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ORIGINAL ARTICLE

Levobupivacaine plasma concentrations following major liver resection

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Abstract
Purpose Levobupivacaine is metabolized hepatically. Whether postoperative epidural analgesia with levobupivacaine can lead to critical accumulation in patients undergoing major hepatic resection is unknown. Therefore, levobupivacaine concentrations were prospectively monitored in patients undergoing major liver resection and compared to patients undergoing rectal resection, who served as controls. Furthermore, we correlated levobupivacaine plasma concentrations with established liver function tests.
Methods We analyzed plasma concentrations of levobupivacaine in 20 patients each scheduled for major liver or anterior rectal resection. All patients received general and epidural anesthesia (10 ml levobupivacaine 0.5% followed by 10 ml levobupivacaine 0.375% every 90 min) and postoperative continuous epidural analgesia (levobupivacaine 0.2%). Intraoperatively, and for 3 days postoperatively, levobupivacaine plasma concentrations were measured and correlated with bilirubin, fibrinogen, indocyanine green (ICG) clearance, and cholinesterase activity. Data (mean ± SD) were analyzed by two-way analysis of variance (ANOVA) with post hoc analysis or regression analysis ($P < 0.05$).
Results Intraoperatively and postoperatively, patients undergoing liver resection revealed significantly higher levobupivacaine concentrations ($P = 0.0013$ and $P = 0.0016$, respectively). Furthermore, significant differences were found for bilirubin ($P = 0.0002$), fibrinogen ($P = 0.0002$), and ICG ($P < 0.0001$). Highest levobupivacaine concentration correlated significantly with lowest ICG ($P = 0.0004$; $R = 0.69$), highest bilirubin ($P = 0.0267$; $R = 0.49$), lowest fibrinogen concentration ($R = 0.32$), but not with cholinesterase activity ($R = 0.02$).
Conclusion Patients undergoing liver resection revealed significantly higher levobupivacaine concentrations compared to patients undergoing anterior rectal resection. However, although intraoperative levobupivacaine concentrations remained below 2.0 μg/ml, postoperative concentrations accumulated to a concentration above this threshold. This risk of levobupivacaine accumulation in patients with compromised liver function correlated best with ICG clearance.

Keywords Levobupivacaine · Local anesthetic intoxication · Liver resection

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Introduction

For abdominal surgery, combined general with thoracic epidural anesthesia has been established as a part of the fast track concept [1–3]. In general, amide local anesthetics are used for intraoperative anesthesia and postoperative analgesia. Amide local anesthetics, such as levobupivacaine, are metabolized hepatically [4]. How liver resections alter the metabolism of local anesthetics is unclear. Therefore, the question arises whether epidural administration can lead to critical accumulation [5–7]. In particular, intraoperative

epidural administration of high concentrations of levobupivacaine may lead to different results compared to epidural administration of rather low concentrations for postoperative analgesia. Furthermore, to avoid critical accumulation of levobupivacaine, a routine parameter to predict levobupivacaine plasma concentrations would be desirable.

The use of routine parameters, such as bilirubin or fibrinogen plasma concentration or cholinesterase activity, to indicate the accumulation of levobupivacaine plasma concentrations is complicated by the transfusion of blood products or hemodilution.

However, indocyanine green (ICG) clearance can give information independent of these effects [8–11].

Overall, the primary aim of the study was to compare prospectively levobupivacaine plasma concentrations in patients undergoing major liver resection to patients undergoing rectal resections. Furthermore, the secondary aim of the study was to evaluate possible correlations of levobupivacaine plasma concentrations with bilirubin, fibrinogen plasma concentrations, cholinesterase activity, and ICG clearance.

Materials and methods

Patients

After approval by the local ethics committee, 20 patients scheduled for major liver resection (at least two liver segments) or laparoscopically assisted low anterior rectal resection gave their informed written consent. Patients with compromised plasmatic coagulation or thrombocytopenia were excluded. All patients received combined general and thoracic epidural anesthesia. Anthropometric data are presented in Table 1.

Table 1 Anthropometric data, duration of surgery, and transfusion requirements

	Liver ($n = 10$)	Rectum ($n = 10$)
Height (cm)	174 ± 10	175 ± 8
Weight (kg)	72 ± 11	74 ± 16
Gender (f/m)	3/7	3/7
Age (years)	54 ± 14	62 ± 12
Surgery (min)	268 ± 76	250 ± 62
Infusioncrystalloid (ml)	5950 ± 791	5370 ± 1112
Infusioncolloid (ml)	375 ± 443	389 ± 333
RBC (units)	3.1 ± 3.2	1.1 ± 2.9
FFP (units)	2.2 ± 4.1	0.4 ± 1.3

There are no differences between the groups

Data are mean ± SD

RBC red blood cells, *FFP* fresh-frozen plasma

Methods

Plasma concentrations of levobupivacaine were measured by high pressure liquid chromatography (HPLC) (Waters, Eschborn, Germany) with photodiode array detector and spectrophotometric election at 200 nm. The lower level of detection was 0.01 μg/ml with a coefficient of variation less than 0.5%.

The technique of ICG measurements is based on the transcutaneous measurement of ICG and fast hepatic elimination of the dye under normal excretory function (LiMon; Pulsion Medical Systems, Munich, Germany). Following a bolus of ICG (0.25 mg/kg body weight dissolved in 10 ml water) via a central venous catheter, the plasma disappearance rate (PDR) can be measured noninvasively with a finger clip in percent per minute [8, 9].

Venous blood was drawn for measurements of bilirubin, fibrinogen plasma concentrations, cholinesterase activity, platelet count, and partial thromboplastin time preoperatively and daily in the morning until the third postoperative day. ICG clearance was repeated every morning; levobupivacaine plasma concentrations were determined every 12 h until the third postoperative morning.

Experimental protocol

On the day of surgery a thoracic epidural catheter was placed (T6–T7 or T7–T8 thoracic vertebral interspace) in sitting position with loss of resistance technique and administration of a test dose of 3 ml levobupivacaine 0.5%. Subsequently, general anesthesia was induced with propofol, rocuronium, and remifentanil, and a baseline ICG test was performed. Two intravenous lines, a gastric tube, a temperature probe, a tri-lumen central venous catheter, and an arterial catheter were placed. Body temperature was maintained above 36.0°C. General anesthesia was maintained with isoflurane and remifentanil. Thirty minutes before skin incision, epidural anesthesia was initiated with 10 ml levobupivacaine 0.5% and maintained with additional doses of 10 ml levobupivacaine 0.375% every 90 min. At 30 min after epidural administration of levobupivacaine, 8 ml blood was drawn for determination of plasma concentrations [12]. Intraoperative fluid management was left to the discretion of the attending anesthesiologist. Duration of surgery and transfusion requirements were documented. At the end of surgery, all patients were awakened, extubated, and transferred to the intensive care unit.

In the evening, blood samples for levobupivacaine plasma concentrations were taken.

Postoperatively, patients received levobupivacaine 0.2% with 0.5 μg sufentanil/ml epidurally with 6 ml/h (range, 5–9 ml/h) depending on the demands of the patients [visual

Table 2 Preoperative baseline and postoperative results of liver function tests, partial thromboplastin time (PTT), and platelet count

	Surgery	Baseline	Day 1	Day 2	Day 3	*P* value
Total bilirubin (mg/dl)	Liver	0.79 ± 0.72	2.10 ± 0.72	2.34 ± 0.75	2.19 ± 1.02	0.0002
	Rectum	0.65 ± 0.27	1.10 ± 0.71	0.80 ± 0.48	0.60 ± 0.31	
Fibrinogen (mg/dl)	Liver	494 ± 193	238 ± 32	362 ± 146	383 ± 89	0.0002
	Rectum	364 ± 113	359 ± 90	549 ± 121	673 ± 133	
Cholinesterase (U/l)	Liver	5829 ± 1776	3544 ± 1161	3390 ± 1201	3161 ± 997	0.2479
	Rectum	6687 ± 3147	5082 ± 2623	4786 ± 2526	5066 ± 2863	
PTT (s)	Liver	31.9 ± 5.9	44.4 ± 6.3	39.1 ± 2.2	37.8 ± 3.4	0.2917
	Rectum	31.6 ± 4.3	37.3 ± 4.7	37.5 ± 8.2	34.6 ± 9.2	
Platelets ($\times 10^9$/l)	Liver	350 ± 160	195 ± 72	219 ± 98	249 ± 107	0.2624
	Rectum	268 ± 57	182 ± 81	177 ± 84	192 ± 89	

Mean ± SD; *P* values of two-way ANOVA for type of surgery

analogue (VAS) score ≤ 3]. Patients were visited two times a day and on request. If pain increased above a VAS score of 3, boluses of levobupivacaine (5 ml, 0.25%) were injected and added to the cumulating dose. Epidural analgesia was maintained until the afternoon of the third day and prolonged when required by the patients.

Segments 5–8 for right hemihepatectomy and segments 4–8 for right extended liver resection were removed. Low anterior rectal resection was performed in a standardized laparoscopically assisted technique creating a stapled circular supraanal anastomosis.

Data analysis

Data are presented as mean ± SD. Sample size was calculated based on an alpha-error of 0.05, a beta-error of 0.1, a standard deviation of 0.3 μg/ml, with a minimal difference to be detected of 0.5 μg/ml [12]. To test the null hypotheses, levobupivacaine plasma concentrations during and after operation between the two groups were compared by two-way analysis of variance (ANOVA) followed by post hoc test with Bonferroni correction for multiple comparisons. Null hypotheses were rejected and significant differences assumed with $P < 0.05$.

As secondary outcome parameters, maximal levobupivacaine plasma concentrations were correlated with minimal ICG test results, maximal bilirubin, minimal fibrinogen plasma concentrations, and minimal cholinesterase activity. Anthropometric parameters were tested by Student's *t* test.

Results

Anthropometric data and surgery

There were no significant differences in the anthropometric data and the preoperative baseline liver function tests between patients who underwent liver resection versus patients who underwent laparoscopically assisted low anterior rectal resection (Tables 1, 2). There was no difference in the time of surgery and no difference in the number of transfused blood units (Table 1). Mean weight of liver parenchyma resected was 1,221 ± 562 g (range, 570–2,482 g).

Table 3 Cumulated levobupivacaine dose

	Liver ($n = 10$)	Rectum ($n = 10$)
Day of surgery (mg)	229 ± 34	226 ± 35
1. Postoperative day early (mg)	402 ± 62	386 ± 55
1. Postoperative day late (mg)	568 ± 79	553 ± 68
2. Postoperative day early (mg)	717 ± 114	737 ± 92
2. Postoperative day late (mg)	894 ± 166	916 ± 123
3. Postoperative day early (mg)	1064 ± 214	1084 ± 159

Mean ± SD

Surgical procedures

Hepatic resections ($n = 10$) included right hemihepatectomies ($n = 3$), extended right hemihepatectomies ($n = 6$), as well as segmental liver resection (IV a/b, I) ($n = 1$) for colorectal metastases, cholangiocellular, gallbladder, and hepatocellular carcinoma. The control group ($n = 10$) underwent laparoscopically assisted low anterior resection of rectal carcinoma.

Levobupivacaine plasma concentrations

During surgery as well as during subsequent epidural analgesia, the same amount of levobupivacaine was administered in both groups of patients (Table 3; $P = 0.9159$). Intraoperatively, and for the first postoperative measurement, the levobupivacaine plasma concentrations were

significantly higher in patients undergoing liver resection (Fig. 1; $P = 0.0013$). In the next following 3 days, levobupivacaine plasma concentrations increased significantly for both groups (Fig. 2; $P < 0.0001$). In comparison of the two groups of patients, plasma concentrations increased significantly for patients who underwent liver resection (Fig. 2; $P = 0.0016$).

Laboratory findings and liver function tests

At baseline there were no significant differences for fibrinogen and bilirubin concentrations, cholinesterase activity, thrombocyte count, and partial thromboplastin time (Table 2).

Until the third postoperative day, patients who underwent liver resection showed significantly lower fibrinogen and significantly higher bilirubin plasma concentrations compared to patients undergoing rectal resection ($P = 0.0002$ for both) and to their baseline ($P < 0.0001$).

Partial thromboplastin time was not significantly different between the two groups ($P = 0.2917$), but was significantly elevated for liver resection patients compared to their baseline ($P < 0.0001$). Cholinesterase activity and thrombocyte count decreased significantly postoperatively for both groups ($P < 0.0001$ and $P < 0.0001$, liver; $P = 0.0018$ and $P < 0.0001$, rectum) but did not differ between the groups ($P = 0.2479$ and $P = 0.2624$, respectively).

At baseline, under mechanical ventilation, ICG clearance was not different between groups ($P = 0.2884$). Postoperatively compared to baseline, ICG clearance decreased significantly for patients with liver resection (Fig. 3; $P = 0.0005$) and increased significantly for patients with low anterior rectum resection (Fig. 3; $P = 0.0251$). ICG clearance was significantly different between groups (Fig. 3; $P < 0.0001$).

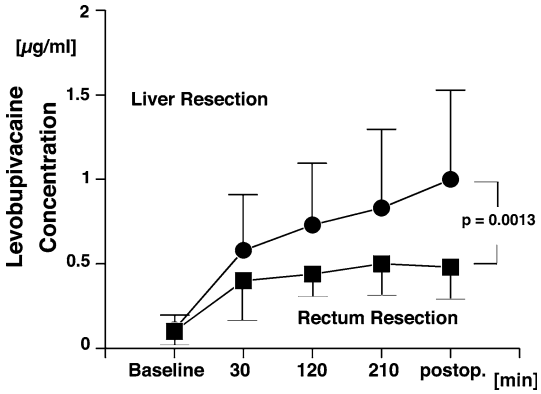

Fig. 1 Plasma concentrations of levobupivacaine during surgery of ten patients undergoing major liver resection (*circles*) and ten patients undergoing laparoscopically assisted low anterior rectal resection (*squares*, mean ± SD). Following a test dose of 3 ml levobupivacaine 0.5%, epidural anesthesia was initiated with 10 ml levobupivacaine 0.5% and maintained with 10 ml levobupivacaine 0.375% every 90 min. Plasma concentrations were measured 30 min after injection

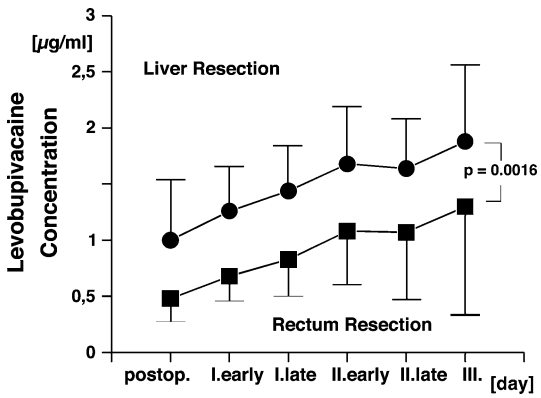

Fig. 2 Plasma concentrations of levobupivacaine during postoperative continuous epidural analgesia following major liver resection (*circles*, $n = 10$) or laparoscopically assisted low anterior rectal resection (*squares*, $n = 10$, mean ± SD). Epidural analgesia was maintained with levobupivacaine 0.2% at 5–10 ml/h according to the patients' pain score (VAS less than 3). Plasma concentrations were measured twice a day

Correlation of maximal levobupivacaine plasma concentrations with liver function tests

Correlations were tested for maximal levobupivacaine plasma concentrations with minimal ICG clearance, maximal plasma bilirubin concentration, minimal plasma fibrinogen concentrations, and minimal cholinesterase activity.

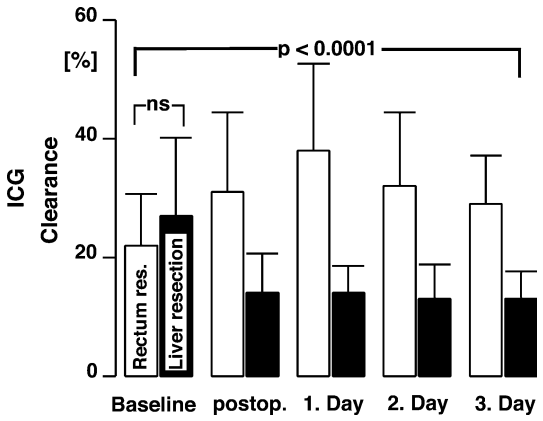

Fig. 3 Indocyanine green (*ICG*) clearance (plasma disappearance rate in percent, mean ± SD) for ten patients with liver or rectal resection each, at baseline, after induction of anesthesia, following surgery (*postop.*), and at the morning of the first 3 postoperative days. At baseline there was no difference between the two groups of patients. Following surgery, ICG clearance increased in patients with rectal resection whereas clearance decreased significantly in patients undergoing liver resection

Individual maximal levobupivacaine concentrations correlated best with minimal ICG clearance ($R = 0.69$; Fig. 4) and subsequently less with maximal bilirubin concentrations ($R = 0.49$; Fig. 5), minimal fibrinogen plasma concentration ($R = 0.32$), and minimal cholinesterase activity ($R = 0.02$).

Hemodynamic and fluid management

Intraoperative hypotension was managed with infusion of crystalloid (Ringer's solution), or colloid (6% hetastarch 130/0.4) solutions at the discretion of the responsible anesthesiologist. Depending on the expected individual anemia tolerance of the patient, the anesthesiologist decided to transfuse blood components. In addition a mild vasopressor (cafedrine/theodrenaline) was administered to maintain a mean blood pressure of more than 60 mmHg. There was no need for continuous administration of direct sympathomimetics.

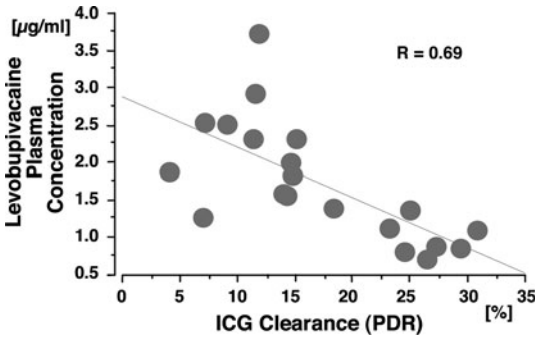

Fig. 4 Individual minimal ICG clearance presented with respect to the respective, maximal levobupivacaine plasma concentrations in ten patients following liver and rectal resection each. Individual results show a significant correlation ($R = 0.69$). All levobupivacaine concentrations ≥2.0 µg/ml occur with an ICG clearance of less than 16%. *PDR*, plasma disappearance rate

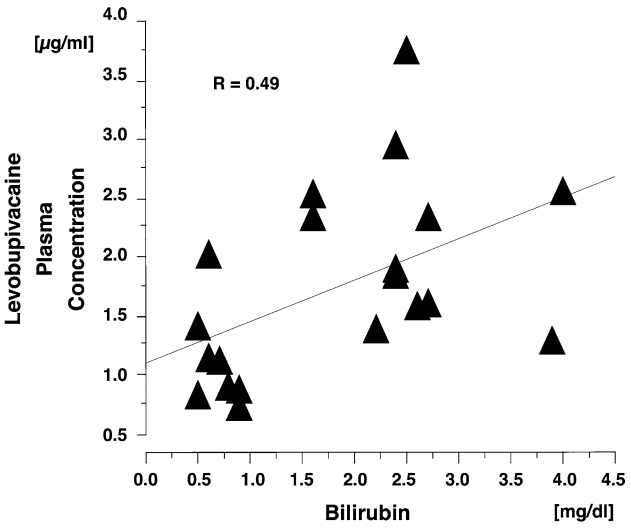

Fig. 5 Individual maximal bilirubin concentrations correlated with maximal levobupivacaine plasma concentrations in ten patients following liver or rectal resection (mean ± SD). Individual maxima show a significant correlation ($R = 0.49$). All levobupivacaine concentrations ≥2.0 µg/ml occurred with a bilirubin concentration higher than 1.5 mg/dl

Discussion

Following major liver resection, patients developed significantly higher levobupivacaine plasma concentrations compared to control patients. The maximal plasma concentrations correlated best with ICG clearance and bilirubin plasma concentrations.

We enrolled patients scheduled for major liver resection, as patients having minor resection do not have much impairment of their liver function [13, 14]. Patients undergoing laparoscopically assisted low anterior rectal resection served as control patients and were matched with their anthropometric data, duration of surgery, and need for postoperative analgesic therapy. Overall, the same total amount of levobupivacaine was administered epidurally in both groups.

Levobupivacaine is metabolized via the cytochrome P-450 pathway (CYP3A4 and CYP1A2) [4]. To avoid alterations of the capacity of cytochrome P-450 activity, none of the patients received medication that is metabolized via this pathway such as aminophylline, phenytoin, or barbiturates. We deliberately chose ICG clearance as a liver function test that does not interfere with cytochrome P-450 activity [4]. Tests such as the MEGX test, which involves P-450 activity, would have given more information about the metabolic capacity of the liver parenchyma but also would have altered the capacity to metabolize levobupivacaine.

Levobupivacaine plasma concentration measurement is usually not available as a routine laboratory parameter. Hence, a standard parameter to give an estimate of the risk of local anesthetic accumulation would be desirable. As potential candidates to predict levobupivacaine accumulation the correlation of cholinesterase activity, bilirubin and fibrinogen plasma concentration, and ICG clearance were compared to the maximal levobupivacaine plasma concentrations.

Because of the differences in the dose of levobupivacaine, the perioperative determination of levobupivacaine plasma concentrations was split into two separate observational periods. At first, we observed the course of levobupivacaine concentrations resulting from the high-dose administration for intraoperative epidural anesthesia. Thereafter, we assessed levobupivacaine concentrations resulting from low-dose continuous administration for postoperative analgesia. The observation period ended at

the third postoperative day. After 3 days, postoperative administration decreased and the dose of levobupivacaine was constantly reduced and finally terminated [15, 16].

To date, there is no exact plasma concentration defined as a threshold for levobupivacaine toxicity. Although with meticulous measurements cardiac effects, such as QRS widening and decrease of stroke volume index, can be detected at plasma concentrations below 2 μg/ml, subjective symptoms of intoxication occur with plasma concentrations of levobupivacaine higher than 2 μg/ml [4, 17–24]. The first symptoms that are described are neurological symptoms such as disorientation, restlessness, and slurred speech at plasma concentration of 2.70 μg/ml and higher [22]. Life-threatening cardiac symptoms and cardiovascular collapse are described in animal studies at plasma concentrations of 9.4 μg/ml and higher [23, 24]. However, all these results were described in settings of acute intoxication from unintentional intravascular injections in humans or deliberate high-dose intoxications in animals.

In 1975 Scott had already demonstrated that the threshold of critical intoxication with amide local anesthetics depends on the duration of administration. Administration over a longer period of time leads to tolerance of higher plasma concentrations [25]; this might explain why we did not find any neurological symptoms of intoxication in our patients.

Intraoperatively, levobupivacaine was administered as 0.5% and subsequently 0.375% concentration. Although a significant accumulation of levobupivacaine in patients with major liver resection compared to patients with rectal resection could be detected, the intraoperative concentrations were still far below toxic thresholds. Therefore, we see no reason to recommend a restriction for the intraoperative administration of local anesthetics.

During postoperative epidural analgesia, we found again significantly higher levobupivacaine plasma concentrations in patients following liver resection. Until the third postoperative day, levobupivacaine plasma concentrations increased to a mean concentration of 2.4 ± 1.8 μg/ml. In individual patients, levobupivacaine concentrations exceeded concentrations of 3.0 μg/ml. None of these patients complained about signs of local anesthetic intoxication.

To prevent the risk of local anesthetic intoxication under prolonged continuous epidural analgesia, a reliable surrogate parameter for the prediction of levobupivacaine plasma concentrations would be desirable. Hence, we tested the correlation of three routine laboratory parameters reflecting liver function and the ICG clearance with the maximal levobupivacaine plasma concentrations.

The usefulness of classical parameters of liver function is determined in part by its half-life. Therefore, the correlation of levobupivacaine concentration with cholinesterase activity with a half-life of 7.8–12 days is very poor [26]. Fibrinogen has a shorter half-life, but plasma concentration changes also according to the activation of coagulation following surgery. Therefore, minimal fibrinogen concentrations as well did show a poor correlation with maximal levobupivacaine concentrations.

In contrast, bilirubin concentrations have been described as a predictor of early liver dysfunction [27–29]. Accordingly, the increase in bilirubin concentrations reflects maximal levobupivacaine concentrations with a higher correlation ($R = 0.49$).

Finally, we performed ICG clearance tests. ICG is excreted unmetabolized into the bile. The advantage of this test over most of the classical liver function tests is that it is unaltered by hemodilution and transfusion of blood components.

Starting from the same baseline, patients following liver resection revealed significantly lower results directly after surgery, which remained low for the next 3 days. Following rectal resection, patients show significantly increased results directly after surgery. The low baseline in patients who underwent rectal resections can be explained by the side effect in mechanically ventilated patients, i.e., decreased liver function, which is aggravated by mild volume depletion from overnight fastening [29, 30]. Accordingly, ICG clearance improved significantly in these patients under postoperative spontaneous breathing and normalized volume status.

The fact that all our nonseptic patients with liver resection survived despite a PDR less than 17% in nine of ten patients (3 postoperative days) can be explained by their transient single organ failure compared to septic patients with multiorgan failure. In the group of patients with rectal resection, only one patient developed a decrease in his PDR results below 17%, caused by a transient liver failure in the course of a septic episode. The levobupivacaine plasma concentration of this patient also increased (third postoperative day, 3.74 μg/ml) far beyond the average of the group, 1.33 ± 1.02 μg/ml, which range would have been 1.03 ± 0.43 μg/ml without including this patient. With the idea of an intention to treat, we retained this patient in the analysis of the control group.

Overall, the minimal ICG clearance results correlated best ($R = 0.68$) with the maximal increase of levobupivacaine concentrations. All patients with levobupivacaine concentrations above 2.0 μg/ml developed an ICG clearance less than 17%.

In general, the ICG clearance is a measure of the acute liver function at the respective time and reveals an altered liver function long before the cholinesterase activity has decreased or the bilirubin and levobupivacaine concentrations have increased because of accumulation.

In conclusion, we found that thoracic epidural anesthesia and analgesia, with an equal total dose of levobupivacaine,

led to significantly higher levobupivacaine plasma concentrations in patients following major liver resection compared to control patients. However, concentrations resulting from high-dose intraoperative epidural anesthesia remained far below toxic concentrations, whereas plasma concentrations caused by postoperative epidural analgesia accumulated at the third day in seven patients to concentrations in a range that can be considered as toxic. However, these concentrations are in the low toxic range, far below cardiac toxic concentrations, and none of the patients felt symptoms of levobupivacaine intoxication. Therefore, we see no need to restrict the intraoperative use of local anesthetics. Maximal levobupivacaine concentration correlated best with minimal ICG clearances (PDR $< 16\%$) and second best with maximal bilirubin concentrations (>2.0 mg/dl).

References

1. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183:630–41.
2. van Dam RM, Hendry PO, Coolsen MME, Bemelmans MHA, Lassen K, Revhaug A, Fearon KCH, Garden OJ, Dejong CHC. Initial experience with a multimodal enhanced recovery program in patients undergoing liver resection. Br J Surg. 2008;95:969–75.
3. Rodgers A, Walker N, Schug S, McKlee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomized trials. BMJ. 2000;321:1–12.
4. Foster RH, Markham A. Levobupivacaine—a review of its pharmacology and use as a local anaesthetic. Drugs. 2000; 59:551–79.
5. Mather LE, McCall P, McNicol PL. Bupivacaine enantiomer pharmacokinetics after intercostals neural blockade in liver transplantation patients. Anesth Analg. 1995;80:328–35.
6. Meunier JF, Goujard E, Dubousset AM, Samii K, Mazoit JX. Pharmacokinetics of bupivacaine after continuous epidural infusion in infants with and without biliary atresia. Anesthesiology. 2001;95:87–95.
7. Jokinen MJ, Neuvonen PJ, Lindgren L, Höckerstedt K, Sjövall J, Breuer O, Askemark Y, Ahonen J, Olkkola KT. Pharmacokinetics of ropivacaine in patients with chronic end-stage liver disease. Anesthesiology. 2007;106:43–55.
8. Hofmann D, Thuemer O, Schelenz C, van Hout N, Sakka SG, et al. Increasing cardiac output by fluid loading: effects on indocyanine green plasma disappearance rate and splanchnic microcirculation. Acta Anaesthesiol Scand. 2005;49:1280–6.
9. Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. Intensive Care Med. 2000;26:1553–6.
10. Clavien PA, Petrowsky H, DeOliviera ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. New Engl J Med. 2007;356:1545–59.
11. Oellerich M, Burdelski M, Lautz HU, Rodeck B, Duewel J, Schulz M, Schmidt FW, Brodehl J, Pichelmayr R. Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation. 1991;51:801–6.
12. Groeben H, Schäfer B, Pavlakovic G, Silvanus MT, Peters J. Lung function under high thoracic segmental epidural anesthesia with ropivacaine or bupivacaine in patients with severe obstructive pulmonary disease undergoing breast surgery. Anesthesiology. 2002;96:536–41.
13. Matot I, Scheinin O, Eid A, Jurim O. Epidural anesthesia and analgesia in liver resection. Anesth Analg. 2002;95:1179–81.
14. Nishiyama T, Fujimoto T, Hanaoka K. A comparison of liver function after hepatectomy in cirrhotic patients between sevoflurane and isoflurane in anesthesia with nitrous oxide and epidural block. Anesth Analg. 2004;98:990–3.
15. Cywinski JB, Parker BM, Xu M, Irefin SA. A comparison of postoperative pain control in patients after right lobe donor hepatectomy and major hepatic resection for tumor. Anesth Analg. 2004;99:1747–52.
16. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290:2455–63.
17. Bardsley H, Gristwood R, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46:245–9.
18. Knudsen K, Suurküla B, Blomberg S, Sjövall J, Edvardsson N, et al. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth. 1997;78:507–14.
19. Scott BD, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg. 1989;69:563–9.
20. Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to non-pregnant and pregnant ewes. Anesthesiology. 2001;95:1256–64.
21. McLeod GA, Burke D. Levobupivacaine. Anaesthesia. 2001; 56:331–41.
22. Kopacz DJ, Allen HW. Accidental intravenous levobupivacaine. Anesth Analg. 1999;89:1027–9.
23. Groban L, Deal DD, Vernon JC, James RL, Butterworth J. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. Anesth Analg. 2001;92:37–43.
24. Hicks SD, Salcido DD, Logue ES, Suffoletto BP, Empey PE, Poloyac SM, Miller DR, Callaway CW, Menegazzi JJ. Lipid emulsion combined with epinephrine and vasopressin does not improve survival in a swine model of bupivacaine-induced cardiac arrest. Anesthesiology. 2009;111:138–46.
25. Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. Br J Anaesth. 1975;47:328–31.
26. Gamsjaeger T, Brenner L, Sitzwohl C, Weinstabl C. Half-lives of albumin and cholinesterase in critically ill patients. Clin Chem Lab Med. 2008;46:1140–2.
27. Ostergaard D, Viby-Mogensen, Hanel HK, Skovgaard LT, et al. Half-life of plasma cholinesterase. Acta Anaesthesiol Scand. 1988;32:266–9.
28. Kimura S, Yoshioka T, Shibuya M, Sakano T, Tanaka R, Matsuyama S. Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. Crit Care Med. 2001;29:1159–63.
29. Kredel M, Muellenbach RM, Brock RW, Wilckens HH, Brederlau J, Roewer N, Wunder C. Liver dysfunction after lung recruitment manoeuvres during pressure-controlled ventilation in experimental acute respiratory distress. Crit Care. 2007;11:R13.
30. Krenn CG, Krafft P, Schaefer B, Pokorny H, Schneider B, Pinsky MR, Steltzer H. Effects of positive end-expiratory pressure on hemodynamics and indocyanine green kinetics in patients after orthotopic liver transplantation. Crit Care Med. 2000;28:1760–5.