Adequacy of Rifampin Absorption after Jejunostomy Tube Administration

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It is not always possible to administer antituberculosis pharmacotherapy orally for reasons that may be a direct consequence of tuberculosis itself. To our knowledge, no published literature is available regarding antituberculosis drug absorption via feeding tube. We present the case of a patient with tuberculosis meningitis who required medication administration via percutaneous endoscopic jejunostomy (PEJ) tube. Blood samples were collected during the continuation phase of antituberculosis therapy, immediately before dose administration, and then at 1, 2, 4, and 6 hours after dose administration for quantification of serum rifampin concentrations. Assaying these concentrations by high-pressure liquid chromatography demonstrated a peak serum rifampin level (C_{max}) of 18 μg/ml and total rifampin exposure (area under the curve from 0–6 hours [$AUC_{0–6}$]) of 50.1 μg/ml. These are high compared with rifampin C_{max} and $AUC_{0–6}$ values reported in patients after oral rifampin administration; C_{max} tends to range between 4.0–10.5 μg/ml and $AUC_{0–6}$ 7.0–52.9 μg/ml after oral administration of 600 mg at steady state. Based on our patient's results, therefore, rifampin administered by PEJ tube appears to be well absorbed, with preservation of adequate C_{max} and AUC values. It is worth noting that this was in the context of drug administration in the fasted state. In the absence of any published evidence of adequate absorption via jejunal feeding tube in the nonfasted state, it would seem prudent to ensure that patients are fasted when rifampin is administered via PEJ tube, just as patients are when oral rifampin is administered. This report represents the first documented evidence, to our knowledge, of adequate rifampin absorption when administered via PEJ tube and provides important reassurance for health care providers, patients, and families facing similar clinical scenarios.

Key Words rifampin, rifampicin, pharmacokinetics, jejunal feeding, jejunal absorption, tuberculosis, meningitis, dysphagia.

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Rifampin is an important part of the first-line treatment regimen for tuberculosis, driving sterilizing activity.[1, 2] Its bactericidal effect on *Mycobacterium tuberculosis* is intracellular and concentration dependent, with microbial killing linked to the area under the curve to minimum

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inhibitory concentration (AUC:MIC) ratio and suppression of resistance linked to the free-drug peak concentration (C_{max}):MIC ratio.[3, 4] Rifampin is rapidly and almost completely absorbed after oral administration on an empty stomach, with C_{max} achieved ~2 hours after ingestion.[5–7] Rifampin induces its own metabolism via increased prehepatic and hepatic clearance,[8] and the induced steady state is achieved after ~40 days of treatment.[9]

We performed a search for relevant literature regarding administration of antituberculosis pharmacotherapy via percutaneous endoscopic jejunostomy (PEJ) tube, and no published evidence or guidance was found. Thus we conducted a pharmacokinetic investigation to assess whether absorption via this route would be adequate, using serum samples from a patient with tuberculosis meningitis who required rifampin administration via PEJ tube.

Case Report

A 61-year-old man was admitted to our regional tropical and infectious diseases unit with vomiting, back pain, and urinary retention on a background of fever and weight loss. He became confused and developed impaired consciousness, and was diagnosed with tuberculosis meningitis on a clinical and radiologic basis. Neurologic impairment included dysphagia, and a PEJ tube was placed for nutritional support and medication administration. Local discussions between the medical staff and pharmacy staff raised concerns that jejunal administration may lead to impaired drug absorption, raising the possibility of treatment failure and the development of drug resistance.

The patient was 8 weeks into the continuation phase of his daily-dosed therapy and thus had reached the fully induced metabolic steady state. Over 8 hours after and 6 hours before any food or enteral feeding solution was given, and 24 hours after the previous dose, 600 mg rifampin solution (100 mg/5 ml; Rifadin; Sanofi, Guildford, UK) and 300 mg isoniazid oral solution were administered via PEJ tube. Serum samples were collected immediately before dose administration and at 1, 2, 4, and 6 hours after dose administration. Rifampin concentrations were assayed by high-pressure liquid chromatography at the Antimicrobial Reference Laboratory (Bristol, UK) (Table 1). These values equated to a C_{max} of 18 μg/ml and area under the curve from 0–6 hours (AUC_{0-6}) of 50.1 μg/ml.

Table 1. Serum Rifampin Concentrations after PEJ Tube Administration

Time point	Rifampin concentration, μg/ml
Before dosing	< 0.3
1 hr after dosing	18.0
2 hrs after dosing	11.0
4 hrs after dosing	6.1
6 hrs after dosing	3.4

PEJ = percutaneous endoscopic jejunostomy.

Discussion

The serum rifampin levels reached in this patient were high compared with levels described in the published literature after oral administration. Average C_{max} values reported in studies assessing rifampin pharmacokinetics after oral administration of 600 mg at steady state generally ranged from 4.0–10.5 μg/ml.[10–17] Importantly, we were able to calculate an AUC to enable an estimation of bactericidal activity. The total drug exposure achieved in our patient (50.1 μg/ml) falls at the very upper end of the range reported by other investigators after oral administration of the same dose: a median AUC_{0-6} of 24.0 μg/ml (range 7–52.4 μg/ml) and 21.7 μg/ml (range 7.1–52.9 μg/ml) in human immunodeficiency virus (HIV)-positive and HIV-negative patients, respectively.[17] After a similar dose of 9.6 mg/kg, another study reported a mean AUC_{0-6} of 16.52 μg/ml (SD 8.84 μg/ml) in HIV-positive patients and 17.94 μg/ml (SD 10.36 μg/ml) in HIV-negative patients.[18]

A multitude of factors need to be accounted for when planning to deliver drugs by jejunal feeding tubes. Product alterations necessary to allow tube delivery may interfere with product stability, compatibility with concomitant medications, and tolerability, as well as pharmacokinetic parameters.[19] These considerations are drug specific. The accepted practice of administering rifampin on an empty stomach is supported by evidence that ingestion of food with rifampin reduces C_{max} by more than a third.[2, 20] Because jejunal pH is significantly higher than gastric pH,[21] a concern in our unit was that relative alkalinity would impair rifampin absorption in our patient. This was not the case; indeed, in patients taking rifampin orally, concomitant antacid administration has no effect on serum rifampin levels.[2, 20]

Some evidence exists that many viable targets may be available for rifampin absorption in the gastrointestinal tract. Subtotal or total gastrectomies, celiac disease, and diverticulosis of the

small bowel do not result in differences in AUC compared with those attained in patients with healthy gastrointestinal tracts.[22] A study conducted in India demonstrated C_{max} and AUC values that were, in fact, slightly higher in 12 patients with gastrointestinal tuberculosis affecting the ileum, cecum, and/or duodenum than in 18 comparable patients with pulmonary tuberculosis without evidence of gastrointestinal involvement.[23] Rifampin is zwitterionic with an acidic pK_a of 1.7 and an alkaline pK_a of 7.9.[24] Its permeability is high in the relatively alkaline environments of the duodenum and colon in comparison with the acidic stomach, and solubility is moderate to high throughout.[25] It is also known to be highly lipophilic. These qualities mean that it is perhaps not surprising that absorption can occur at many gastrointestinal sites.

Conclusion

Based on our case study, it appears that rifampin administered by jejunal tube is well absorbed, with preservation of adequate C_{max} and AUC values. It is worth noting that this was in the context of drug administration in the fasted state. In the absence of any published evidence of adequate absorption via jejunal feeding tube in the nonfasted state, it would seem prudent to ensure that patients are fasted when rifampin is administered via PEJ tube, just as patients are when oral rifampin is administered.

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