Interaction of Moxifloxacin with Monocarboxylate Transporter on Human Retinal Pigmented Epithelium Cell

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Purpose
Moxifloxacin is safe and effective via intra-cameral route and possesses potent and rapid bactericidal activity against postoperative endophthalmitis pathogens. Apart from lipophilicity, the substrate specificity of drugs for transporters expressed on retinal pigmented epithelium (RPE) has also displayed significant effects on its vitreous half-lives. Therefore, we aimed to evaluate the in vitro interaction of Moxifloxacin with monocarboxylate transporter (MCT) using human RPE cells (ARPE-19).

Methods
The LC-MS/MS method was developed following cold ethyl acetate extraction for the uptake assay of Moxifloxacin using levofloxacin as an internal standard. Uptake study for Moxifloxacin was performed at 37°C for 60 sec. [14C] L-lactic acid was used as a competitive substrate to delineate Moxifloxacin kinetics with MCT. Substrate specificity, pH dependency, metabolic and MCT inhibitors mediated inhibition uptake studies were conducted to delineate the mechanism of Moxifloxacin influx via MCT.

Results
The LC-MS/MS method was successfully developed for the uptake analysis of Moxifloxacin. The LLOQ value was 5.0 ng/ml and 7.8 ng/ml for Moxifloxacin and levofloxacin, respectively. Moxifloxacin uptake by ARPE-19 cells was found to exhibit saturable kinetics (Km = 2.02 ± 0.06 µM and Vmax = 14.51 ± 2.94 pmol/min/mg of protein). Higher uptake of Moxifloxacin was observed at acidic pH of 5.0. Monocarboxylic acids such as salicylic acid, ofloxacin and L-lactic acid, significantly inhibited the uptake of Moxifloxacin. Furthermore, the uptake was significantly reduced in the presence of metabolic inhibitors (ouabain & sodium azide) and MCT inhibitors (Quercetin, pCMBA & pCMBS). The cellular accumulation of Moxifloxacin was reduced in the presence of protonophore (DNP) and sulfhydryl modifying agent (NEM & DDT).

Conclusion
An interaction study of Moxifloxacin with Na+ and H+-coupled MCT on ARPE-19 cells was demonstrated. The understanding of elimination pharmacokinetics from vitreous humor is vital for designing dosage regime and clinical study for posterior segment diseases such as endophthalmitis. We anticipated that lowest vitreal half-life of intra-vitreally injected Moxifloxacin compared to other fluoroquinolones may be also due to its interaction with MCT influx transporter. This information might be crucial in clinical settings when Moxifloxacin administered intra-vitreally and can be further explored to improve vitreous half-life and therapeutic efficacy.