemotherapy 16: 356-370.

18. Egelund EF, Alsultan A, Peloquin CA (2015) Optimizing the clinical pharmacology of tuberculosis medications. Clin Pharmacol Ther 98: 387-393.

19. Guillaume M, Garraffo R, Bensalem M, Janssen C, Bland S, et al. (2012) Pharmacokinetic and dynamic study of levofloxacin and rifampicin in bone and joint infections. Med Mal Infect 42: 414-420.

20. Wehrli W (1983) Rifampin: mechanisms of action and resistance. Rev Infect Dis l 3: S407-411.

21. Hirai J, Hagihara M, Kato H, Sakanashi D, Nishiyama N, et al. (2016) Investigation on rifampicin administration from the standpoint of pharmacokinetics/pharmacodynamics in a neutropenic murine thigh infection model. J Infect Chemother 22: 387-394.

22. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, et al. (2013) Reply to Eisen and Denholm, Dauchy et al, Fierer, and Nguyen and Jones. Clin Infect Dis 57: 162-164.

23. Senneville E, Joulie D, Legout L, Valette M, Dezeque H, et al. (2011) Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis 53: 334-340.

24. Aboltins CA, Page MA, Buising KL, Jenney AW, Daffy JR, et al (2007) Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid. Clin Microbiol Infect 13: 586-591.