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Rifaximin intake leads to emergence of rifampin-resistant staphylococci

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KEYWORDS
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Summary *Objectives:* Rifaximin is a poorly absorbed non-systemic antimicrobial agent used in various gastrointestinal disorders. Rifampin is pivotal for the treatment of staphylococcal foreign body infections and resistance develops rapidly during monotherapy. The close structural relation of rifaximin to rifampin may lead to cross-resistance. The aim of our study was to determine whether rifampin-resistance emerges in human skin staphylococci during or after oral intake of rifaximin.
Methods: Rifampin resistance of skin staphylococci in healthy volunteers during and after intake of rifaximin was determined by E-Test.
Results: Seven out of eleven volunteers developed rifampin-resistant staphylococci after intake of rifaximin. A total of eleven rifampin-resistant and three rifampin-intermediate staphylococcal isolates were found. Before or during intake no resistant isolate was detected. Shortly after discontinuation the rifampin-resistant strains were primarily isolated from the perianal skin, a few weeks later they were found more frequently on the skin of the hands and lower arms.
Conclusion: Our data show that rifampin-resistant staphylococci emerge after intake of rifaximin. Since rifampin resistance is associated with treatment failure in staphylococcal foreign body infections, we conclude that rifaximin should be avoided in patients at risk for these infections.

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Introduction

Foreign body infections account for approximately half of all hospital-acquired infections and staphylococci are the main causative organisms.[1] The economic burden of these infections is huge[2] and with an annually increasing number of implants it is likely to rise further. Rifampin plays an important role as combination partner in the treatment of staphylococcal foreign body infections.[3,4] Rifampin-based oral step-down therapy for *Staphylococcus aureus* ostemyelitis has proven to be very efficient,[5] and its indications include the treatment of osteomyelitis due to MRSA.[6] The advantages of rifampin in these infections include its high level of biofilm activity,[7] the prevention of resistance development to fluoroquinolones[8] and its excellent availability after oral intake. The latter is important as staphylococcal foreign body infections often require long term treatment. Treatment failure has been associated with rifampin-resistance of staphylococci in prosthetic joint infections[9] and cerebrospinal fluid shunt-associated infection.[10] It is well known that monotherapy with rifampin leads to rapid development of resistance in staphylococci[11] and that a single point mutation is responsible for clinically relevant high-level-resistance.[12] Resistance to rifampin renders staphylococcal foreign body infections difficult to treat.Rifampin is closely related to rifaximin in structure,[12] which allows the possibility of cross-resistance between these two substances.

Rifaximin is a widely distributed antimicrobial agent used to treat traveller's diarrhea,[13,14] *Clostridium difficile* associated diarrhea[15,16] and hepatic encephalopathy.[17,18] It is virtually not absorbed and reaches very high concentrations in the human bowel, where it is active against many enteropathogens.[19] When excreted with the stool rifaximin comes in contact with human skin staphylococci.

The development of rifaximin-resistance in staphylococci has already been shown in-vitro[20] and spontaneous rifaximin-resistance has also been described.[21] The possibility of cross-resistance between rifampin and rifaximin has been discussed,[22] but no evidence has been put forward. The aim of our study was to determine whether rifaximin intake leads to the development of rifampin-resistant staphylococci in healthy volunteers.

Materials and methods

The study was approved by the local ethics committee and was registered at EudraCT (trial number 2008-006382-91, https://eudract.emea.europa.eu/). Twelve healthy volunteers were recruited for the study. Oral and written informed consent was provided. The mean age of the volunteers was 38 years (range 28—59). Nine volunteers were male and three female. Pregnancy was excluded in the female volunteers prior to intake of the drug. Swabs from the hands, lower arms and perianal skin were obtained on days 0, 2, 8, 14 (one volunteer was not available on day 14), 21, 35 and 70. From day 1—7 the volunteers took rifaximin 400 mg bid orally. Swabs were cultured on sheep blood agar and incubated for 18—24 h at 35 °C in ambient air. Colonies morphologically compatible with staphylococci were further processed and identified by Gram staining, catalase reaction, coagulase reaction and API Staph (bioMérieux, Vienna, Austria). All staphylococci were tested for their rifampin MIC using E-test (AB Biotest, Solna, Sweden) according to CLSI methods.[23] Rifampin MIC of ≥ 4 μg/mL was considered resistant, intermediate between 1 and 4 and susceptible ≤ 1 μg/mL.

A randomly selected subset of 240 rifampin-susceptible staphylococci and all isolates with a rifampin MIC >1 μg/mL (intermediate and resistant) were tested for their rifaximin inhibition zone on disk diffusion using a disk containing 40 μg of rifaximin (manufactured by Dr. Friedrich Bertoni GmBH, Vienna, Austria). Isolates with rifampin MIC >1 μg/mL (intermediate and resistant) were further genetically compared applying the DiversiLab *Staphylococcus* DNA fingerprinting kit for repetitive-sequence PCR (rep-PCR). The rep-PCR amplicons were detected and analysed using the DiversiLab System (BioMerieux, Vienna, Austria) with the Pearson correlation coefficient to determine the distance matrices and the unweighted pair group method with arithmetic mean to create dendrograms.

Statistics

For data entry and analysis Microsoft Excel and the Statistical Package for Social Sciences (SPSS) version 17 were used. A p-value of less than 0.05 (two-sided) was considered to indicate statistical significance.

Results

One volunteer had to discontinue the intake of rifaximin because of adverse events on day 2 (diarrhea and nausea). Eleven volunteers completed the study. During the study 739 staphylococcal isolates were obtained (Table 1). The mean number of cumulative isolates per volunteer was 66 (range 49—86), the mean number of cumulative isolates per swab location was 148 (range 126—167) and the mean number of isolates per day was 105 (range 85—118). The number of isolates per volunteer who completed the study did not differ significantly concerning swab location (Cramer's V, $p = 0.985$) or study day (Cramer's V, $p = 0.692$).

On days 0, 2 and 8 (before and during intake) no rifampin-resistant staphylococcal skin isolate was found. On day 14 the first isolates with a MIC >32 μg/mL were detected (two isolates in two volunteers, Table 2). Seven volunteers developed rifampin-resistant staphylococci, two out of these additionally had rifampin-intermediate isolates and in one volunteer only a rifampin-intermediate strain was found. A total of eleven rifampin-resistant and three rifampin-intermediate isolates were obtained throughout the study from eight out of eleven volunteers. The resistant isolates were *Staphylococcus epidermidis* ($n = 6$), *Staphylococcus capitis* ($n = 2$), *Staphylococcus aureus* ($n = 2$) and one *Staphylococcus lugdunensis* isolate. On days 14 and 21 (one and two weeks after discontinuation of rifaximin-intake), the rifampin-resistant isolates were primarily isolated from perianal skin, on day 70 (nine weeks after discontinuation of rifaximin intake) the isolates were found mainly on the skin of the upper extremities. There was a statistically significant number of non-susceptible isolates after discontinuation of rifaximin