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P2210 Microdosing as a tool to enhance clinical development of novel antibiotics: a tissue and plasma PK feasibility study

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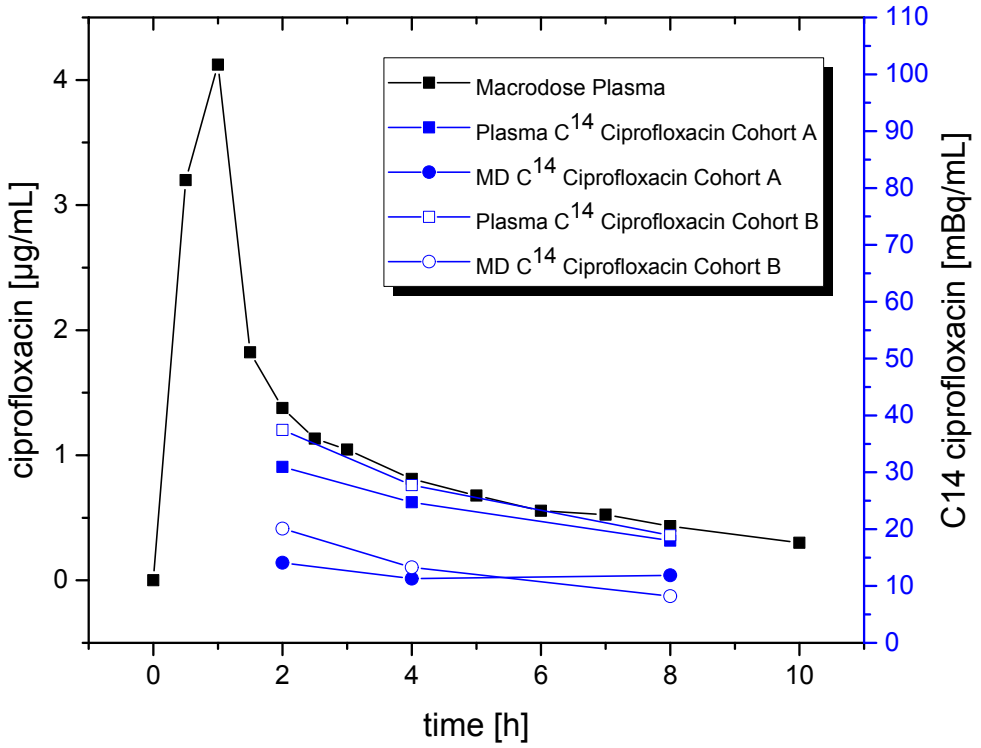
Background: The microdosing concept, also termed as phase 0 studies, comprises the application of a single sub-pharmacological radiolabelled dose (<100 µg) of a drug candidate to humans in order to describe the drug's pharmacokinetic (PK) profile while exposing study participants to minimal risk. Since requiring less pre-clinical testing, microdosing studies can be performed earlier during drug development, thereby potentially saving time and costs. Since previous studies only focused on plasma PK, we set out to evaluate the feasibility of the microdosing concept for ciprofloxacin in plasma and subcutaneous tissue using microdialysis.

Materials/methods: 18 healthy subjects were included in this study. To assess the impact of a therapeutic dose 9 received 400mg of ciprofloxacin (macrodose, cohort A only) as infusion, whereas all 18 subjects received 190mBq C^{14} radioactive labelled ciprofloxacin (microdose, cohort A and B) intravenously. Concentration-time profiles of ciprofloxacin macrodose were obtained in plasma. In addition, plasma samples for determination of C^{14} ciprofloxacin were drawn at selected time points and microdialysis was applied for determination of subcutaneous C^{14} ciprofloxacin concentrations. Macrodose was quantified by LC-MS/MS and microdose by accelerator mass spectrometry (AMS).

Results: Ciprofloxacin macrodose PK data were in accordance with previous data (C_{max} 4.24µg/mL ±0.95, $AUC_{0\text{-}10h}$ 9.98µg/mL*h ±1.97 and t/2 4.69h). As shown in figure1 there was no significant impact on C^{14} ciprofloxacin PK by the presence of the macrodose for plasma and tissue. For C^{14} ciprofloxacin $AUC_{2\text{-}8h}$ and C_{max} values in plasma were 171.16mBq/mL*h and 31mBq/mL in cohort A, and 194.27mBq/mL*h and 37.43mBq/mL in cohort B. In subcutaneous tissue $AUC_{2\text{-}8h}$ and Cmax values were 82.39mBq/mL*h ±31.54 and 15.53mBq/mL ±4.33 in cohort A, and 91.97 mBq/mL*h ±20.99 and 19.21mBq/mL ±5.54 in cohort B. Concentrations of C^{14} ciprofloxacin in plasma correlated with

respective values of the macrodose (pearson's r of 0.911). The tissue to plasma ratio for the AUC of C^{14} ciprofloxacin was 0.53, which is in line with the previously published macrodose ratio of 0.57.

Conclusions: The present study confirms feasibility of microdosing for determination of PK of antibiotics in plasma and tissue. The microdose concept thereby might be a powerful tool in clinical antimicrobial drug development.


Macrodose Plasma
Plasma C14 Ciprofloxacin Cohort A
MD C14 Ciprofloxacin Cohort A
Plasma C14 Ciprofloxacin Cohort B
MD C14 Ciprofloxacin Cohort B
ciprofloxacin [µg/mL]
C14 ciprofloxacin [mBq/mL]
time [h]
0
1
2
3
4
0
10
20
30
40
50
60
70
80
90
100
110
0
2
4
6
8
10