Comparison of lidocaine metabolism for different anesthesia techniques in rabbits with liver disease

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Objective. This study was designed to investigate the serum lidocaine concentrations (SLC) after local infiltration anesthesia (IA) and mandibular anesthesias (MA) in rabbits with carbon tetrachloride (CCl_4)–induced chronic liver damage (CLD).
Study Design. Fourteen rabbits were administered CCl_4 in group 1, MA (CLD-MA; n = 7); in group 2, IA (CLD-IA; n = 7); in group 3, MA (H-MA; n = 7); and in group 4, IA (H-IA; n = 6) was performed. SLC were measured.
Results. SLC showed difference over time. At the 10th minute, mean SLC in IA groups were higher than in MA groups. At the 120th minute, the highest mean concentration was found in the CLD-IA group.
Conclusions. SLC increases in CLD, and serum lidocaine concentration after IA in the mandibular anterior region is higher than it is after MA. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:e23-e26)

The liver plays a major role in drug metabolism,[1] and patients with liver disease might be expected to have a reduced capacity to metabolize drugs.[2] Consequently, these patients may be more sensitive to the effects, both desired and adverse, of several drugs.[3] In marginal patients with little hepatic functional reserve, anesthetics and surgery can precipitate hepatic decompensation.[4] Dosage adjustment of many drugs in patients with liver dysfunction is therefore essential to avoid excessive accumulation of the drug which may lead to serious adverse reactions.[3]

Local anesthetics are used to produce anesthesia by blocking the conduction of impulses in nerve fibers.[5] Systemic absorption of local anesthetics depends on the pharmacologic structure of the drug, binding to the tissues, the addition of vasoconstrictors, and the vascularization of the injection site.[4] Different blood concentrations occur as a result of local anesthetic injections to different anatomic regions.[6]

Lidocaine is the local anesthetic most widely used for pain control in dental practice.[7] It is an amide-type local anesthetic, and eliminated almost exclusively by hepatic biotransformation.[8] The plasma concentration of lidocaine depends on total dose and rates of systemic absorption and elimination.[9] Earlier studies have shown that the methabolism of lidocaine is altered in patients with liver diseases.[10] Therefore, excessive blood concentrations of the drug can occur owing to accidental intravascular or repeated injections, leading to systemic toxicity.[11]

The present study was designed to investigate the serum lidocaine concentrations after local infiltration anesthesia (IA) and mandibular anesthesia (MA) in rabbits with carbon tetrachloride (CCl_4)–induced chronic liver damage (CLD).

MATERIALS AND METHODS

The study protocol was approved by the Local Animal Ethics Committee of the University of Ondokuz Mayıs, and followed the international legislature on care and use of laboratory animals. Animals were allowed to adapt to the animal care facility for 4 weeks, with access to standard rabbit chow and tap water ad libitum.

Twenty-one male New Zealand rabbits (mean weight 3.05 ± 0.15 kg, 1 year old) were used. The animals were subjected to the following experimental protocol. Fourteen rabbits were administered CCl_4 (Merck, Darm-

Statement of Clinical Relevance

Considering the risk of toxicity, inferior alveolar nerve block may be the choise of anesthetic technique in patients with liver disease.

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stadt, Germany) subcutaneously for 12 weeks. The initial dose of CCl_4 used was 0.5 mL/kg[12] diluted in 1:1 olive:oil suspension twice a week. Because acute intoxication and death occurred, subsequent doses were reduced incrementally to 0.125 mL/kg of CCl_4 once a week. CCl_4-administered rabbits were randomly divided into 2 groups. In group 1, MA (CLD-MA; n = 7) and in group 2, IA (CLD-IA; n = 7) was performed. Seven healthy rabbits served as control groups by repeated use of the animals with 10 days' interval: in group 3, MA (H-MA; n = 7) and in group 4, IA (H-IA; n = 6) was performed. Biochemical parameters, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and total/direct bilirubin, were analyzed during the study (Autolab; AMS, Holland).

IA was administered in the vestibular mucosa adjacent to the mandibular right first incisor, and MA to the right mandible. All animals received 0.4 mL 2% lidocaine HCl (Jetmonal Ampul 5 mL; Adeka, Samsun, Turkey), and blood samples were taken immediately before the injection, at the 10th and 30th minutes, and at the 1st, 2nd, 6th, 8th and 24th hours. Liver samples were taken from the sacrificed animals at the end of the study. Serum lidocaine concentrations were measured by using gas chromatography–mass spectrometry.

One-way analysis of variance (ANOVA) test for variables and Tukey or Duncan tests for multiple comparisons (SPSS for Windows, version 11.0; SPSS, Chicago, IL) were performed. Unless otherwise indicated, the data are expressed as mean ± SD.

RESULTS

Twelve weeks of CCl_4 treatment resulted in chronic (n = 13) and acute (n = 1) liver toxication and fibrosis (n = 14) (Figures 1 and 2). At the end of 12 weeks, mean serum ALT, AST, and GGT values were significantly increased ($P < .05$), whereas serum direct and total bilirubin levels were not statistically different in diseased animals compared with healthy ones ($P > .05$; 1-way ANOVA; Table I).

Serum lidocaine concentrations were detectable only at the 10th, 30th, 60th, and 120th minutes. Serum lidocaine concentration showed differences over time (Figure 3) and the highest concentration was at the 10th minute ($P < .05$; 1-way ANOVA, Duncan).

At the 10th minute, mean serum lidocaine concentration in CLD-IA and H-IA was higher than in CLD-MA and in H-MA. At the 30th and 60th minutes, the highest concentrations were seen in the CLD-IA group, and the lowest concentrations were seen in the H-MA group. At the 120th minute, the highest mean concentration was found in the CLD-IA group, whereas the lowest was found in the H-MA group ($P < .01$; 1-way ANOVA, Duncan; Table 2).

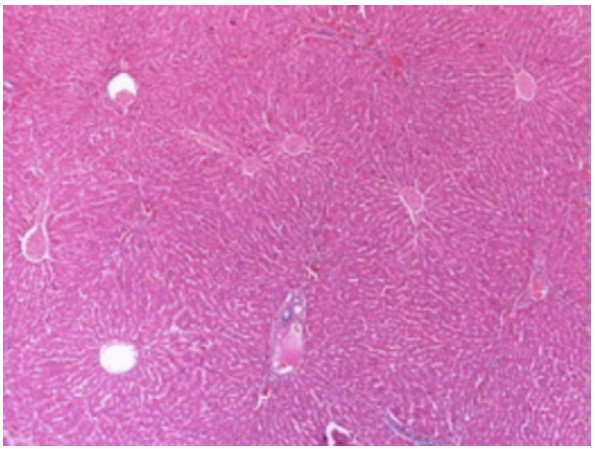

Fig. 1. Normal presentation of hepatocytes in healthy liver tissue. Hematoxylin and eosin stain, original magnification ×50.

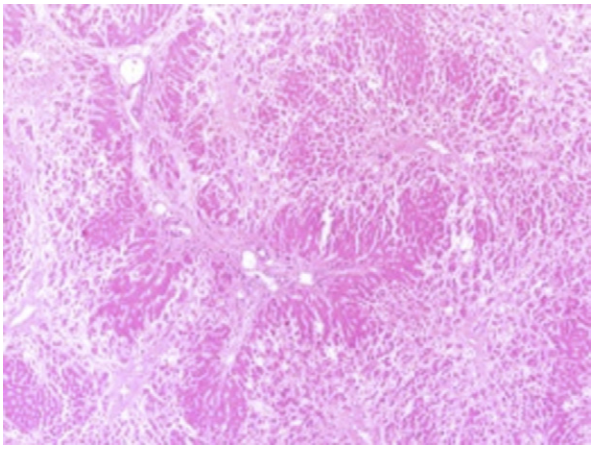

Fig. 2. The pseudolobulus formation and widespread septal fibrosis in the liver tissue treated with CCl_4. Hematoxylin and eosin stain, original magnification ×50.

Table I. Biochemical parameters in healthy (H) and diseased (D) animals at the end of 12th week, mean (SD)

	H	*D*	*P value*
ALT (U/L)	25.57 (2.6)	502.71 (68.70)	.00*
AST (U/L)	48.28 (14.64)	330.78 (38.33)	.00*
GGT (U/L)	11.14 (3.2)	24.57 (3.01)	.01*
Direct bilirubin (mg/dL)	0.13 (0.01)	0.11 (0.02)	.28
Total bilirubin (mg/dL)	0.28 (0.05)	0.31 (0.03)	.62

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CGT*, γ-glutamyl transferase.
*$P < .05$.

DISCUSSION

The liver is the most important organ in which drugs are metabolized.[13] Hepatic disfunction causes an impaired production of albumin, which results in reduced plasma binding of several drugs and thus an increased