Low Concentrations of Mupirocin in the Pharynx following Intranasal Application May Contribute to Mupirocin Resistance in Methicillin-Resistant Staphylococcus aureus

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We describe a patient with methicillin-resistant Staphylococcus aureus (MRSA) colonizing the pharynx. The MIC of mupirocin was 0.25 μg/ml before treatment and increased after treatment to 8 μg/ml. Using pulsed-field gel electrophoresis, we confirmed that the genotypes of MRSA that colonized the pharynx before and after the use of mupirocin were identical. We measured the delivery of mupirocin to the pharynx in three normal volunteers and two patients. Low concentrations of mupirocin were present in the pharynx in all cases 10 min to 3 days after intranasal application. Our data suggested that low concentrations of the drug in the pharynx after intranasal application of mupirocin ointment might explain the selection of mupirocin resistance in MRSA.

Methicillin-resistant Staphylococcus aureus (MRSA) is an important pathogen and a major cause of nosocomial infection (19). MRSA strains easily colonize a host, particularly immunodeficient patients, and can cause a variety of serious infections that are often difficult to control, such as septicemia, endocarditis, meningitis, and postoperative intra-abdominal infection (3, 12, 13). Mupirocin is the most effective antibiotic for elimination of MRSA from the nasal passages (6). Moreover, intranasal application of mupirocin ointment is effective in reducing surgical-site infections and the likelihood of bronchopulmonary tract infection (5, 15). However, cases of mupirocin-resistant MRSA have already been reported (11). In Japan, mupirocin has been used only for the eradication of nasal colonization by MRSA since September 1996, and low-level mupirocin-resistant MRSA appeared in the early stages (17). We had a patient in whom the MRSA that colonized in the pharynx changed to low-level mupirocin-resistant MRSA after intranasal application of mupirocin ointment. We examined the genotypes of MRSA that colonized the pharynx before and after the use of mupirocin in the same patient and the delivery of mupirocin to the pharynx after intranasal application in three healthy volunteers and two patients with MRSA colonization of the pharynx.

All studies described herein were approved by the Human Ethics Review Boards of our institutions, and a signed consent form was obtained from each subject. The patient with low-level mupirocin-resistant MRSA was a 78-year-old male who had an old cerebral infarction. Spread of low-level mupirocin-resistant MRSA had been reported in the hospital to which the patient was admitted (17). MRSA is a common cause of nosocomial infection (3, 12, 13). Mupirocin is the most effective antibiotic for elimination of MRSA from the nasal passages (6). More-resistant MRSA have already been reported (11). In Japan, mupirocin has been used only for the eradication of nasal colonization by MRSA since September 1996, and low-level mupirocin-resistant MRSA appeared in the early stages (17). We had a patient in whom the MRSA that colonized in the pharynx changed to low-level mupirocin-resistant MRSA after intranasal application of mupirocin ointment. We examined the genotypes of MRSA that colonized the pharynx before and after the use of mupirocin in the same patient and the delivery of mupirocin to the pharynx after intranasal application in three healthy volunteers and two patients with MRSA colonization of the pharynx.

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zation in the pharynx (one in only the pharynx and the other in both the nasal cavity and pharynx) using a simple in vitro bioassay. For the bioassay, a standard curve was constructed by twofold serial dilutions of mupirocin-lithium phosphate buffer at pH 6.5. The bioassay was performed in brain heart infusion agar seeded with \textit{S. aureus} ATCC 6538P. The detection limit of the assay was 0.05 g/µl. Two patients had bronchiectasis and allergic rhinitis or chronic sinusitis as the underlying disease. The MICs of MRSA against mupirocin were 4.0 and 0.25 g/ml for the two patients. Mupirocin was applied to the anterior nares for 3 days. Cotton-tipped swab sticks were used to obtain pharyngeal secretions transorally, and the collected swabs were fixed samples were dissolved in 0.1 M phosphate buffer and analyzed. The concentration of mupirocin in the pharynx ranged from 0.13 to 27.7 µg/sample, although the local concentration of mupirocin was 20,000 µg/ml. At these concentrations, MRSA colonization in the pharynx was identical by PFGE with \textit{Sma}I.

Cilia in the nasopharynx are known to move particles from the nasal cavity into the pharynx, and such a process might be involved in the transport of mupirocin nasal ointment to the pharynx, resulting in low concentrations of the antibiotic in the pharynx, thus enhancing the selection of mupirocin resistance. Low-level and high-level mupirocin-resistant MRSA strains have been described previously (1, 4). Mupirocin resistance in MRSA results from changes in the target enzyme, isoleucyl-tRNA synthetase, while high-level mupirocin resistance is plasmid encoded. Mupirocin-resistant MRSA was first isolated from the skin of patients who were treated with mupirocin for long periods (11, 14), and several reports have cautioned against the long-term use of mupirocin in patients with skin infection (2, 10). Other studies have reported the development of mupirocin-resistant MRSA after widespread use of nasal mupirocin ointment (7). On the basis of these studies, it could be speculated that the cause of such resistance is related to our results, i.e., low concentrations of the antibiotic in the pharynx.

In conclusion, nasal application of mupirocin at clinically effective concentrations may result in low levels of the antibiotic in the pharynx, which could consequently induce or select for the emergence of mupirocin-resistant MRSA.

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FIG. 1. Mupirocin-susceptible MRSA (A; MIC, 0.25 µg/ml) that colonized the pharynx of our patient was transformed into low-level mupirocin-resistant MRSA (B; MIC, 8 µg/ml) after intranasal application of mupirocin ointment. The genotypes of MRSA that colonized the pharynx before and after the use of mupirocin in the same patient were identical by PFGE with \textit{Sma}I.

REFERENCES


