ELSEVIER

Change in Oral Absorption of Tacrolimus in a Liver Transplant Recipient After Reversal of Jejunoileal Bypass: Case Report

M. Kelley, A. Jain, R. Kashyap, M. Orloff, P. Abt, K. Wrobble, R. Venkataramanan, and A. Bozorgzadeh

ABSTRACT

Introduction. Jejunoileal bypass (JIB) was, at one time, a popular surgical technique for the treatment of morbid obesity. However, this operation was also associated with major complications. Consequently, many such procedures were eventually reversed. One of the most serious of these complications was liver failure. For those patients who developed cirrhosis, liver transplantation was one therapeutic alternative. Tacrolimus is one of the primary immunosuppressive agents used in liver transplantation. It is effective to prevent acute rejection episodes, but shows a narrow therapeutic index and can cause nephrotoxicity and neurotoxicity. This report describes the change in tacrolimus absorption that was observed after JIB reversal in a 57-year-old female liver transplant recipient.

Results. Prior to JIB reversal, the mean tacrolimus dose was 7 mg twice daily with a whole-blood tacrolimus concentration ranging from 5.2 to 6.4 ng/mL. There was no appreciable peak in tacrolimus concentration, and the area under the concentration-time curve (AUC) was 10.9 ng/mL/h. After reversal, the daily tacrolimus dose was decreased to 5 mg twice daily, with a now-discernable peak concentration at 3 hours postdose. Furthermore, the AUC increased 90% to 20.7 ng/mL/h.

Conclusion. After JIB reversal, the patient showed higher systemic levels of tacrolimus and required lower steady-state doses. It is therefore imperative that such patients be monitored closely to avoid tacrolimus-related toxicity.

JEJUNOILEAL BYPASS (JIB) was a popular surgical procedure for treating morbid obesity in the 1960s and 1970s. While it was effective to achieve weight loss, JIB was also associated with severe complications, including liver failure. Indeed, these complications were responsible for the eventual reversal of a significant number of these procedures.[1–3] One of the primary mechanisms of liver failure after JIB is believed to be overgrowth of gut flora in the bypassed segment of small intestine, resulting in the production of endotoxins.[1,2,4–6] Liver transplantation is a therapeutic option for patients who develop liver failure after JIB.

Tacrolimus is a potent, effective immunosuppressive agent that is used to prevent acute rejection in liver transplant patients. However, this drug has a narrow therapeutic index, and whole-blood trough concentrations must be monitored to avoid potentially serious adverse effects, including nephrotoxicity and neurotoxicity.[7] In this case report, we describe the pharmacokinetics of tacrolimus in the setting of JIB and after JIB reversal in a liver transplant recipient.

CASE REPORT

In 1983 a 57-year-old woman underwent JIB to treat morbid obesity. She later developed liver failure, reaching endstage in January 2003 and undergoing orthotopic liver transplantation (OLT) in February of that year. Reversal of her JIB was performed 8 months after OLT, at which time she was on a stable tacrolimus dosing regimen of 7 mg twice daily. The

From the Departments of Pharmacy (M.K.) and Surgery (A.J., R.K., M.O., P.A., K.W., A.B.), Division of Transplantation, University of Rochester Medical Center—Strong Memorial Hospital, Rochester, New York, USA, and Department of Pharmaceutical Sciences and Pathology (R.V.), University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Address reprint requests to Ashokkumar Jain, MD, University of Rochester Medical Center, 601 Elmwood Avenue, Department of Surgery, Division of Transplantation, Box SURG, Rochester, NY 14642. E-mail: ashok_jain@urmc.rochester.edu

0041-1345/05/$–see front matter
doi:10.1016/j.transproceed.2005.07.038

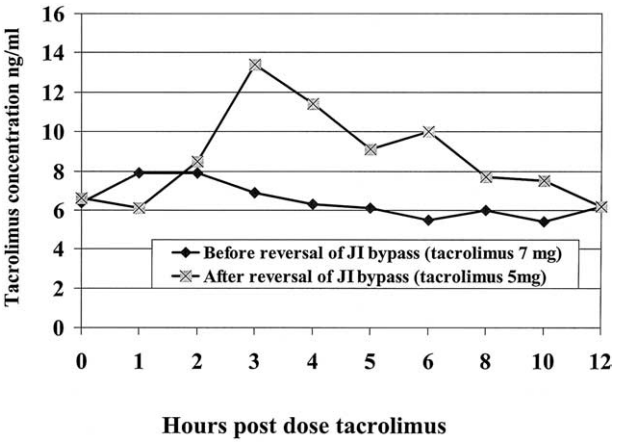

Fig 1. Changes in the kinetic profile of tacrolimus: before and after jejunoileal bypass reversal.

whole-blood trough tacrolimus concentrations on this regimen ranged from 5.2 to 6.4 ng/mL.

The pharmacokinetics of tacrolimus were evaluated just prior to and approximately 3 months after JIB reversal. During each study, blood samples were collected just prior to as well as at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after tacrolimus administration. The whole-blood tacrolimus concentrations were determined using a microparticulate enzyme immunoassay and an IMX analyzer. The area under the concentration-time curve (AUC) was calculated for each study by the trapezoidal rule using a proprietary computer program.

Results from the prereversal pharmacokinetic study are depicted graphically in Fig 1. Tacrolimus blood concentrations were fairly consistent over the dosing interval, but the normal postabsorptive peak was absent (peak-to-trough ratio = 1.2). The AUC at this stage was 76.6 ng/mL/h. After the JIB reversal, the patient received her normal dose of tacrolimus postoperatively. On postoperative day 1, the trough tacrolimus concentration increased dramatically from 6.2 to 25.4 ng/mL. As a result, it was necessary to withhold three consecutive doses of tacrolimus before the trough level decreased to baseline (6.1 ng/mL on postoperative day 3). Thereafter, the patient required doses no higher than 5 mg twice daily and as low as 2 mg twice daily, with trough tacrolimus concentrations ranging from 3.8 to 15.1 ng/mL (Fig 2).

Three months after her JIB reversal, the patient was on a stable oral tacrolimus dose of 5 mg twice daily, with trough concentrations similar to those recorded before reversal (4.1 to 6.6 ng/mL; Fig 2). The results of the post–JIB reversal pharmacokinetic study are also shown in Fig 1. As the figure indicates, a normal postabsorption peak in tacrolimus blood concentration was restored after JIB reversal (peak-to-trough ratio = 2.0), with the peak of 13.4 ng/mL being reached 3 hours postdose in this patient. The half-life was approximately 10.2 hours. The AUC over the dosing interval was 103.4 ng/mL/h. The apparent increase in absorption contributed to a 90% increase in dose-normalized AUC (10.9 ng/mL/h/mg prereversal vs 20.7 ng/mL/h/mg postreversal).

DISCUSSION

For a period of roughly 20 years, JIB was a popular means of managing patients with morbid obesity. Only a handful of cases of transplantation for JIB-related liver failure have been reported in the literature.[2,5,6,8,9] It can take up to 20 years or more for patients who have undergone JIB to develop cirrhosis.

Several factors could lead one to suspect higher systemic drug exposure after reversal of JIB. First, the surface area available for drug absorption increases considerably after the reversal procedure. This is due to the fact that a significant portion of the jejunum and ileum that is rendered nonfunctional after JIB is restored by reversal. This factor is particularly important in the case of tacrolimus, given the low intrinsic bioavailability of this agent (average of approximately 20% to 30%).[10,11] In addition, animal studies have indicated that although tacrolimus is absorbed throughout the gastrointestinal tract, the jejunum is the primary site of absorption (jejunum > duodenum > ileum > colon > stomach). The second factor that may contribute to increased drug absorption after JIB reversal is decreased bowel motility. This factor can occur after any major abdominal procedure, leading to prolonged gastrointestinal transit time and possibly prolonged absorption time, thereby favoring increased drug absorption.

The results of our pharmacokinetic studies appear to be consistent with these factors. The postreversal study showed the return of a normal peak in the tacrolimus blood concentration-time profile, which confirms that the jejunum and ileum are major sites of tacrolimus absorption. Furthermore, systemic drug exposure (as measured by dose-normalized AUC) rose dramatically (90%), while steady-state doses were reduced to maintain adequate immunosuppression.

This is the first description of the effect of JIB reversal on the pharmacokinetics of tacrolimus in a liver transplant patient. Our results indicate that such patients are exposed to higher systemic whole-blood levels of tacrolimus, requiring lower doses after JIB reversal. It is, therefore, imperative that such patients be monitored closely to avoid tacrolimus-related toxicity.

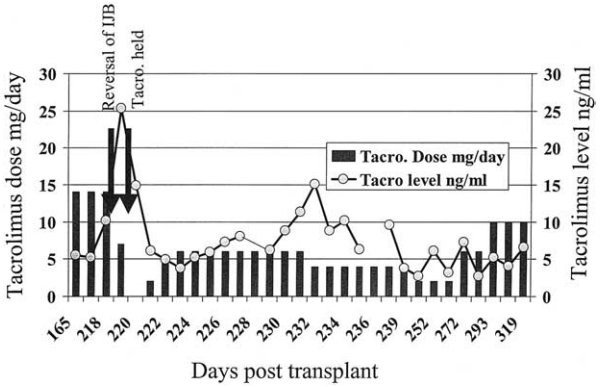

Fig 2. Daily changes in the patient's oral dosages of tacrolimus and tacrolimus concentrations.

REFERENCES

1. Brunicardi FC, Reardon PR, Matthews BD: The surgical treatment of morbid obesity. In: Townsend CM, Beauchamp RD, Evers BM, et al (eds): Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice. 16th ed. Philadelphia: Saunders; 2001, 247

2. Burke GW 3rd, Cirocco R, Hensley G, et al: Liver transplantation for cirrhosis following jejuno-ileal bypass—regional cytokine differences associated with pathological changes in the transplant. Liver Transplantation 54:374, 1992

3. Dean P, Joshi S, Kaminski DL: Long-term outcome of reversal of small intestinal bypass operations. Am J Surg 159:118, 1990

4. Powell-Jackson PR, Maudgal DP, Sharp D, et al: Intestinal bacterial metabolism of protein and bile acids: role in pathogenesis of hepatic disease after jejuno-ileal bypass surgery. Br J Surg 66:772, 1979

5. Markowitz JS, Seu P, Goss JA, et al: Liver transplantation for decompensated cirrhosis after jejunoileal bypass: a strategy for management. Transplantation 65:570, 1998

6. Lowell JA, Shenoy S, Ghalib R, et al: Liver transplantation after jejunoileal bypass for morbid obesity. J Am Coll Surg 185:123, 1997

7. Fujisawa Healthcare, Inc: Tacrolimus prescribing information, 2003

8. Kim WR, Poterucha JJ, Porayko MK, et al: Recurrence of nonalcoholic steatohepatitis following liver transplantation. Transplantation 62:1802, 1996

9. Keefe EB, Gettys C, Esquivel CO: Liver transplantation in patients with severe obesity. Transplantation 57:309, 1994

10. Venkataramanan R, Jain A, Cadoff E, et al: Pharmacokinetics of FK506: preclinical and clinical studies. Transplant Proc 22:52, 1990

11. Venkataramanan R, Jain A, Warty VS, et al: Pharmacokinetics of FK506 in transplant patients. Transplantation Proc 23: 2736, 1991