Amelioration of Lactic Acidosis with Dichloroacetate during Liver Transplantation in Humans

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Background: Marked lactic acidosis occurs during orthotopic liver transplantation (OLT), especially during the anhepatic phase. Current standard therapy is NaHCO₃, although it may exacerbate intracellular acidosis, increase plasma lactate, and contribute to hypernatremia. Alternatively, dichloroacetate (DCA) stimulates pyruvate oxidation in vitro, reduces plasma lactate, and moderates intracellular acidosis. The aims of this study were to test the efficacy of DCA to control lactic acidosis, reduce the NaHCO₃ requirement and incidence of hypernatremia, and stabilize perioperative acid-base homeostasis. Others also examined the DCA pharmacokinetic profile during OLT and the role of lactate metabolism in OLT-associated hyperglycemia.

Methods: Patients (n = 66) for OLT were divided into two equal groups to receive or not receive DCA during OLT. DCA 40 mg·kg⁻¹ was infused over 60 min after induction of anesthesia and 4 h later. Plasma DCA concentration was measured by gas chromatography–mass spectroscopy, and pharmacokinetics were assessed by a one-compartment model. Serial arterial blood gases, lactate, Na⁺, glucose, and hemodynamic measurements were compared, as were intraoperative utilization of blood products, CaCl₂, and NaHCO₃.

Results: Plasma DCA concentration was maintained between 0.28 and 1.18 mm during OLT, with peak concentrations of 0.73 ± 0.06 (mean ± SE) and 1.18 ± 0.09 mm, respectively after the first and second doses. In control patients, plasma lactate was 1.07 ± 0.04 at baseline and 1.20 ± 0.06 before incision and reached a peak of 7.30 ± 0.41 mm after graft reperfusion. In DCA-treated patients, the respective values were 1.07 ± 0.06 (difference not significant), 0.63 ± 0.05 (P < 0.001), and 3.39 ± 0.20 (P < 0.001) mm. Intraoperative changes in arterial blood pH, HCO₃⁻, and base excess were comparable though less marked in DCA-treated patients, whose NaHCO₃ requirement was reduced (0.59 ± 0.36 vs. 2.85 ± 0.53 mEq·kg⁻¹ in control patients, P < 0.001). There was no difference between groups in requirements for CaCl₂ or blood products, in intraoperative hemodynamics, in duration of the surgical stages, or in graft ischemia times. Twelve control and 4 DCA-treated patients exhibited a plasma Na⁺ concentration > 145 mEq/l at completion of surgery (P < 0.05). Hyperglycemia was not attenuated by DCA despite decreased plasma lactate concentration. Sixteen and 28 h after graft reperfusion, when plasma DCA had been eliminated, plasma lactate and degree of metabolic alkalosis did not differ between groups.

Conclusions: DCA safely and effectively attenuated lactic acid accumulation and moderated acidosis during OLT. DCA decreased the requirement for NaHCO₃ therapy and the incidence of hypernatremia. OLT-associated hyperglycemia did not result from lactate-induced stimulation of hepatic gluconeogenesis. Postoperative metabolic alkalosis was not substantially influenced by lactate metabolism. (Key words: Acid–base equilibrium; bicarbonate; dichloroacetate. Metabolism: glucose; lactate; sodium. Transplantation: liver.)

ORTHOTOPIC liver transplantation (OLT) is the definitive treatment for patients with end-stage liver disease. A consistent problem during OLT is progressive lactic acidosis, which only begins to abate several minutes after graft liver reperfusion. This metabolic acidosis is followed by a metabolic alkalosis which persists for several days. Current standard treatment for severe acidosis during OLT is NaHCO₃, often with a cumulative dose of 200–300 mEq. However, NaHCO₃ has recently been criticized on the basis of its HCO₃⁻ moiety and its Na⁺ content. Administration of NaHCO₃ has been questioned because it fails to increase intracellular pH
even with marked alkalization of the plasma, and may exacerbate intracellular acidosis.1–4 In certain settings, NaHCO₃ compromises myocardial performance, which has been ascribed to its failure to correct intracellular acidosis or other metabolic deficits.2,5,6 NaHCO₃ also exacerbates plasma lactate accumulation, which is problematic because (1) lactate release is accompanied by H⁺ release and metabolic acidosis, and (2) its subsequent metabolism leads to H⁺ consumption which may exacerbate postoperative metabolic alkalosis.6–9 In addition, large doses of NaHCO₃ may contribute to hypernatremia, putting patients at risk for central nervous system demyelination.10–12

Dichloroacetate (DCA) is an alternative treatment for metabolic acidosis, which, rather than simply neutralizing plasma H⁺, decreases circulating lactic acid.13,14 It stimulates pyruvate dehydrogenase, augmenting pyruvate oxidation to CO₂ and decreasing the availability of pyruvate to form lactic acid.15,16 In animals, DCA decreases the severity of metabolic acidosis caused by heptectomy, phenformin intoxication, hepatectomy, or hypoxia.17–20 In contrast to NaHCO₃, DCA promotes intracellular acid–base homeostasis in heart and liver, and preserves myocardial function, during metabolic acidosis.3,18,20–22 Furthermore, its Na⁺ content is much smaller than that of an “equipotent” NaHCO₃ dose.

The purpose of this study was to test whether prophylactic treatment with DCA can ameliorate metabolic acidosis in patients undergoing OLT. The hypothesis was that DCA provides better acid–base homeostasis, with less perioperative hyperlactatemia and hypernatremia. In addition, the study was designed to test whether DCA, which exerts a hypoglycemic effect by restricting gluconeogenic substrate (alanine, lactate) supply, can limit the hyperglycemia associated with OLT.23,24 Finally, an attempt was made to examine the pharmacokinetics of DCA in patients undergoing OLT by using a one-compartment model and to compare the results with those of previous one-compartment analyses in normal humans and humans with clinical lactic acidosis.14,25,26

Materials and Methods

Patients

The protocol was approved by institutional review boards of Oregon Health Sciences University, the Portland (Oregon) Veterans Administration Medical Center, and the United States Food and Drug Administration (R.E.S., IND 35,790). After written informed consent, 66 patients scheduled for OLT at the Portland Veterans Administration Medical Center were assigned to one of two equal groups. Group 1 received only conventional NaHCO₃ therapy for metabolic acidosis, and group 2 received intraoperative sodium DCA. The first 58 patients were randomly assigned by coin toss, which resulted in 8 more patients in the DCA-treated group. A subsequent set of 8 control patients was studied to provide groups of equal size. The severity of liver disease was assessed by the Pugh-Childs scoring system.27

Preparation of Dichloroacetate

Stock DCA solution (100 mg·ml⁻¹) was prepared by dissolving raw sodium DCA (>99%, TCI America, Portland, OR) in 0.45% NaCl under aseptic conditions. The stock solution was sterilized by 0.22-μm filtration, and tested for sterility and pyrogenicity before use. Stock aqueous DCA was stored at 4°C, where it is stable for greater than 1 yr.28 Purity and stability of the stock solution were tested by gas chromatography–mass spectroscopy.

Procedure

All patients fasted for 8–12 h before surgery. Patients were monitored by noninvasive blood pressure cuff, electrocardiogram, arterial pulse oximetry, mixed venous oximetry, exhaled gas analysis, as well as continuous pulmonary and radial artery indwelling catheters. A contralateral radial artery catheter was used for blood sampling. Venovenous bypass was not employed.

Anesthesia was induced with sufentanil (3 μg·kg⁻¹) or fentanyl (1–3 μg·kg⁻¹) and thiopental (2–4 mg·kg⁻¹); with succinylcholine (1.5 mg·kg⁻¹) to facilitate intubation. Maintenance anesthesia consisted of sufentanil or fentanyl, isoflurane, midazolam, and pancuronium as needed. Before skin incision, methylprednisolone 1 g, ampicillin 1 g, and cefotaxime 1 g were administered intravenously, and the antibiotics were repeated at 6-h intervals. No other immunosuppressive drugs or subsequent methylprednisolone were administered in the operating room. In group 2, DCA 40 mg·kg⁻¹ was administered intravenously over 60 min immediately after induction of anesthesia and again 4 h later. This dosing schedule was chosen because, in volunteers, a single 50-mg dose causes a plasma DCA concentration of 1 μM and achieves a maximal effect on plasma lactate concentration (a 40–50% decrease) which persists for approximately 3 h.25,26,28 The second DCA dose was used to ensure that the maximal effect
on plasma lactate persisted throughout the duration of the dissection and anhepatic stages of the operation, which at our institution usually exceed 3 h.

Graft livers were preserved in ice-cold “University of Wisconsin” solution (Viaspan, DuPont Pharmaceuticals, Wilmington, DE), and were flushed with several liters of heparinized 6% hetastarch (Hespan, DuPont Pharmaceuticals) before warming and surgical anastomosis. Shed blood was replaced via a rapid-infusion pump (Sorin, Irvine, CA) equipped with a filtered 4:1 cardiectomy reservoir (Capiox, Terumo, Tokyo, Japan), a Gisch heat exchanger and an in-line bubble trap. In addition to banked blood products, the rapid infuser utilized salvaged erythrocytes (Cell-Saver, Haemonetics, Braintree, MA). Blood was transfused through two large-bore (7-French) intravenous catheters. Replacement with packed erythrocytes was guided by hematocrit, fresh frozen plasma by prothrombin time, and platelets by platelet count. CaCl₂ was administered as necessary to maintain a plasma ionized Ca²⁺ at 1.0 mEq·L⁻¹. A balanced salt solution (Normosol, DuPont Pharmaceuticals) was used for crystalloid infusion.

Intraoperative metabolic acidosis in both groups was treated in identical fashion: metabolic acidosis (pH < 7.30 with HCO₃⁻ concentration < 17 mm) was treated with NaHCO₃ (1 mEq·ml⁻¹ intravenously) to half-correct the HCO₃⁻ deficit, which was calculated according to the equation:

\[
\text{HCO}_3^- \text{ deficit} = 0.3 \times \text{body weight (kg)} \times \text{base deficit (mm)}
\]

The HCO₃⁻ space was taken to be 0.3 l·kg⁻¹. This aggressive treatment of acidosis was employed because acidosis can, in theory, impair cardiac performance.

**Sampling**

Arterial blood was collected into iced tubes at 0, 15, 30, 45, 60, 75, 90, 120, 180 and 240 min after the start of each DCA infusion, and at 2-h intervals for the subsequent 16 h after the second infusion, for determination of plasma DCA. Arterial blood was also collected at induction of anesthesia; 5 min before surgical incision; during heparatomy at 60 min before portal vein clamping; during the anhepatic phase at 30 and 60 min; and after portal vein unclamping at 15, 30, 60, 120, and 180 min; and 16 and 28 h after portal vein unclamping. Blood samples for arterial blood pH; CO₂ and O₂ tensions; base excess; plasma glucose, lactic acid, and Na⁺ concentrations; and hematocrit were centrifuged at 4°C and analyzed immediately upon collection. Plasma for DCA determination was stored at −70°C until analysis. All tubes contained heparin except those for lactate determination, which contained NaF, and those for hematocrit, which contained ethylenediaminetetraacetic acid. Cardiac output, systemic vascular resistance and pulmonary artery pressures were recorded at 30-60-min intervals throughout the operation. Hemodynamic measurements were recorded coincidentally with blood sampling and, in addition, at 5 min after portal vein unclamping.

**Biochemical Analyses**

DCA concentration in plasma and infusates was assayed by gas chromatography–mass spectrometry using the methyl ester derivative. In brief, methyl DCA was formed by reacting plasma or infusate samples with 12% BF₃ in methanol (Aldrich Chemical, Milwaukee, WI). Methyl DCA was extracted into toluene, and an aliquot quantitated by gas chromatography–mass spectrometry (5890/5970, Hewlett-Packard, Fullerton, CA), using a 25-m capillary chromatography column (DB-5, J & W Scientific, Folsom, CA). Conditions for the gas chromatograph were: Helium carrier gas at 60 psi, initial temperature = 40°C, with ramp of 5°C to a final temperature of 70°C. The mass spectrometer utilized electron impact ionization, with single ion monitoring, integrated at m/z 83. This peak corresponds to a C-Cl₂ fragment, which is not naturally apparent even in the presence of severe liver disease, as confirmed in several control patients. Fresh standard curves were made daily in human plasma (for patients) or saline (for infusates). In either medium, the standard curve for DCA was curvilinear for concentrations up to 3,300 μM, best described by a power equation with a correlation coefficient of 0.998. The assay detection limit was 12 μM.

Arterial blood gases were determined using an automated analyzer (1312 Blood Gas Manager, Instrumentation Laboratories, Lexington, MA) and whole blood base excess was calculated using the Siggaard-Anderson alignment nomogram (Radiometer A/S, Copenhagen, Denmark). Plasma lactate was assayed by lactic dehydrogenase, using an autoanalyzer (Monarch 760, Instrumentation Laboratories). Plasma glucose was assayed by glucose oxidase with an autoanalyzer (Glucose Analyzer 2, Beckman Instruments, Brea, CA). Sodium was determined by ion-specific electrode (CX-3, Beckman Instruments).
Table 1. Demographics of Liver Transplant Patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 33)</th>
<th>DCA (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/8</td>
<td>20/13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 ± 3</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Pugh–Childs score*</td>
<td>10 ± 0</td>
<td>10 ± 0</td>
</tr>
</tbody>
</table>

Etiology of liver disease

- Hepatitis C cirrhosis: 9
- Ethanol cirrhosis: 7
- Autoimmune cirrhosis: 2
- Primary biliary cirrhosis: 3
- Cryptogenic cirrhosis: 4
- α1-Antitrypsin deficiency: 1
- Primary sclerosing cholangitis: 0
- Secondary sclerosing cholangitis: 1
- Graft rejection: 1
- Subacute hepatic failure: 1

Values are mean ± SE. There were no differences between groups.

* The Pugh–Childs score was used to index severity of liver disease.

Pharmacokinetics

Individual plasma DCA concentrations were plotted on a logarithmic scale against a linear time scale for each subject, using a commercial computer program (Cricket Graph III version 10, Computer Associates, San Diego, CA). The slope of the curve was determined by linear regression to yield the elimination constant. Plasma half-life (\(t_\text{1/2}\)) of DCA was calculated as 0.693 divided by the elimination constant. For each subject, the linear portion of the logarithmic decay curve was extrapolated to time = 0 to yield the initial DCA concentration, and the effective volume of distribution (\(V_\text{D}\)) was calculated as dose divided by initial DCA concentration.

Statistical Analysis

Data were expressed as means ± standard error. Statistical comparisons of arterial \(pH\), \(CO_2\) tension, \(HCO_3^−\), base excess, lactate and glucose were made between groups at baseline, during and after OLT by two-way analysis of variance with Tukey’s post hoc test. Comparisons within a group over time were made by one-way analysis of variance technique with Tukey’s post hoc test. Incidence of hypernatremia (\(Na^+ > 145\) mEq \(\cdot l^{-1}\)) was compared by chi-squared analysis, and Student’s \(t\) test was used to compare the surgical and ischemia times, increment in natremia, and replacement of blood products, \(CaCl_2\), and \(NaHCO_3\) between groups. The Mann–Whitney test was used to compare the severity of liver disease. Statistical tests were performed using a specialized software program (Crunch version 4, Crunch Software, Oakland, CA). Differences were considered statistically significant at \(P < 0.05\).

Results

Table 1 shows that the most common etiologies of liver disease in both groups were hepatitis C (HCV) and ethanol-induced cirrhosis. There is considerable overlap between these diseases. Of the seven patients in each group with the principal diagnosis of ethanol-induced cirrhosis, two control and three DCA-treated patients have a positive titer for HCV. Furthermore, of the nine patients per group with principal diagnosis of HCV-induced cirrhosis, all had a history of some ethanol intake, with significant binge drinking by one control and two DCA-treated patients. The two groups did not differ in age, weight, or severity of liver disease. Durations of graft ischemia, and of the dissection, anhepatic, and reperfusion stages of surgery were not different (table 2).

Plasma DCA concentration, despite large fluid shifts, was maintained between 0.28 and 1.18 \(\mu\)mol during OLT (fig. 1). Peak DCA levels were 0.73 ± 0.06 and 1.18 ± 0.09 \(\mu\)mol, respectively, after the first and second doses. The \(V_\text{D}\) was 0.232 ± 0.025 \(l \cdot kg^{-1}\). Plasma \(t_\text{1/2}\) of the first dose was 101 ± 8 min (range 64–164 min), and for the second dose was 236 ± 35 min (range 92–410 min). By 24 h after skin incision (20 h after final DCA administration), there was no detectable plasma DCA in all but one patient. Even in this patient, whose

Table 2. Duration of Graft Ischemia and Surgery

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 33)</th>
<th>DCA-treated (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft ischemia (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>10.91 ± 0.53</td>
<td>9.69 ± 0.37</td>
</tr>
<tr>
<td>Warm</td>
<td>0.96 ± 0.02</td>
<td>0.97 ± 0.03</td>
</tr>
<tr>
<td>Total</td>
<td>11.87 ± 0.54</td>
<td>10.66 ± 0.37</td>
</tr>
<tr>
<td>Surgery (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I</td>
<td>3.98 ± 0.25</td>
<td>3.55 ± 0.23</td>
</tr>
<tr>
<td>Period II</td>
<td>1.13 ± 0.03</td>
<td>1.17 ± 0.05</td>
</tr>
<tr>
<td>Period III</td>
<td>5.67 ± 0.30</td>
<td>5.27 ± 0.22</td>
</tr>
<tr>
<td>Total</td>
<td>11.02 ± 0.53</td>
<td>9.97 ± 0.41</td>
</tr>
</tbody>
</table>

Period I = dissection (incision to portal vein clamping); Period II = anhepatic; Period III = reperfusion (portal vein unclamping to skin closure).

Values are mean ± SE. There were no differences between control and DCA-treated groups.
DICHLOROACETATE IN LIVER TRANSPLANTATION

![Graph showing temporal relation between dichloroacetate (DCA) administration and plasma DCA concentration.](image)

Fig. 1. Temporal relation between dichloroacetate (DCA) administration (40 mg·kg⁻¹ × 2), plasma DCA concentration, and surgical procedure in 25 patients who received DCA during liver transplantation. The DCA administration times are shown at the top of the graph. Data are means ± standard error.

Liver exhibited primary nonfunction, plasma DCA was 23 μM (compared with a second-dose peak of 2.08 mM). The patient, who had refused retransplantation preoperatively, expired postoperatively day 5. A second patient exhibited milder primary allograft nonfunction which was not accompanied by lactic acidosis. In this patient, peak plasma DCA concentration was 1.57 mM after the second dose, and was not detectable at 24 h postincision. The second patient was retransplanted on postoperative day 10.

Basal plasma lactate concentration in both patient groups was 1.07 mM (Fig. 2A). Control patients showed no change in plasma lactate during the average 80 min between anesthesia induction and surgical incision. During the dissection and anhepatic stages there was a progressive increase in plasma lactate concentration, reaching a peak of 7.30 ± 0.41 mM during the first 60 min after graft reperfusion. Plasma lactate remained increased during the subsequent 2 h. In patients who received DCA, plasma lactate decreased to 0.63 ± 0.05 mM immediately before surgical incision (P < 0.05 vs. baseline). Subsequently, DCA-treated patients also exhibited a progressive increase in plasma lactate concentration, reaching a peak of 3.39 ± 0.20 mM within the first 60 min after graft reperfusion. Throughout the operation, DCA-treated patients exhibited a 54–62% decrease in plasma lactate concentration compared to that in control patients. The increment in plasma lactate during the anhepatic stage was 1.5 mM in DCA-treated subjects and 2.4 mM in control subjects (P < 0.01). At 16 h after reperfusion, plasma lactate was not different from baseline in either group, and there was no difference between groups.

Basal arterial acid–base parameters did not differ between groups (Fig. 3). Both patient groups exhibited a progressive acidosis throughout the dissection period, anhepatic period and the initial 15 min of graft reperfusion, which paralleled the plasma accumulation of lactic acid (Fig. 3A). By 30 min of graft reperfusion, there was a trend toward alkalosis, which continued postoperatively. Arterial pH in the control group was lower than baseline during the anhepatic phase, and at 15 and 30 min postreperfusion, while arterial pH in the DCA group differed from baseline only at 15 min postreperfusion. Arterial pH of DCA-treated patients was higher than in control patients for the first 60 min after reperfusion (P < 0.04). Furthermore, the decrease in arterial pH from 60 min anhepatic to 15 min reperfusion was less pronounced in the DCA-treated group.

![Graph showing effect of dichloroacetate (DCA) on arterial plasma lactate (a) and glucose (b) during and after OLT.](image)

Fig. 2. Effect of dichloroacetate (DCA) on arterial plasma lactate (a) and glucose (b) during and after OLT. Open circles = control patients (n = 33); filled circles = DCA-treated patients (n = 33). The second DCA infusion had been completed in all patients by the early anhepatic phase. *Difference between control patients and DCA-treated patients (P < 0.001). **Differences from baseline within groups (P < 0.05). There was no difference between groups in plasma glucose at any time.

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Fig. 3. Effect of dichloroacetate (DCA) on arterial pH (a), CO₂ tension (b), HCO₃⁻ concentration (c), and base excess (d) during and after orthotopic liver transplantation. Open circles = control patients (n = 35); filled circles = DCA-treated patients (n = 35). The second DCA infusion had been completed in all patients by the early anhepatic phase. *Difference between control patients and DCA-treated patients (P < 0.04). †Difference from baseline within groups (P < 0.05).

Arterial CO₂ tension in both patient groups never differed from baseline intraoperatively, but was increased above baseline postoperatively, reflecting a response to metabolic alkalosis and possible opioid-induced respiratory depression (fig. 3b). There was no difference in arterial CO₂ tension between groups at any time. Arterial HCO₃⁻ content of both patient groups decreased from baseline during the anhepatic stage and at 15 min postreperfusion (fig. 3c). Postoperatively, it was increased above baseline at 16 and 28 h after reperfusion. DCA-treated patients showed a modest increase in plasma HCO₃⁻, which persisted through the dissection stage, after which the difference between groups was eliminated. Both groups showed a progressive base deficit compared with baseline, through the anhepatic phase and extending to 15 min after reperfusion (fig. 3d). All patients subsequently accumulated base equivalents, yielding a base excess greater than baseline by 3 h after reperfusion. When compared to results in control patients, DCA modestly increased base excess before skin incision, and attenuated the base deficit during the initial 60 min postreperfusion. At 16 and 28 h postreperfusion, base excess of the two groups did not differ.

The two groups had similar requirements for erythrocytes, fresh frozen plasma, platelets and CaCl₂ (table 3). In contrast, the NaHCO₃ requirement of DCA-treated patients was only 20% of that for control patients. DCA thus led to a more stable acid–base environment accomplished with one-fifth the NaHCO₃ dose of control patients. Of note, only 10 DCA-treated patients required NaHCO₃, compared to 29 control patients (P < 0.002). NaHCO₃ provides one Na⁺ equivalent for each HCO₃⁻. Alternatively, the Na⁺ load of sodium DCA, with a molecular weight of 151, is 6.623 mEq.g, which translates to 49.7 mEq of Na⁺ for the entire 80 mg·kg⁻¹ DCA dose in a 70 kg patient. The Na⁺ load of combined DCA and NaHCO₃ was 207 ± 30 mEq for control and 84 ± 17 mEq for DCA-treated patients (P < 0.001). The Na⁺ load of the respective crystalloid administrations was 910 ± 87 and 1,095 ± 145 mEq.
Table 3. Replacements during Liver Transplantation

<table>
<thead>
<tr>
<th>Blood products</th>
<th>Control (n = 33)</th>
<th>DCA (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (units)</td>
<td>16 ± 2</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>RBC + cell saver (&quot;units&quot;)</td>
<td>23 ± 2</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>FFP (units)</td>
<td>33 ± 4</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>Platelets (units)</td>
<td>35 ± 5</td>
<td>37 ± 5</td>
</tr>
<tr>
<td>CaCl₂ (g)</td>
<td>6.1 ± 0.7</td>
<td>6.9 ± 1.0</td>
</tr>
<tr>
<td>NaHCO₃ (mEq)</td>
<td>212 ± 35</td>
<td>42 ± 15*</td>
</tr>
<tr>
<td>NaHCO₃ (mEq/kg body weight)</td>
<td>2.43 ± 0.35</td>
<td>0.57 ± 0.22*</td>
</tr>
</tbody>
</table>

Values are mean ± SE.
RBC = packed erythrocytes, CPD-preserved; FFP = fresh frozen plasma. The cell saver "unit" was defined as 400 ml of salvaged blood.

* Significant difference from control (P < 0.01).

mEq (difference not significant). Although both groups began with similar plasma Na⁺ concentrations, both the final intraoperative Na⁺ concentration and the increment in plasma Na⁺ concentration during OLT were reduced in the DCA-treated group compared with those in the control group (table 4). Furthermore, the incidence of hypernatremia (Na⁺ > 145 mEq·L⁻¹) in the DCA-treated group was one third of that in control patients.

Because of the potential impact of exchange transfusion(s) on circulating blood composition, the composition of the reservoir blood was analyzed (table 5). At the time of sampling, the reservoir contained exclusively banked blood (reconstituted from packed red cells and fresh frozen plasma, at 1:2). Reservoir blood exhibited a marked lactic acidemia, with decreased pH, increased lactate and depleted HCO₃⁻ compared to the blood it replaced. Other abnormalities of reservoir blood were increases in glucose, Na⁺, and K⁺ concentrations. There was no difference between groups in any reservoir constituent.

Arterial plasma glucose concentration progressively increased during the course of the procedure in both groups and remained increased postoperatively (fig. 2B). Despite a 50% reduction of intraoperative plasma lactate concentration in the DCA group, there was no difference in intraoperative plasma glucose between groups at any time. There thus appears to be no cause-and-effect relation between hyperlactatemia and hyperglycemia associated with OLT. In one DCA-treated patient, plasma glucose decreased from an initial value of 80 mg·dl⁻¹ to 65 mg·dl⁻¹ immediately before surgical incision, accompanied by a decrease in plasma lactate from 0.8 to 0.4 mm. Intravenous glucose 25 g returned plasma glucose concentration to 116 mg·dl⁻¹, and hypoglycemia did not recur. No other patient, in whom plasma lactate was as low as 0.27 mm, ever exhibited hypoglycemia.

Patients in both groups exhibited a hyperdynamic circulation, with low vascular resistance and high cardiac index (table 6). Cardiac index was reduced during the anhepatic stage, then returned to baseline after graft reperfusion for the remainder of the operation. There was no difference between control and DCA-treated subjects in heart rate, filling pressure, mean arterial pressure, cardiac index, or vascular resistance at any time.

Discussion

This study confirms previous reports of intraoperative lactic acidemia, subsequent metabolic alkalosis and persistent hyperglycemia in patients undergoing OLT.²³,²⁴,¹¹ It also demonstrates that DCA can be administered to humans with end-stage liver disease, with predictable plasma levels, during OLT.²⁸ DCA decreased plasma lactate in patients with end-stage liver disease, and attenuated the OLT-associated increase in plasma lactate. DCA thus stabilized arterial acid–base homeostasis, and markedly reduced the intraoperative NaHCO₃ requirement.

Normal nonanesthetized humans produce and metabolize lactate at approximately 14 μmol·kg⁻¹·min⁻¹.¹⁶ Each lactate molecule is accompanied by an H⁺. Skeletal muscle, visceral organs, and erythrocytes all contribute to whole-body lactate production. The liver, however, is principal organ responsible for removal of plasma lactate, accounting for 40–50% of whole-body lactate clearance under basal conditions, with the kidney responsible for 30%, and another 20% removed by peripheral tissues.²⁰,²¹,²² Under basal conditions, 70–80% of lactate is oxidized to CO₂, while 20% is utilized for gluconeogenesis.³³,³⁴ Regardless of

Table 4. Plasma Na⁺ during Liver Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DCA</th>
</tr>
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<tbody>
<tr>
<td>Initial (preincision)</td>
<td>136 ± 1</td>
<td>135 ± 1</td>
</tr>
<tr>
<td>Final (3 h postreperfusion)</td>
<td>145 ± 1</td>
<td>142 ± 1*</td>
</tr>
<tr>
<td>Δ[Na⁺] plasma</td>
<td>8 ± 1</td>
<td>6 ± 1*</td>
</tr>
<tr>
<td>Hypernatremia incidence (Na⁺ &gt; 145)</td>
<td>12/33</td>
<td>4/33*</td>
</tr>
</tbody>
</table>

Values are mean ± SE. Plasma Na⁺ concentration is mEq/L.

* Significant difference from control (P < 0.05).
its ultimate fate, lactate metabolism ultimately removes a free $\text{H}^+$. A complete round of the Cori cycle is proton-neutral, because the $\text{H}^+$ produced by production of lactate from glucose is subsequently removed during synthesis of glucose from lactate.

Several mechanisms likely converge to produce lactic acidosis during OLT. First, peripheral tissues of cirrhotic subjects produce an exaggerated lactic acid output in response to a glucose challenge, as certainly occurs during blood transfusion. Second, the plasma $t_{1/2}$ of administered lactate is prolonged in cirrhotic subjects even in the absence of increased basal lactate concentration, revealing an impaired reserve capacity of the diseased liver to handle a lactate challenge. Third, surgical manipulation during OLT may cause visceral ischemia, concomitantly increasing endogenous lactic acid production and compromising its hepatic and renal uptake. Impairment of lactic acid metabolism is most extreme during the 1-h anhepatic stage. Fourth, stored erythrocytes are an exogenous source of lactic acid. Our study shows that banked blood transfusion represents a substantial lactic acid challenge. In addition, cell-saver salvaged blood is also $\text{HCO}_3^-$-depleted independent of changes in its lactate content. Thus, both banked and recycled blood are $\text{HCO}_3^-$-depleted. Massive transfusion during OLT would be expected to produce a metabolic acidosis even independently of the physiologic factors within the patient.

Lactic acidosis can be treated by ignoring the lactate per se and neutralizing the accompanying $\text{H}^+$, the mechanism of NaHCO$_3$ or other buffer therapy. One defect of this strategy is that NaHCO$_3$ acts almost exclusively in the extracellular space, neutralizing plasma $\text{H}^+$ much more effectively than that in the intracellular compartment. The ability of NaHCO$_3$ to rectify cellular dysfunction resulting from acidosis is limited. NaHCO$_3$ increases rather than decreases plasma lactate concentration. Therefore, a risk exists that the postoperative clearance of the additional plasma lactate produced by intraoperative NaHCO$_3$ therapy may exacerbate postoperative metabolic alkalosis. Aggressive use of NaHCO$_3$ also presents a hypernatremic Na$^+$ load to the patient which can lead to an acute increase in plasma Na$^+$ concentration. There appears to be an association between a rapid increase in plasma Na$^+$ in patients undergoing OLT and the development of demyelinating brain injury.

DCA represents an alternative approach to the regulation of arterial acid–base homeostasis which attenuates lactic acid accumulation. Uniquely, it is not a buffer. It acts by stimulating pyruvate dehydrogenase, thus (1) decreasing the availability of pyruvate to form lactate, (2) facilitating the oxidation of lactate via its equilibrium with pyruvate, or (3) both. The present study shows that DCA causes a 50% decrease in plasma lactic acid during OLT. These data are in agreement with findings in volunteers, and in patients with diabetes, severe burn injury, biguanide intoxication and sepsis. The DCA-induced attenuation of plasma lactate accumulation during the 70 min anhepatic phase is consistent with observations after hepatectomy in rats or dogs.

The pharmacokinetics of DCA are complex even in normal humans. The most striking feature is that repeated doses of DCA result is progressively longer plasma $t_{1/2}$ accompanied by changes in maximum initial velocity of reaction ($V_{\text{max}}$) and Michaelis-Menton constant for enzyme kinetics ($K_m$). Curry et al. found that serial DCA doses at 2-h intervals resulted in an increase in plasma $t_{1/2}$ from 56 min for the first dose to 374 min (range 38–1,386 min) for the fifth dose. The mechanism responsible for this apparent prolongation of DCA metabolism is uncertain, although it has been postulated that DCA inhibits its own metabolism. Alternatively, it is possible that single compartment models fail to account for the distribution of DCA in the tissues, especially since it acts intracellularly at the level of the mitochondrion.
Table 6. Hemodynamics during Liver Transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I-5</th>
<th>II-30</th>
<th>III-50</th>
<th>III+30</th>
<th>III+60</th>
<th>III+120</th>
<th>III+180</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>77 ± 3</td>
<td>93 ± 2</td>
<td>96 ± 3</td>
<td>94 ± 3</td>
<td>91 ± 3</td>
<td>89 ± 2</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>C</td>
<td>85 ± 3</td>
<td>97 ± 3</td>
<td>101 ± 4</td>
<td>101 ± 3</td>
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<td>96 ± 3</td>
<td>93 ± 3</td>
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<tr>
<td>CVP (mmHg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
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<td>11 ± 1</td>
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<td>11 ± 1</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
<td>15 ± 1</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>65 ± 2</td>
<td>79 ± 2</td>
<td>93 ± 2</td>
<td>90 ± 2</td>
<td>74 ± 3</td>
<td>82 ± 1</td>
<td>78 ± 1</td>
</tr>
<tr>
<td>C</td>
<td>69 ± 2</td>
<td>79 ± 2</td>
<td>90 ± 2</td>
<td>90 ± 2</td>
<td>64 ± 2</td>
<td>78 ± 2</td>
<td>76 ± 2</td>
</tr>
<tr>
<td>CI</td>
<td>4.36 ± 0.18</td>
<td>4.80 ± 0.24</td>
<td>3.24 ± 0.25</td>
<td>3.70 ± 0.34</td>
<td>5.24 ± 0.33</td>
<td>5.25 ± 0.44</td>
<td>5.21 ± 0.30</td>
</tr>
<tr>
<td>SVRI</td>
<td>4.07 ± 0.22</td>
<td>5.16 ± 0.31</td>
<td>3.28 ± 0.22</td>
<td>3.62 ± 0.24</td>
<td>5.61 ± 0.39</td>
<td>5.20 ± 0.30</td>
<td>5.07 ± 0.28</td>
</tr>
</tbody>
</table>

HR = heart rate; CVP = central venous pressure; MAP = mean arterial pressure; CI = cardiac index (L min⁻¹ m²); SVRI = systemic vascular resistance index (dyne·cm⁻²·s⁻¹·m⁻²); D = DCA-treated patients; C = control patients. I-5 = 5 min before incision; II-60 = 60 min before, 60 min after, and 60 min after portal vein clamping, respectively; III+5, +30, +60, +120, +180 = 5, 30, 60, 120, 180 min after portal vein unclamping, respectively.

Values are mean ± SE. There were no differences at any time between control and DCA-treated groups.

It is beyond the scope of the present study to evaluate the true DCA pharmaco kinetic profile to estimate the extent of plasma DCA concentration that would be achieved with the DCA administration. The results of this study indicate that DCA may be useful in the treatment of liver disease if administered in the appropriate dosage range. Further studies are required to determine the optimal dosage and duration of DCA treatment.
high or prolonged in end-stage liver disease. However, DCA administered to patients undergoing OLT produced plasma concentrations comparable to those obtained in normal humans, and the drug was eliminated from the plasma within hours postoperatively, indicating that the level of function necessary for adequate DCA metabolism was preserved in our patients.

The maximal effect of DCA in decreasing plasma lactate concentration in volunteers is obtained at a plasma DCA concentration of 1 mm. Serious toxicity, however, appears to require a much higher plasma DCA concentration. Irisinger et al. administered 20–34 g over a few hours, with a priming bolus of 4 g, to treat three patients with bupivacaine-induced lactic acidosis. This dose, which is 5–10 times the dose used in the present study (plasma DCA concentration was not reported) decreased plasma lactate and increased pH without any reported toxicity. In animals, the LD 50 of a single intravenous DCA dose is 500–1,000 mg/kg, a dose at which seizures, respiratory depression, and generalized CNS depression occur. Thus, the therapeutic index for DCA is relatively large, and the dose used in the present study was well within the range which could be considered safe.

Side effects of a comparable acute DCA dose (and blood level) in volunteers are limited to drowsiness, which is irrelevant during general anesthesia, and a 10–13% decrease in plasma glucose resulting from compromised gluconeogenic substrate availability. In diabetics, DCA decreases fasting hyperglycemia by 24%. We were concerned that hypoglycemia could occur in patients with end-stage liver disease because of the compromised status of hepatic glucose production in these patients. However, hypoglycemia was not a problem in our study patients. It is possible that our patients did not exhibit hypoglycemia because of (1) blood transfusion containing high glucose concentration; (2) marked peripheral insulin resistance caused by liver disease; (3) the hyperglycemic actions of methylprednisolone, of which 1 g was administered coincidentally with the first DCA dose for immunosuppression; and, finally, (4) catecholamine-induced hepatic glycogenolysis during surgical stimulation.

NaHCO 3 has a Na concentration of 1,000 mEq·l⁻¹. Decreasing the NaHCO 3 administered was hypothesized to decrease the hypernatremic Na⁺ load and the consequent rise in plasma Na⁺ concentration during OLT. DCA-treated patients had an incidence of hypernatremia which was one-third that of control patients, and the average increment in plasma Na⁺ was marginally smaller than that in control patients. Failure of DCA to have a larger effect on plasma Na⁺ was due at least in part to the high Na⁺ concentration in replacement banked blood (see table 4). Thus, a modest improvement in Na⁺ balance was achieved by a marked reduction in NaHCO 3 administration.

It was anticipated that DCA would decrease the severity of postoperative metabolic alkalosis, because it decreased the peak intraoperative plasma lactate concentration by 50% while the difference 16 h after reperfusion was eliminated. Thus, DCA reduced lactate metabolism during the early postoperative hours. Lactate challenge has been shown to increase both arterial pH and HCO₃⁻ concentration in humans. However, DCA failed to attenuate metabolic alkalosis after OLT. Three other potential mechanisms for postoperative metabolic alkalosis must be considered. First, citrate metabolism, like lactate metabolism, consumes H⁺. Citrate is a component of FFP and (to a lesser extent) packed RBCs. In our patients, the volume of blood products replacement, and presumably the citrate challenge, did not differ between groups. Citrate metabolism is directly related its plasma concentration during OLT. However, the peak metabolic alkalosis after OLT occurs at a time when plasma citrate, like plasma lactate, has already returned to baseline. Second, impaired urea synthesis by the graft liver would decrease the utilization of plasma HCO₃⁻, raising plasma HCO₃⁻ and exacberating metabolic alkalosis. Blood urea concentration is increased postoperatively, but it is a poor indicator of urea kinetics, especially in the setting of abnormal renal function. Third, our patients are infused with furosemide for the first 1–2 postoperative days to diurese them to preoperative body weight, which could result in contraction alkalosis.

The relation between hyperlactatemia and hyperglycemia during OLT is unclear. The liver removes plasma lactic acid and converts it to glucose, which is released into the plasma. Lactate is the predominant gluconeogenic precursor, and its hepatic utilization in vitro is directly proportional to its plasma concentration. Furthermore, the normal liver has a large reserve capacity to metabolize lactate, although the excess capacity may be reduced by liver disease.
Alberti demonstrated that lactate administration (Hartmann's solution) exacerbates hyperglycemia during abdominal surgery, raising the possibility that hyperglycemia is induced by hyperlactatemia. 49 Consistent with this hypothesis was the finding in our control group that the time course of hyperglycemia tended to parallel that of hyperlactatemia during OLT (fig. 2). DCA decreases plasma glucose at least in part by limiting lactate-derived gluconeogenesis. 88 However, the failure of a 50% reduction of plasma lactic acid to reduce hyperglycemia indicates that hyperglycemia during OLT is not driven by excessive lactate-induced glucose production. This finding is consistent with evidence in nonanesthetized humans in whom a marked challenge of gluconeogenic substrate failed to augment hepatic glucose output. 43 It does not preclude, however, the possibility of marked glycolysis by either the native or graft liver during OLT. Alternatively, the role of peripheral glucose utilization during OLT is unknown. Thus, the mechanism(s) of OLT-associated hyperglycemia remain(s) to be elucidated.

In conclusion, DCA can be safely administered to patients during OLT, and it effectively reduces the severity of lactic acidosis by decreasing the plasma lactic acid concentration. By limiting the requirement for NaHCO 3 therapy, it also decreases the incidence of hypernatremia during OLT. DCA does not appear to affect the hyperglycemia or metabolic alkalosis associated with OLT. Its role in promoting graft liver function and the prevention of hemodynamic complications of graft reperfusion (the "postreperfusion syndrome") remains to be determined.

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