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BRIEF REPORT

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Oral absorption of tacrolimus in children with intestinal failure due to short or absent small bowel

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Abstract We describe two children with intestinal failure due to short or absent small bowel who underwent isolated liver transplantation for liver disease related to parenteral nutrition. Both received reduced-size liver grafts whilst awaiting a suitable small bowel donor. Immunosuppressive therapy was based on oral tacrolimus and intravenous steroids. Therapeutic levels of tacrolimus were achieved at low dosage of 0.14–0.28 mg/kg per day. Median and mean blood tacrolimus levels were 9.9 and 13.7 ng/ml (range 4.9–42.3 ng/ml) in case 1 and 5.8 and 7.2 ng/ml (range 1–30 ng/ml) in case 2 before small bowel transplantation, respectively. Following small bowel transplantation, levels were 17.1 and 20.1 ng/ml (range 9.2–30 ng/ml), with oral doses of 0.54–1.35 mg/kg per day. Both children died of adenovirus pneumonia, with functioning grafts. Our experience demonstrates that effective levels of immunosuppression can be achieved by oral administration of tacrolimus in children with short or absent small bowel.

Key words Tacrolimus · Absorption · Short bowel syndrome

Introduction

Orthotopic liver transplantation (OLT), alone or with sequential small bowel grafting, is an option in the management of children with intestinal failure and liver disease related to parenteral nutrition (TPN) [5]. The achievement of effective immunosuppression by oral administration of tacrolimus in children with transplants and partial or complete absence of the small bowel has not been reported previously. We present two children with intestinal failure who underwent isolated liver transplantation using reduced-size grafts whilst awating a suitable small bowel donor. Oral administration (by nasogastric tube) was chosen in preference to parenteral administration because of the short and long-term risks associated with tacrolimus toxicity [1, 3]. Therapeutic trough blood levels of tacrolimus were easily achieved with oral administration at low dosage, and maintenance of therapeutic concentrations was possible.

Case reports

Case 1

A child born at 35 weeks of gestation by emergency caesarian section had multiple small bowel atresias that were excised at day 2 and day 30 of life, leaving a residual 12 cm of small bowel, the ileocaecal valve and the colon. He developed TPN-related cholestatic liver disease and, at 9 months, was listed for combined liver and small bowel transplantation. His liver function deteriorated rapidly, resulting in encephalopathy necessitating ventilation and inotrope support. It was therefore decided to perform a sequential liver and small bowel transplantation, as no size-matched donor was yet available for the latter. He received a left lateral segment liver graft at 10 months of age, weighing 7.3 kg. At the time of transplantation, his serum bilirubin was 823 μmol/L, aspartate transaminase (AST) 722 IU/L and International Normalised Ratio (INR) 2.7. Postoperatively, he underwent 3 laparotomies for recurrent intestinal perforation. His immunosuppressive therapy was initially intravenous cyclosporine (7 mg BD), azathioprine (10 mg OD) and methylprednisolone (15 mg OD, gradually reduced over 10 days to 2.5 mg OD). He was switched to tacrolimus on day 22 after transplantation, to treat ongoing acute rejection that had not responded to increased cyclosporine levels (trough 361 μg/ml). He received 1 mg oral tacrolimus BD and a 3-day course of 125 mg

IV methylprednisolone per day (in addition to his maintenance dose of 2.5 mg OD). Liver function values settled, but on day 26 after transplantation, tacrolimus was discontinued because of a high blood level (18.4 ng/ml). Oral doses were reduced to 0.5 mg BD; nonetheless, on day 34 another 24-hour break in tacrolimus was needed (blood level 42.3 ng/ml). The oral dose range was 0.5–1 mg BD, with blood levels between 4.9 and 42.3 ng/ml (median 9.9, mean 13.7 ng/ml).

Five weeks after transplantation, he developed adenovirus infection and, although tacrolimus was discontinued and methylprednisolone reduced to 1 mg a day, he died of respiratory failure with a functioning liver graft on day 40 after transplantation.

Case 2

A girl, diagnosed at birth to have megacystic microcolon syndrome, was referred to our unit at the age of 2 years, having required TPN from the first week of life. At 5 months of age, she developed cholestatic liver disease that progressed over the next 18 months to liver failure. At referral she had severe bowel dysfunction and gastroparesis, for which a gastrostomy had been performed. She weighed 7.4 kg; her serum bilirubin was 818 μmol/L, AST 1024 IU/L and INR 2.5. She was listed for combined liver and small bowel transplantation. Whilst waiting for a suitable donor, she suffered chest sepsis, metabolic disturbances and two cardiac arrests with successful resuscitation, but required ventilation and inotrope support. Due to the severity of liver failure (INR 3.8), a reduced-size liver was grafted (segment II–III) with complete excision of the abnormal small bowel. Biliary continuity was established by hepaticogastrostomy. Postoperatively, graft function was excellent and she made a complete neurological recovery.

She was immunosuppressed with oral tacrolimus (dose range 0.5–0.7 mg BD, corresponding to 0.15–0.2 mg/kg per day) and IV methylprednisolone (20 mg OD on day 1, reduced to 2.5 mg OD in the first week after transplantation). The tacrolimus trough blood level range was 1–30 ng/ml (median 5.8, mean 7.15 ng/ml). On two occasions the dose was omitted for 24 hours because of high blood levels. Seven weeks after OLT a six-month-old, CMV-negative small bowel donor became available, and she received an isolated small bowel graft. A feeding jejunostomy and a terminal ileostomy were performed. She was weaned off TPN onto enteral nutrition by day 10. Immunosuppression was increased (2 mg oral tacrolimus BD, 17.5 mg IV methylprednisolone OD and 500 mg mycophenolate moefetil OD). Two episodes of biopsy-proven small bowel rejection were well treated with high doses of steroids (125 mg IV methylprednisolone for 3 days) and an increase in oral tacrolimus (5 mg BD). The tacrolimus blood levels ranged from 9.2 to 30 ng/ml (median 17.1, mean 20.1 ng/ml). Her postoperative course was complicated by cholestasis related to sepsis.

She underwent repeat laparotomies for abdominal sepsis, finally resulting in removal of a necrotic 20-cm distal segment of ileum, after which oral nutrition was re-established. At week 12 after OLT (5 weeks after small bowel transplantation), she developed fever and respiratory failure and was found to have adenovirus pneumonia, which failed to respond to treatment with intravenous ribavirin and extracorporeal membrane oxygenation. She died 42 days after small bowel transplantation.

Discussion

A recent report described a single-dose pharmacokinetic study on cyclosporine and tacrolimus absorption in a 39-year-old woman with short bowel syndrome secondary to Crohn's disease and TPN-related liver dysfunction. However, no details were given other than that 2 feet of residual small intestine were left intact. It was not clear if the small and large bowel were in continuity. The study was conducted during transplant evaluation and suggested that oral tacrolimus and Neoral may be suitable for patients with short bowel who require immunosuppression [8].

Tacrolimus absorption varies between individual patients. The mean oral bioavailability in liver transplant recipients varies widely between 5 and 67% [9]. In enterectomized pigs, absence of the small bowel results in higher tacrolimus levels after oral administration than those observed in pigs after small bowel transplantation [7]. This may be explained by the presence of tacrolimus-metabolising enzymes, predominantly cytochrome P-450, in the intestinal mucosa of animals and man [2]. Tacrolimus gut wall metabolism might therefore justify the lower extent of bioavailability in pigs with small bowel transplants than in enterectomized pigs with reduced or absent gut metabolism [7]. Our experience with these two children would support this observation. Tacrolimus absorption takes place predominantly in the upper part of the small intestine [4]; however, a significant amount can be absorbed from the stomach and duodenum. This absorption produced therapeutic levels in both children, probably as a result of persistence of the drug within the stomach and duodenum caused by the adynamic bowel in the case of the first child and the second child having only the stomach and a blind-ending duodenum.

From our experience with these two children who underwent liver transplantation with short or absent small bowel, tacrolimus absorption is sufficient after oral administration via nasogastric tube to achieve therapeutic levels in the blood. Adenovirus pneumonia was the cause of death in both children. A significant correlation between different immunosuppression protocols and adenovirus infection could not be demonstrated in an extensive study on paediatric liver recipients [6]. However, tacrolimus blood levels were very high (> 25 ng/ml) on one occasion in case 1 and four times in case 2 (the blood levels were deliberately higher after small bowel transplantation), and this overimmunosuppression may have contributed to the development of adenovirus infection. Effective immunosuppression was provided at low tacrolimus doses, and variations in blood levels were overcome by not aspirating the stomach for 4 hours after administration of tacrolimus. Our practice has thereby changed to avoiding intravenous administration and relying on oral tacrolimus to achieve immunosuppression in children with short or absent small bowel. Close monitoring of tacrolimus blood levels is important, however, as overimmunosuppression may be a problem.

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