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Treatment of renal abscesses caused by *Staphylococcus aureus* MW2, using delafloxacin and moxifloxacin

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Abstract

Background and Objectives

Abscesses are a common type of infection that often involves methicillin-resistant *S. aureus*. Antibiotics are in general poorly effective in treatment of abscesses, at least in part because of reduced activity against bacteria in a stationary phase of growth, in an acidic environment, and with physiologic overproduction of efflux pumps, conditions that all occur in the abscess environment. Delafloxacin (DFX), a new quinolone under development, exhibits distinctive properties that suggest it may offer advantages against bacteria that have formed an abscess, notably activity against stationary phase bacteria and increased activity under acidic conditions. We tested the activity of delafloxacin (DFX) in comparison to that of moxifloxacin (MFX) against renal abscesses formed by *S. aureus* MW2 in a murine model of systemic infection.

Methods

On day 0, 7- to 8-week old male Swiss-Webster mice were injected intravenously with *S. aureus* MW2. On days 4, 5, and 6, by which time renal abscesses had developed, twice daily treatment with DFX, MFX (10 and 30 mg/kg), or vehicle was given subcutaneously. Kidneys were harvested, homogenized, and plated quantitatively on day 7. In addition, a 2-day early-treatment regimen was begun 24 h after injection and renal CFU measured in a similar manner.

Results

Renal abscesses formed reliably by 4 days after systematic injection with *S. aureus* inocula in the range of 3–8×10^6 CFU. Both DFX and MFX at 10 mg/kg significantly reduced CFU (1.7×10^6 and 8.1×10^6 CFU/g kidney, p=0.0003 and 0.0009, respectively) compared to controls (9.8×10^7 CFU/g kidney). The reduction of bacterial load by DFX was significantly greater than that by MXF (p=0.0121). The bacterial load in mice given 30 mg/kg DFX was reduced significantly relative to controls (from 2.0×10^7 to 5.0×10^5 CFU/g kidney, p=0.0205). MXF at this dose also reduced the CFU, but the effect did not reach statistical significance (2.0×10^6 cfu/g kidney, p=0.0541). In the early treatment regimen, both DFX and MXF (10mg/kg) showed a significant reduction in bacterial load (1.1×10^5 and 5.0×10^5 CFU/g kidney, p=0.0019 and 0.007, respectively), compared to that in controls (2.3×10^8 CFU/g kidney).

Conclusion

S. aureus MW2 reliably produces renal abscesses in mice when injected intravenously. Both DFX and MFX were effective in reducing the bacterial load in established renal abscesses, but DFX was superior to MXF. DFX and MXF showed similar efficacy in an early treatment regimen whereby mice were treated prior to the formation of mature renal abscesses.

Methods and Results

Bacteria and Chemicals. MW2, a community-associated MRSA, was cultivated in tryptic soy broth (TSB). Moxifloxacin HCl (MFX) (MW 437.9) was prepared in phosphate buffered saline (PBS, pH 7.4) with 5% DMSO and 5% Tween 80. Delafloxacin (DFX) (the N methlyglucamine salt, MW 635.95) was prepared in 0.9% saline consisting 6% hydroxypropyl-β-cyclodextrin (Cavitron), 1.2 mM xylitol, and 5 mM meglumine. MXF was obtained from LKT Laboratories (St. Paul, MN, USA). DFX was provided by Rib-X Pharmaceuticals, Inc. (New Haven, CT, USA).

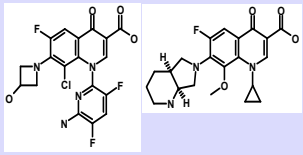

Fig. 1. Structure of DFX (left) and MFX (right).

Murine renal abscess model. Renal abscesses were generated as previously described (1,2). *S. aureus* MW2 was grown in TSB to OD_{600nm} 0.8 and washed and suspended in saline. Male Swiss-Webster mice, aged 7- to 8-week, were infected intravenously (0.2 ml) by tail vein. Renal abscess formation and bacterial load were evaluated at 4 days after injection (Fig. 2).

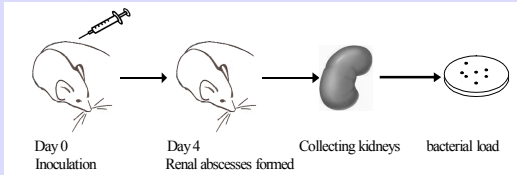

Fig.2. Murine renal abscess model

Ideal inoculum. To induce renal abscesses reliably without fatality, the inoculum was determined to be 3-6×10^6 CFU. The bacterial load in kidneys on day 4 was 1.5×10^7 CFU (Fig. 3). The typical appearance of renal abscesses is shown in Fig. 4.

Statistical analysis. The difference of renal bacterial load of different groups of mice was analyzed using the Mann-Whitney U test.

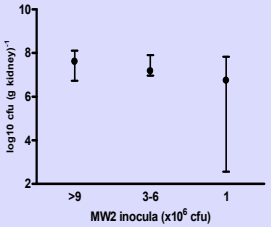

Fig. 3. Inocula and bacterial load in renal abscesses. Medians and interquartile range of renal CFU on day 4 were shown.

Fig. 4. Appearance of renal abscesses on day 4.

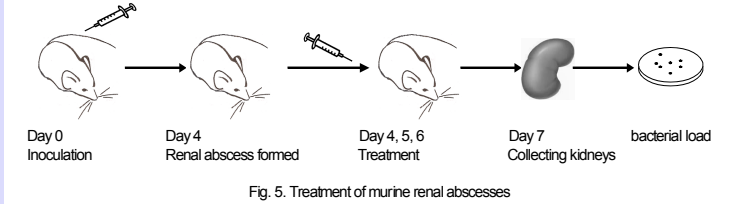

Fig. 5. Treatment of murine renal abscesses

Treatment of renal abscesses by DFX and MFX (Fig 5.). Both DFX and MFX at 10 mg/kg significantly reduced bacterial load in renal abscesses (recovery of 1.7×10^6 and 8.1×10^6 CFU/g kidney, p=0.0003 and 0.0009, respectively) compared to controls (9.8×10^7 CFU/g kidney), and the reduction of bacterial load by DFX was significantly greater than that by MXF (p=0.0121) (Fig. 6). The bacterial load in mice given 30 mg/kg DFX was reduced significantly relative to controls (from 2.0×10^7 to 5.0×10^5 CFU/g kidney, p=0.0205). MXF at this dose also reduced the CFU, but the effect did not reach statistical significance (from 2.0×10^7 to 2.0×10^6 CFU/g kidney, p=0.0541) (Fig. 7).

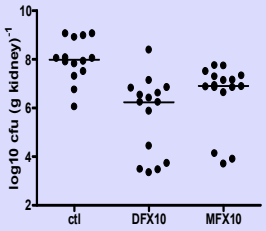

Fig. 6. Renal bacterial load after treatment with 10 mg/kg of DFX and MFX. Inoculum of MW2 was 7.1-7.4×10^6 cfu.

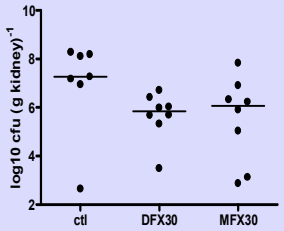

Fig. 7. Renal bacterial load after treatment with 30 mg/kg of DFX and MFX. Inoculum of MW2 was 8.5×10^6 cfu.

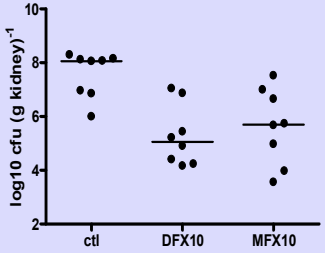

Fig. 8. Early treatment against renal abscess formation with 10 mg/Kg of DFX and MFX. Inocula of MW2 was 6.4×10^6 cfu.

Early treatment to prevent renal abscess formation. Treatment was initiated at 24 h after intravenous injection. Treatment (10 mg/kg) was then given twice daily for two days. After two day's treatment, MW2 load for each mouse was measured as above. In the early treatment regimen, both DFX and MXF (10mg/kg) showed a significant reduction in bacterial load (1.1×10^5 and 5.0×10^5 CFU/g kidney, p=0.0019 and 0.007, respectively), compared to that in controls (2.3×10^8 CFU/g kidney), after treatment for 2 days. There was, however, no significant difference between the two treatment groups (p=0.6454) (Fig. 8).

Conclusions

1. ***S. aureus* MW2 reliably produces renal abscesses after intravenous injection in the murine model.**
2. **Both delafloxacin and moxifloxacin are effective in treating renal abscesses.**
3. **Delafloxacin was superior to moxifloxacin in reducing bacterial counts in established renal abscesses in the murine model.**
4. **Delafloxacin and moxifloxacin have similar efficacy in reducing bacterial recovery in kidneys prior to formation of renal abscesses.**

Bibliography

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