Drug Metabolism, Drug Interactions, and Drug-Induced Liver Injury in Living Donor Liver Transplant Patients

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KEYWORDS

• Living donor liver transplantation • Hepatic regeneration • Drug metabolism
• Cytochrome P450 • Pharmacokinetics • Hepatotoxicity

KEY POINTS

- Living donor liver transplant (LDLT) is increasingly being performed given the shortage of deceased donor livers available for liver transplant.
- Limited pharmacokinetic and metabolism studies have been performed in LDLT patients.
- Given the reduced liver mass, altered blood flow, altered bile production, altered plasma protein production, and increased proinflammatory cytokine levels, the capacity of the liver to metabolize endogenous and exogenous compounds is expected to be decreased in LDLT patients, especially during the hepatic regeneration phase.
- Given these expectations, hepatotoxicity is more likely to be observed in LDLT patients than in deceased donor liver transplant patients.

INTRODUCTION

Liver transplant (LT) has been well established as a therapeutic option for patients with various end-stage liver diseases. Dr Thomas Starzl performed the first successful LT in 1967.[1] Deceased donors have been the primary source of livers for LT. However,

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because of the significant shortage of deceased donor organs and the long waiting time for LT, attempts have been made to expand the donor pool, including the use of livers from extended criteria donors, split livers from deceased donors, and liver segments from living donors.[2] The advantages of living donor LT (LDLT) include shorter waiting time for organs, minimal ischemic time for the grafts, elective surgery time for the patients, the options for the recipients to be medically stabilized before surgery, improved overall transplant outcomes, and improved patient and graft survival compared with those receiving deceased donor LTs (DDLTs).[3–5] LDLT may provide additional advantages depending on the severity of the liver disease, because living donors are typically younger.[6,7] The first successful LDLT was performed in 1989 in a pediatric patient and in 1997 in an adult patient.[8,9] The recipients receive either the left lobe or right lobe of the liver from a living donor. The liver regenerates both in the donor and in the recipient over time to accommodate the needs of the individuals.

DRUG THERAPY IN LIVING DONOR LIVER TRANSPLANT PATIENTS

The donor and recipients of the LDLT receive multiple drug therapy during and after surgery. In the donors, the medications used typically include the following. During surgery, drugs such as lidocaine, metoprolol, midazolam, propofol, rocuronium, succinyl choline, vasopressin, neostigmine, ondansetron, phenylephrine, and labetalol may be used. Following surgery, antibiotics such as ampicillin, sulbactam, amikacin, and vancomycin may be used. Pain medications such as fentanyl, morphine, hydromorphone, oxycodone, or ketorolac may be used intraoperatively or postoperatively. Postoperatively docusate, bisacodyl, pantoprazole, phytonadione, and metoclopramide may be used. In addition to these medications, recipients also receive immunosuppressants such as basiliximab, mycophenolate mofetil (MMF), tacrolimus, methylprednisolone, and prednisone. Postoperative prophylaxis with Bactrim or Dapsone (for sulfa allergy), acyclovir or valganciclovir (cytomegalovirus [CMV] high-risk only), isavuconazole (or voriconazole previously) are also common in recipients. In addition, other drugs, such as docusate, bisacodyl, pantoprazole, entecavir, or tenofovir may also be used in certain patients. Specific information on how these drugs are used in humans is given in **Table 1**. Pharmacokinetics of some selected drugs and hepatotoxicity in LDLT are discussed later.

Immunosuppression

Solid organ transplant recipients normally require lifelong treatment with potent immunosuppressants, which reduce the risk of allograft rejection but increase patient morbidity and mortality after long-term use. Optimal immunosuppressive therapy balances the risk of rejection caused by an inadequately suppressed immune system with potential side effects of immunosuppression. Immunosuppression is personalized to individual patients using several factors, including the underlying cause of original liver disease (eg, hepatitis C virus [HCV], hepatocellular carcinoma), underlying renal function, other comorbidities, and the patient's immunologic state.[10] The most commonly used immunosuppressive regimens in solid organ transplantation include a combination of calcineurin inhibitor (CNIs), antimetabolites (MMF or azathioprine), and corticosteroids. In selected patients, inhibitors of mammalian target of rapamycin (mTORi) such as a sirolimus or everolimus are also used. Some transplant centers use initial induction therapy with biologic T-cell–depleting agents (anti-CD52, OKT3, antithymocyte globulin) or non–T-cell–depleting agents (interleukin [IL]-2 receptor agonists, basiliximab).[11–13]