Population pharmacokinetics modeling of gemifloxacin in plasma and unbound lung concentrations in Wistar rats

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[Objetives]

Gemifoxacin is a thirty generation fluorquinolone that presents a high potency compared to other quinolones used in the treatment of respiratory infections. Recently the role of efflux transporters P-gp and MRP2 in the drug's absorption and distribution were described in literature. Regarding that P-gp is expressed in the human's lung as well as in rat's lung, the present study aimed to evaluate the lung's distribution of gemifloxacin, by microdialysis, and investigate the influence of experimental pneumonia associated to *Streptococcus pneumoniae* on total plasma and free interstitial lung's concentration in Wistar rats.

[Methods]

The infection was induced by the administration of 100 µL of inoculum (1 x 108 CFU) by intranasal delivery. After intravenous administration of GEM (20 mg/kg) to non-infected and infected rats blood and microdialysis samples were harvested at pre-determined time points up to 12h and 6h, respectively. All experiments were approved by Ethics Committee on Animal Use of UFRGS (# 29956/2016). The concentration-time profiles were analysed by non-compartmental and population pharmacokinetics approaches using the softwares Phoenix and Monolix. A total of 360 observations (121 plasma, 132 lung measurements), derived from 22 rats (11 non-infected and 11 infected), were included in the dataset for the popPK analysis

[Results and Discussion]

The AUC values determined by trapezoidal rule for plasma and tissue in non-infected and infected animals were 33.33 ± 6.96 µg·h/mL, 7.56 ± 1.54 µg·h/mL, 41.05 ± 12.02 µg·h/mL, and 4.52 ± 0.85 µg·h/mL, respectively. Statistic differences between non-infected and infected animals ($p < 0.001$) were observed by Student's t test only for the AUC_{tissue} values. A two-compartmental popPK model was able to simultaneously describe plasma and free drug's concentrations in the lung for both groups when the infection was include in the model, as a categorical covariate. The final parameters obtained, expressed as poppk values and (residual standard error) were: V1 = 0.499 L (8%), V2 = 0.217 L (12%), $V2_{infected}$ = 0.374 L (15%), k_{12} =4.28 (19%), k_{21} =8.18 (18%), $k_{21infected}$ =3.97 (20%) and k_{10} =0.34 (11%). The IIV were included in the parameters V1, V2 and k_{21} and the values were

0.132 (24%), 0.255 (28%) and 3.17 (2%), respectively. A proportional residual error was employed for plasma and tissue data and equal to 0.232 ug/mL (9%) and 0.218 ug/mL (7%), respectively.

Some physiological changes related to infection may explain this result. A hypothesis for this higher distribution of GEM in infected tissues could be associated to the difference in pH of the site of infection (ion trapping effect) or by injuries associated to the experimental pneumonia and the inflammatory response, which can change the permeability, and improve the drug diffusion.

[Conclusions]

According to our results, gemifloxacin presents a poor penetration in non-infected lungs, showing that the drug is not able to diffuse easily in this tissue. On the other hand, during the experimental pneumonia, the drug's distribution ability is increased possible due to the changes in permeability, associated to inflammatory response.