Anesthesiology
82:251–258, 1995
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Recovery of Hepatic Drug Extraction after Hypothermic Preservation

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Background: **To determine whether liver preservation before transplantation impairs hepatic drug metabolism, hepatic extraction of drugs with different metabolic pathways (fentanyl, morphine, and vecuronium) in isolated rat livers was measured either immediately or after 24 h of hypothermia at 4°C using a standard preservation-reperfusion sequence.**

Methods: **Isolated rat livers were perfused *via* the portal vein for 30 min to document initial viability. Test livers (n = 5) were perfused with iced Belzer solution, stored for 24 h at 4°C, and flushed with 6% hetastarch. After hypothermic preservation for 24 h, or in control livers (n = 5) immediately after the 30-min perfusion, livers were perfused single-pass at a constant flow rate with solutions containing fentanyl, morphine, and vecuronium at 37°C. Perfusate and bile samples were obtained at regular intervals for 64 min, after which liver tissue was harvested for analysis. Drug concentrations were measured using radioimmunoassay and gas chromatography. Metabolic capacity of the liver was estimated from the extraction fraction of each drug at steady-state.**

Results: **After warming to 37°C, preserved livers consumed oxygen and produced bile at rates similar to that of control livers. Hypothermic preservation did not affect extraction of fentanyl and morphine. Vecuronium extraction was initially less in preserved livers, but this difference disappeared as the preserved livers returned to 37°C (<16 min). Biliary excretion and tissue concentrations of vecuronium were similar in each group.**

Conclusions: **Hypothermic preservation does not significantly impair extraction of these drugs in this liver preservation model. If these results apply to human liver transplantation, little danger of drug accumulation exists during the early postoperative period if hepatic function is normal. (Key words: Anesthetics, intravenous: fentanyl; morphine. Drug metabolism: hepatic. Neuromuscular relaxants: vecuronium. Transplantation, liver: preservation.)**

DESPITE the increasing frequency of liver transplantation, little is known about the ability of the newly transplanted liver to metabolize drugs in the immediate perianesthetic period. The insults sustained by the transplanted liver—hepatectomy, hypothermic preservation, and reperfusion—could compromise hepatic function and, therefore, drug metabolism. Qualitative evidence of hepatic metabolism of drugs has been reported after transplantation.[1,2] However, poor hepatic drug metabolism has been noted in livers that fail to function adequately.[3] The liver is primarily responsible for elimination of many drugs, including opioids and muscle relaxants, that are routinely administered during liver transplantation. Metabolic clearance of drugs by the liver is particularly important during the neohepatic period (*i.e.,* after perfusion of the newly grafted liver) because the mental status of the patient cannot be assessed until central nervous function has been restored. In addition, early tracheal extubation probably minimizes the likelihood of sepsis in these immunocompromised patients. Thus, knowledge of the ability of the newly transplanted liver to metabolize drugs should allow more rational use of sedative-hypnotic, analgesic, and paralyzing drugs during the perioperative period.

To address this issue, we examined the effect of hypothermic preservation and reperfusion on hepatic drug metabolism in an animal model. Our hypothesis was that drug extraction would be compromised during the early postoperative period. To test this hypothesis, we measured the effect of hypothermic preservation, storage, and reperfusion on the ability of isolated livers

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Received from the Departments of Anesthesia and Medicine, and the Liver Center, University of California, San Francisco, California. Submitted for publication May 31, 1994. Accepted for publication September 20, 1994. Supported in part by the Committee on Research of the Academic Senate of the University of California and by National Institutes of Health grants DK-26743 and DK-32898.

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to extract three anesthetic drugs: fentanyl, morphine, and vecuronium. These drugs were chosen because they are commonly used during liver transplantation and they represent different metabolic pathways and efficiencies of extraction.

Methods and Materials

The experimental protocol was approved by the institutional Committee on Animal Research. Male Sprague-Dawley rats (230–275 g, Benton & Kingman, Fremont, CA) had access to rat chow and water *ad libitum*. Isolated perfused rat livers were prepared using a standard method.[4,5] Ether was used for anesthesia because it is rapidly eliminated by the perfusion system lung, thus reducing the chance for interaction with drug-metabolizing pathways. Liver and portal structures were mobilized, and the common bile duct was cannulated. The hepatic artery was ligated and the liver perfused *via* a 16-G cannula in the portal vein, with oxygenated Krebs-Henseleit solution maintained at 37°C. The inferior vena cava was ligated and the confluence of hepatic veins cannulated *via* the right atrium. After isolation, livers were transferred to a temperature-controlled chamber and perfused for 30 min with a recirculating perfluorocarbon oxygen carrier (FC-43 emulsion, Alpha Therapeutic, Los Angeles).[5,6] Perfusate was equilibrated with oxygen and carbon dioxide using an artificial lung consisting of thin-walled silastic tubing.[7] Flows of oxygen and carbon dioxide to the lung were adjusted to maintain the inflow perfusate *p*H, measured *via* an indwelling probe, at 7.40 ± 0.05. Liver viability was assessed during this period by visual inspection, bile production, oxygen consumption, and perfusion pressure. Livers in the preservation group (n = 5) were perfused for 2 min with iced lactated Ringer's solution containing 0.1 mg/ml procaine and 10 U/ml heparin, followed by perfusion for 3 min with iced Belzer UW cold storage solution (Viaspan, Du Pont, Wilmington, DE) containing 0.04 U/ml insulin and 0.02 mg/ml dexamethasone. Livers were immersed in Belzer solution, and the perfusion dish was sealed with plastic wrap. After storage at 4°C for 24 h, livers were drained *via* gravity, returned to the perfusion chamber, and flushed for 2 min *via* the portal vein with iced 6% hetastarch solution (Hespan, DuPont). After this sequence of hypothermic preservation and in control livers (n = 5) immediately after the 30-min perfusion, livers were perfused single-pass at a constant flow rate with 12–17% washed human erythrocytes, 1% albumin, and 30 mM sodium taurocholate in Krebs-Henselheit solution. Target drug concentrations in the perfusate were: fentanyl 100 ng/ml, morphine 600 ng/ml, and vecuronium 1 μg/ml. In control livers, the drugs were added to the erythrocyte-containing perfusate immediately before surgery; in preserved livers, drugs were added to this perfusate before the hetastarch flush. Portal vein inflow pressure and hepatic temperature were continuously monitored during perfusion. Inflow perfusate samples were collected at 4, 16, 32, and 48 min after initiation of the erythrocyte-containing perfusate (reperfusion). Effluent perfusate samples were collected at 1, 2, 4, 8, 16, 32, 48, and 64 min. Bile was collected continuously over 16-min intervals in preweighed tubes. At 64 min, perfusion was stopped and the liver was trimmed of nonhepatic tissue, weighed, and homogenized to determine the tissue concentration of vecuronium and its metabolite, 3-desacetylvecuronium. After inflow and outflow perfusate samples were centrifuged to remove erythrocytes, drug concentrations in the supernatant were determined. Samples of perfusate, bile, and homogenized liver for analysis of vecuronium were acidified to prevent spontaneous degradation of vecuronium. Fentanyl was measured by radioimmunoassay (Research Diagnostics, Flanders, NJ), sensitive to 0.1 ng/ml with a coefficient of variation of <10% at that concentration. Morphine also was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA), sensitive to 0.8 ng/ml with a coefficient of variation < 10% at that concentration. Vecuronium and 3-desacetylvecuronium were measured by capillary gas chromatography, sensitive to 10 ng/ml with a coefficient of variation of 11% at that concentration.[8] Hepatic oxygen consumption ($\dot{V}O_2$) was calculated from the oxygen content of inflow and outflow perfusate samples measured at 4, 16, 32, and 48 min using a Clark electrode (Radiometer, Copenhagen, Denmark). Blood gases were determined at the same times (Stat Profile 5 Analyzer, Nova Biomedical, Waltham, MA). Perfusate concentrations of Na^+, K^+, Ca^{++}, and glucose were determined (Stat Profile 5 Analyzer) to confirm physiologic concentrations.

Because these initial experiments demonstrated net extraction (rather than production) of 3-desacetylvecuronium in control and preserved livers, we studied an additional nine livers (five control, four preserved) with identical technique except that the perfusate contained only 1 μg/ml 3-desacetylvecuronium rather than morphine, fentanyl, and vecuronium.

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For each drug, hepatic drug metabolic function was estimated by determining the extraction ratio for each liver, defined as:

$$\text{extraction ratio} = \left(1 - \frac{\text{drug outflow concentration}}{\text{drug inflow concentration}}\right).$$

For fentanyl or morphine (whose inflow concentrations remained constant over time), inflow concentration for each liver was determined as the mean of measured inflow values. For vecuronium (whose inflow concentration decreased over time, see Results), measured inflow concentrations were fitted to a single exponential decay ($r = 0.85–0.99$) to estimate the inflow concentration at each time. Extraction ratios were determined at 1, 2, 4, 8, 16, 32, 48, and 64 min using the measured outflow concentrations and the mean or fitted inflow concentrations. Mass balance for vecuronium plus 3-desacetylvecuronium was calculated based on molar quantities of these drugs in perfusate, effluent, bile, and liver tissue (collected at completion of each experiment).

Values for preserved and control livers were compared using the Mann-Whitney U-test. Changes over time within each group were assessed by repeated measures analysis of variance and Student-Newman-Keuls test or with Student's *t* test for unpaired or paired data. Data are reported as mean ± SD. $P < 0.05$ was considered statistically significant.

Table 1. Perfusion Characteristics During Recirculating, Preservation, and Eyrthrocyte–Perfusion Phases

	Control	Preserved
Number of livers	5	5
Recirculating perfusion phase		
Liver temperature (°C)		
Start of perfusion	28.2 ± 2.0	28.0 ± 3.2
End of perfusion	37.0 ± 0.1	36.5 ± 0.9
Portal vein pressure (cm H_2O)	11.5 ± 2.1	9.7 ± 1.8
Bile production (μl)	178 ± 50	189 ± 23
End of preservation sequence (preserved livers only)		
Liver temperature (°C)	—	15.1 ± 1.2*
Portal vein pressure (cm H_2O)	—	19.9 ± 4.1*
Erythrocyte perfusion phase		
Liver temperature (°C)		
4 min	36.6 ± 0.5	30.8 ± 2.5†
8–64 min	37.1 ± 0.4	36.5 ± 1.5
*p*H	7.38 ± 0.06	7.41 ± 0.03
Portal venous pressure (cm H_2O)	13.7 ± 3.9	13.9 ± 2.6
Perfusate flow rate ($ml \cdot min^{-1} \cdot g^{-1}$)	1.4 ± 0.1	1.4 ± 0.2
Oxygen content (ml/100 ml perfusate)	8.6 ± 1.1	8.3 ± 0.3
$\dot{V}O_2$ ($\mu mol \cdot min^{-1} \cdot g^{-1}$) at:		
4 min	2.3 ± 0.3	1.4 ± 0.4†
8 min	2.1 ± 0.5	1.9 ± 0.5
16 min	2.1 ± 0.5	2.0 ± 0.7
Bile production (μl)		
0–16 min	246 ± 98	73 ± 49†
17–32 min	196 ± 64	127 ± 82
33–48 min	160 ± 64	144 ± 114
49–64 min	138 ± 77	144 ± 120
Total	740 ± 288	487 ± 357
Liver weight at end of experiment (g)	11.2 ± 1.2	10.5 ± 0.8

Values are mean ± SD.

* Significantly different from value during perfluorocarbon perfusion ($P < 0.05$).

† Significantly different from control ($P < 0.05$).

Results

During the initial 30-min perfusion with perfluorocarbon emulsion, hepatic temperature increased from 28°C to 37°C, whereas portal vein pressure remained constant (table 1). There was no difference between groups in either of these values or in the rate of bile production during this period. During the preservation sequence (preserved livers only), hepatic temperature decreased to 4°C and hepatic inflow pressure increased.

During perfusion with the erythrocyte-containing solutions, inflow *p*H, oxygen content, and flow rate were similar in control and preserved livers. Portal venous pressure during this phase was similar to that recorded during the baseline perfusion. Four minutes after the beginning of erythrocyte perfusion, liver temperature and $\dot{V}O_2$ were significantly less in preserved livers (table 1). By 16 min and for the remainder of the perfusion, $\dot{V}O_2$ and hepatic temperature were similar in both groups. During the first 16 min, preserved livers produced less bile than control livers, but bile production for the subsequent intervals was similar, and there was no difference in total bile production. Hepatic weight at the end of the experiment was similar in control and preserved livers.

Fentanyl inflow concentration (target = 100 ng/ml) remained constant at 92.8 ± 34.2 ng/ml. For both groups, fentanyl extraction was greater during the first 4 min than during the 16–64 min interval (fig. 1 and table 2). After the initial warming phase, mean fentanyl extraction in preserved livers was similar to that in control livers, except at 48 min when it exceeded that in control livers.

Morphine inflow concentrations (target = 600 ng/ml) were constant at 575 ± 204 ng/ml. For control

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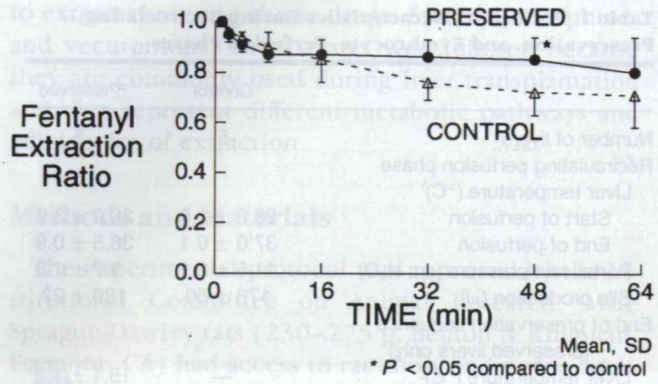

Fig. 1. Hepatic extraction of fentanyl in freshly isolated livers and in livers after 24 h of hypothermic preservation. Extraction was greater during the first 4 min, consistent with rapid initial uptake by the liver, and then declined to a stable value from 16 to 64 min. The extraction by preserved livers at 48 min is greater than in control livers.

livers, morphine extraction was greater in the initial 4 min than the later interval (fig. 2 and table 2). For preserved livers, morphine extraction did not change over time. Morphine extraction in preserved livers was similar to that in control livers, except at 4 min when it was less than that in control livers.

Inflow concentrations of vecuronium (target = 1 μg/ml) decreased during the perfusion (fig. 3). This was due to spontaneous conversion of vecuronium to 3-desacetylvecuronium, as evidenced by the presence of 3-desacetylvecuronium in the inflow perfusate in all studies. Because the interval between the addition of vecuronium to the perfusate and its administration to the isolated liver was greater in control livers, the inflow concentration of 3-desacetylvecuronium was greater than that for preserved livers.** In control livers, vecuronium extraction was greater in the initial 4 min than during the later interval (fig. 4 and table 2). In contrast, preserved livers had a lower extraction at 4 min than at subsequent times. Extraction was lower for preserved livers than for control livers during the first 4 min, but by 8 min there were no further differences. For both control and preserved livers, outflow concentrations of 3-desacetylvecuronium were lower than inflow concentrations (data not shown). During the 16–64-min interval, extraction of 3-desacetylvecuronium was similar in control livers (0.23 ± 0.23) and preserved livers (0.21 ± 0.20). Biliary excretion and tissue deposition of vecuronium plus 3-desacetylvecuronium were similar in preserved and control livers (table 3). Nearly all vecuronium plus 3-desacetylvecuronium entering the liver could be accounted for in the effluent, bile, and liver tissue. The fraction of the perfused vecuronium metabolized by the liver to 3-desacetylvecuronium was similar in the two groups.

In separate experiments with 3-desacetylvecuronium (target = 1 μg/ml), inflow concentration was stable at 1.2 ± 0.3 μg/ml. In preserved livers, hepatic extraction

Table 2. Extraction of Fentanyl, Morphine, and Fentanyl by Control and Preserved Livers during Early (1–4 min) and Late (16–64 min) Intervals Following Reperfusion

	Control	Preserved
Fentanyl		
1–4 min	0.95 ± 0.11	0.94 ± 0.03
16–64 min	0.76 ± 0.11*	0.84 ± 0.09*
Morphine		
1–4 min	0.63 ± 0.08	0.54 ± 0.15
16–64 min	0.47 ± 0.15*	0.56 ± 0.16
Vecuronium		
1–4 min	0.77 ± 0.10	0.31 ± 0.14†
16–64 min	0.55 ± 0.20*	0.65 ± 0.20*

Values are mean ± SD.

* Significantly different from value at 1–4 min ($P < 0.05$).

† Significantly different from control ($P < 0.05$).

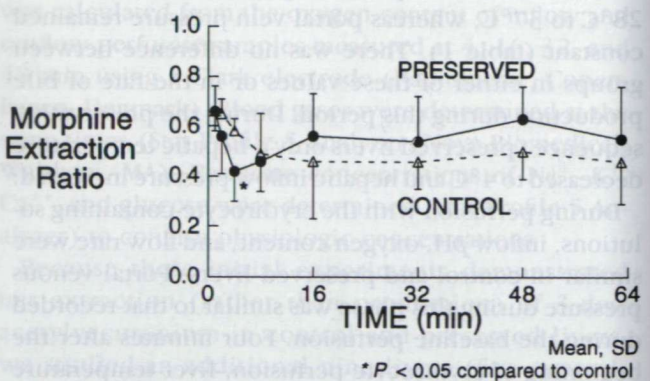

Fig. 2. Hepatic extraction of morphine in freshly isolated liver and in livers after 24 h of hypothermic preservation. At 4 min, preserved livers extracted morphine less efficiently. Otherwise, there was no difference between preserved and control livers.

** This time-dependent conversion of vecuronium to 3-desacetylvecuronium has been observed in blood maintained at physiologic *p*H and temperature (M. Sharma: Personal observation. 1993.). In addition, because the perfusate for control livers remained at 37°C and *p*H 7.4 longer than the perfusate for preserved livers (see Methods), lower concentrations of vecuronium and higher concentrations of 3-desacetylvecuronium should have been anticipated.

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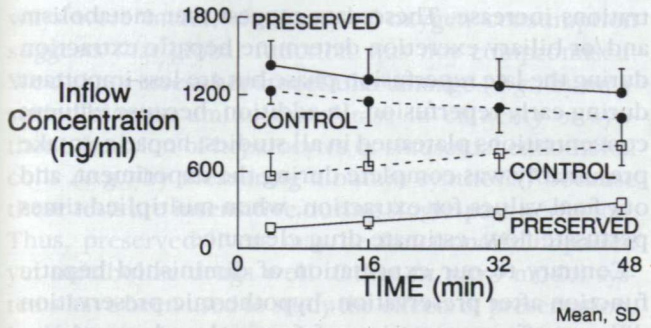

Fig. 3. Inflow concentrations of vecuronium and 3-desacetylvecuronium. Inflow samples were obtained for 48 min only (see Methods). For both freshly isolated livers and livers after 24 h of hypothermic preservation, inflow concentrations of vecuronium (closed circles) decreased, and those of 3-desacetylvecuronium (open squares) increased in the perfusate during the study. Vecuronium concentrations were smaller and 3-desacetylvecuronium concentrations larger in freshly isolated livers (see Results).

was 0.37 ± 0.19 during the first 4 min of perfusion after hypothermic preservation, then increased to 0.47 ± 0.15 during the final 48 min. Extraction of 3-desacetylvecuronium was greater in the control group for the first 4 min (fig. 5). However, by 8 min, there were no further differences.

One liver in the preservation group given morphine, fentanyl, and vecuronium (included in all data analyses) functioned poorly: bile production was minimal (one-fourth of the other preserved livers), oxygen consumption was low (one-half of the other livers, increasing only slightly with rewarming), but portal venous inflow pressure was normal. Consistent with these

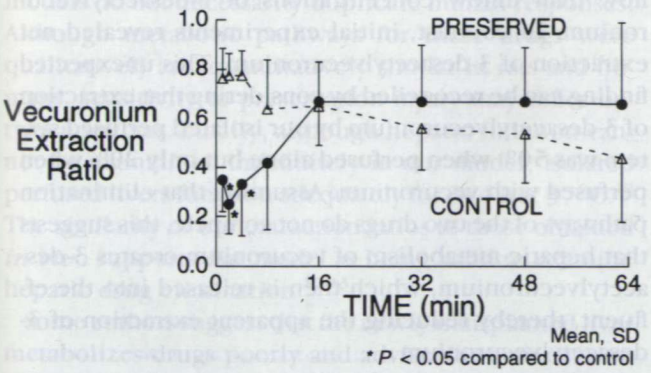

Fig. 4. Hepatic extraction of vecuronium in freshly isolated livers and in livers after 24 h of hypothermic preservation. In the first 4 min, preserved livers extracted significantly less vecuronium, but then increased extraction to values similar to control livers.

Table 3. Mass Balance of Vecuronium + 3-Desacetylvecuronium in Isolated Perfused Livers

	Control	Preserved
Perfusate effluent	54 ± 18	45 ± 16
Bile	14 ± 3	17 ± 2
Hepatic tissue	27 ± 5	32 ± 5
Total	95 ± 18	94 ± 22
Percent of vecuronium metabolized to 3-desacetylvecuronium	18 ± 13	27 ± 8

Values are expressed as percent of vecuronium + 3-desacetylvecuronium infused (mean ± SD).

markers of poor overall function, hepatic drug extraction of fentanyl and morphine decreased over time, and the liver eventually failed to extract 3-desacetylvecuronium. In addition, only 1% of the injected vecuronium dose was excreted in bile, and only 5% remained unchanged in the liver.

Discussion

Our results suggest that the standard method of preparing livers for transplantation—hepatectomy, hypothermic preservation, and reperfusion—did not influence hepatic extraction of fentanyl or morphine. Although hepatic extraction of vecuronium and 3-desacetylvecuronium were impaired during early reperfusion, preservation did not affect hepatic extraction after rewarming or overall biliary excretion and tissue concentration of vecuronium or its metabolite.

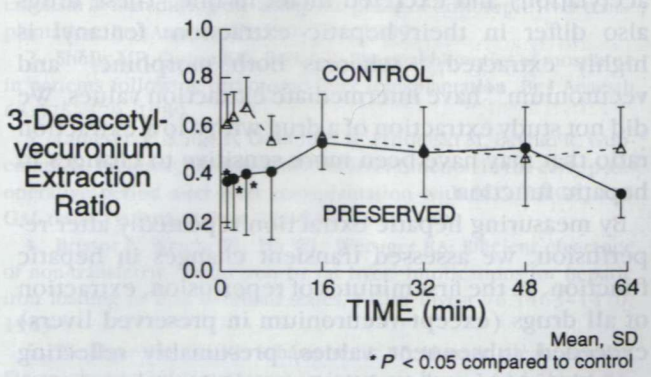

Fig. 5. Hepatic extraction of 3-desacetylvecuronium in freshly isolated livers and in livers after 24 h of hypothermic preservation. In the first 4 min, preserved livers extracted less 3-desacetylvecuronium than control livers, but no difference was evident subsequently.

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Data on the metabolic capacity of the newly transplanted human liver are limited. Bodenham *et al.*[1] gave morphine during the anhepatic phase and noted that concentrations of morphine metabolites were negligible until the liver was reperfused. Although that study demonstrated that the newly transplanted liver conjugates, it lacked a control group, thus providing qualitative, rather that quantitative, evidence of hepatic function. Shelly *et al.*[2] reported that, shortly after liver transplantation, morphine's plasma clearance exceeded published values for normal subjects. Although this suggests that liver function was not compromised, lack of a control group again limits application. A recent study compared muscle relaxant dose requirements during the dissection and neohepatic phases of liver transplantation.[9] However, that study compared native, diseased livers to transplanted livers, and therefore cannot differentiate effects of hepatic disease from those of preservation. Thus, for two important classes of intravenous drugs, opioids and muscle relaxants, effects of hepatic preservation are poorly defined.

Many alterations in the newly transplanted liver—including hypothermia-induced cell swelling, intracellular acidosis, expansion of the interstitial space during reperfusion, free-radical induced cellular injury, and depletion of high-energy phosphates—might impair hepatic metabolism.[10,11] To further define these documented and theoretical insults to hepatic homeostasis, we determined the effect of preservation on hepatic extraction of drugs commonly used during transplantation, selecting drugs with different metabolic pathways: fentanyl is oxidized by mixed function oxidases (cytochrome P450), morphine is glucuronidated, and vecuronium is both metabolized (*via* deacetylation) and excreted intact in bile. These drugs also differ in their hepatic extraction: fentanyl is highly extracted,[12] whereas both morphine[13] and vecuronium[14] have intermediate extraction values. We did not study extraction of a drug with a low extraction ratio that may have been more sensitive to changes in hepatic function.

By measuring hepatic extraction repeatedly after reperfusion, we assessed transient changes in hepatic function. In the first minutes of reperfusion, extraction of all drugs (except vecuronium in preserved livers) exceeded subsequent values, presumably reflecting rapid hepatic uptake while intracellular drug concentrations are small. The subsequent plateau in extraction presumably reflects increasing efflux of drug from the liver into the perfusate as intracellular drug concentrations increase. These data suggest that metabolism and/or biliary excretion determine hepatic extraction during the late reperfusion phase but are less important during early reperfusion. In addition, because effluent concentrations plateaued in all studies, hepatic uptake presumably was complete during the experiment, and our final values for extraction, when multiplied times perfusate flow, estimate drug clearance.

Contrary to our expectation of diminished hepatic function after preservation, hypothermic preservation did not affect extraction of fentanyl and morphine. Preservation for 24 h maximized our likelihood of observing impaired function: Preservation of this duration results in viable grafts in rats but would be expected to reveal more hepatic dysfunction than with shorter periods. We also used drug concentrations exceeding those attained clinically to maximize the likelihood of detecting decreased hepatic function. Although extraction of vecuronium and 3-desacetylvecuronium was transiently affected by preservation, this impairment was temporally related to low hepatic temperature. Thus, we cannot distinguish the effect of hypothermia from that of preservation-induced changes (*e.g.,* alterations in *p*H, depletion of adenosine triphosphate, or membrane changes) during this early period. Despite early differences in hepatic extraction of vecuronium, the overall effect of preservation was minimal: biliary excretion and final tissue content were similar in control and preserved livers. These findings suggest that the liver's ability to extract vecuronium and 3-desacetylvecuronium is minimally impaired by hypothermic preservation.

We expected that hepatic metabolism of vecuronium to 3-desacetylvecuronium would produce greater outflow than inflow concentrations of 3-desacetylvecuronium. In contrast, initial experiments revealed net extraction of 3-desacetylvecuronium. This unexpected finding can be reconciled by considering that extraction of 3-desacetylvecuronium by our isolated perfused system was 50% when perfused alone but only 20% when perfused with vecuronium. Assuming that elimination pathways of the two drugs do not compete, this suggests that hepatic metabolism of vecuronium creates 3-desacetylvecuronium, which then is released into the effluent, thereby reducing the apparent extraction of 3-desacetylvecuronium.

Our model permitted limited assessment of hepatic functions other than drug extraction. Similarity of bile flow and biliary excretion of vecuronium in preserved and control livers suggests that biliary excretory path-

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ways were intact; similarity of oxygen consumption suggests that global function was not compromised. We did not assess hepatocellular damage (*e.g.,* by measuring alanine amino transferase in effluent) or synthetic function of hepatocytes or sinusoidal endothelial cells (*e.g.,* by measuring albumin synthesis) because these tests are insensitive during single-pass perfusion. Thus, preserved livers may be functionally impaired yet metabolize drugs well. Other *in vitro* model systems have been used to study the effects of preservation, including isolated hepatocytes and liver tissue slices[15]; however, these studies have not examined quantitative differences in hepatic drug metabolism between normal and preserved livers.

Although our results suggest that hepatic drug metabolism is protected during hypothermic preservation, our *in vitro* model differs from liver transplantation. First, leukocytes, thought to mediate hepatic injury during reperfusion, are absent[16]; their presence *in vivo* may increase reperfusion injury and thereby impair hepatic drug extraction. Second, we perfused at a constant rate and only through the portal vein. During transplantation, many factors influence liver blood flow,[17,18] including the sequence of portal vein and hepatic artery anastomosis. Marked decreases in liver blood flow would compromise hepatic delivery of drugs, thereby decreasing clearance of highly extracted (perfusion-limited) drugs such as fentanyl and possibly decreasing clearance of drugs with lower extraction ratios. Third, our study examines only hepatic drug extraction but does not address extrahepatic drug distribution. If the neohepatic period were associated with other physiologic changes that alter drug distribution, this would influence drug concentrations *in vivo*. Fourth, animal models do not necessarily duplicate human responses. Although metabolic pathways for these drugs were qualitatively and quantitatively similar in rats and humans, sensitivity to preservation injury may differ between species. Finally, although hepatic function cannot be maintained indefinitely in our model, isolated perfused livers function adequately for 3–4 h at 37°C.[19] The similarity of our extraction ratios to those obtained *in vivo* supports our model as being valid to examine hepatic drug elimination.[12,13]

Some authors suggest that the newly transplanted liver metabolizes drugs poorly and advise extreme caution when administering intravenous anesthetic drugs during this period.[20] In contrast, our results suggest that drug metabolism recovers rapidly after hepatic preservation and reperfusion. However, our results must be interpreted with caution. Clinical experience indicates that some hepatic allografts never regain adequate function after preservation. One of our preserved livers may have demonstrated this "primary nonfunction": decreased bile production, decreased oxygen consumption, and a progressive decrease in hepatic extraction of all three drugs. Recently, production of monoethylglycinexylide, a metabolite of lidocaine, was proposed as a marker of function of donor livers before harvesting.[21] In addition, reduced production of monoethylglycinexylide may indicate that patients with hepatic dysfunction require urgent transplantation.[22] Whether decreased metabolism of other drugs, such as those in the current study, can identify early hepatic dysfunction remains to be determined.

In summary, our animal model suggests that hepatic hypothermic preservation for transplantation affects hepatic extraction of morphine, fentanyl, and vecuronium minimally. Transient impairment of vecuronium extraction may represent hypothermia or preservation-dependent reduction in hepatic uptake but resolves rapidly. Our results suggest that, in the neohepatic period, hepatic metabolism of intravenous anesthetics is minimally affected in livers that function well. Future work may indicate whether compromised drug metabolism is a sensitive and/or specific marker of dysfunction in the transplanted liver.

The authors thank Linda Kendrick, for assistance with the perfusion preparation, and Larry Gruenke, Ph.D., for analytic work.

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