TITLE: PHENOTYPIC COMPARISON OF ISOLATES OBTAINED AFTER EXPOSING THE ST5-SCC*mec*II *Staphylococcus aureus* SA43 TO TEDIZOLID AND LINEZOLID.

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ABSTRACT:
Methicillin-resistant *S. aureus* ST5-SCC*mec*II infections have emerged in Brazilian hospitals and are a challenge to treat due to multidrug-resistance. Tedizolid (TZD) is the last oxazolidinone approved in the country to treat Gram-positive cocci skin infections. We aimed to observe whether TZD or linezolid (LNZ) resistant isolates would emerge after directed evolution (DE) from *S. aureus* SA43, a clinical ST5-SCC*mec*II representative strain. In the derived isolates, we assessed fitness alteration by determining the doubling time (DT), cross-resistance to LNZ or TZD by microdilution and to fusidic acid, amikacin, ciprofloxacin, chloramphenicol, gentamicin, kanamycin, quinupristin/dalfopristin, and sulfamethoxazole/trimethoprim by disk diffusion. We conducted DE by *in vitro* exposing SA43 to TZD or LNZ escalating levels, in parallel, and in triplicates using different colonies (experiments A, B, and C). We used cation-adjusted Mueller-Hinton Broth plus the drug in three concentrations: MIC, ½ CIM, and 2x CIM. After incubation at 37 °C overnight, the tube with the highest drug concentration showing growth served as inoculum for the next culture. After repeating this for 34 days, three drug-free passages were performed for strain stabilization. Resistant populations emerged in some experiments during the DE, but did not remain, resulting in mild changes in TZD or LNZ MICs. Although the susceptibility profile to all antibiotics was unchanged, we observed significant alterations in the diameter of some inhibition halos. After exposure to TZD, the fusidic acid halo diameter increased in the three experiments. Regarding exposure to LNZ, the diameter of amikacin inhibition halos increased in the three experiments, while the quinupristin/dalfopristin`s decreased in experiments A and C. There were more diameter variations of drugs inhibition halos in the experiment A exposed to LNZ. We compared the isolates DT before and after exposure to both oxazolidinones and observed increased DT in all isolates exposed to TZD and in the experiments A and C exposed to LNZ (the DT in experiment B decreased). In conclusion, even with the drug pressure, resistant populations observed during the DE did not remain after passages. Most of the derived isolates had altered DT, suggesting possible changes in fitness. However, this study suggests that TZD is as safe as LNZ for this strain as the DE resulted in LNZ or TZD susceptible isolates without altering susceptibility to all drugs tested.

Keywords: *Staphylococcus aureus*, linezolid, tedizolid, antimicrobial resistance.

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