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Ciprofloxacin penetration into infected hepatic cysts in autosomal dominant polycystic kidney disease: a case report

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Sir,

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the presence of multiple cysts residing in the kidneys and liver. ADPKD may be complicated by hepatic cyst infections. Cyst infections probably arise from translocated gut bacteria, of which *Escherichia coli* is the most frequent isolate.[1] Ciprofloxacin is often selected as first-line therapy in view of its high tissue penetration.[2] However, antibiotic treatment fails in 50% of cases, and recurrence is frequent (20%).[2,3] The reason for antibiotic failure is unclear and may be owing to either low penetration of targeted tissue or bacterial resistance. After administration, ciprofloxacin reaches high concentrations in liver cysts.[4] However, these data were obtained from resected liver tissue and robust human pharmacokinetic data have not been reported.[2,3]

We have followed up an ADPKD patient with two infected hepatic cysts, and have measured plasma and cyst ciprofloxacin levels in order to assess true cyst penetration of the drug in infected hepatic cysts.

Written informed consent was obtained from the patient for publication of this case report.

A female patient suffering from hepatic cysts in the context of ADPKD, Gigot type 2, presented with recurrent abdominal pain. She had a history of two previous hepatic cyst infections (2 years and 4 months prior to admission). Renal function was consistent with chronic kidney disease (CKD) stage G1 {creatinine 59 μmol/L [upper limit of normal (ULN) <90 μmol/L] and estimated glomerular filtration rate [eGFR] >90 mL/min}. The most recent cyst infection was confirmed by positive cyst fluid culture for *E. coli* and *Klebsiella pneumoniae*. She presented 5 weeks after discontinuation of an 8 week course of amoxicillin/clavulanate (500/125 mg, thrice daily) in combination with ciprofloxacin (500 mg, twice daily). At presentation, the patient was afebrile (37.2°C) under acetaminophen, and physical examination revealed right upper quadrant abdominal tenderness. Laboratory investigations showed a C-reactive protein concentration of 45 mg/L (ULN <5 mg/L), which increased to a maximum of 112 mg/L in 3 days.

An ^{18}F-FDG PET/CT scan identified two cysts with enhanced rim activity, indicative of recurrent infection (Figure S1, available as Supplementary data at *JAC* Online). One of these cysts was superficially located with a diameter of 35 mm (cyst 1, liver segment 5/6), and the other cyst was deeply located with a diameter of 45 mm (cyst 2, liver segment 5/8). Oral treatment with ciprofloxacin (500 mg, twice daily) was initiated, guided by cyst fluid cultures of previous hepatic cyst infections. Five days later, drainage of the two hepatic cysts was performed as the patient continued to suffer from abdominal pain and previous infections had not resolved without drainage. The drainage procedure was performed 1.5 h after the most recent ciprofloxacin administration, approximately at peak plasma level. Plasma ciprofloxacin concentration was measured 1 h after cyst puncture. The presence of erythrocytes, leucocytes and bacteria was estimated by Gram-stain microscopy (Table 1). Total ciprofloxacin concentration in the cyst fluid and in the plasma was quantified with an LC–tandem MS method. Intracystic concentrations of ciprofloxacin were higher in both the superficial cyst and the deep cyst (5.51 and 3.77 mg/L, respectively) compared with the plasma concentration (2.25 mg/L). Cyst fluid cultures were negative. The patient improved after drainage and was discharged 2 days later.

The high intracystic ciprofloxacin concentrations support the presence of a mechanism that facilitates transport into hepatic cysts. Important factors that affect passive transport of ciprofloxacin into cyst fluid are fluid acidity, molecule lipophilicity and molecule size. Ciprofloxacin is a lipophilic zwitterion, meaning that it will be predominantly charged in a basic or acidic environment. In this way, a pH gradient can essentially trap the molecules in fluid-rich tissue.[5] In addition, as hepatic cysts are lined with cholangiocytes, we expect similar pharmacokinetic properties as observed in the biliary tree, where ciprofloxacin is actively secreted into bile.[6]

There was a 46% higher concentration in the superficial hepatic cyst (cyst 1) compared with the deep hepatic cyst (cyst 2). Cyst location might be a contributing factor as cysts with a larger blood supply could have increased exposure to ciprofloxacin, leading to increased uptake and thus higher intracystic concentrations.[7] Larger cysts have a lower surface-area-to-volume ratio, which could restrict the uptake.[8] As the intracystic biochemical milieu also

Table 1. Cyst fluid analysis

Measurement	Cyst 1	Cyst 2
Location	superficial	deep
Diameter (mm)	35	45
Lobe	right	right
Segment	5/6	5/8
Aspect of fluid	clear, green	turbid, green/red
Gram stain		
leucocytes	+	+
erythrocytes	+	+++
bacteria	negative	negative
Bacteriological culture	no growth	no growth
Anaerobe culture	no growth	no growth
Mycotic culture	no growth	no growth
Ciprofloxacin (mg/L)	5.51	3.77

plays an important role in drug transport, differences in cyst fluid content (e.g. acidity) could explain the variation in ciprofloxacin concentrations.[5] Differences in the amount of protein binding between the two cysts are unlikely to be an influencing factor in this case, as the total concentration of ciprofloxacin was measured.

The ratio of maximum serum concentration to the MIC (C_{max}/MIC) may be used as a pharmacokinetic/pharmacodynamic index for fluoroquinolones, and values >8 suggest adequate exposure.[9] The MIC for *E. coli* is 0.064 mg/L, leading to intracystic C_{max}/MIC ratios of 86.1 and 58.9 for cysts 1 and 2, respectively.[10] The MIC for *K. pneumoniae* is 0.125 mg/L, leading to C_{max}/MIC ratios of 44.1 and 30.2.[10]

In conclusion, intracystic ciprofloxacin concentrations exceed that of plasma, confirming the pharmacokinetic suitability of ciprofloxacin for treatment of hepatic cyst infections.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

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