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).

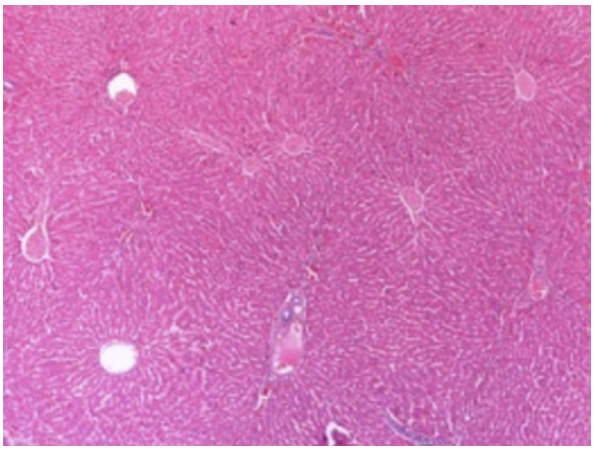

Fig. 1. Normal presentation of hepatocytes in healthy liver tissue. Hematoxylin and eosin stain, original magnification ×50.

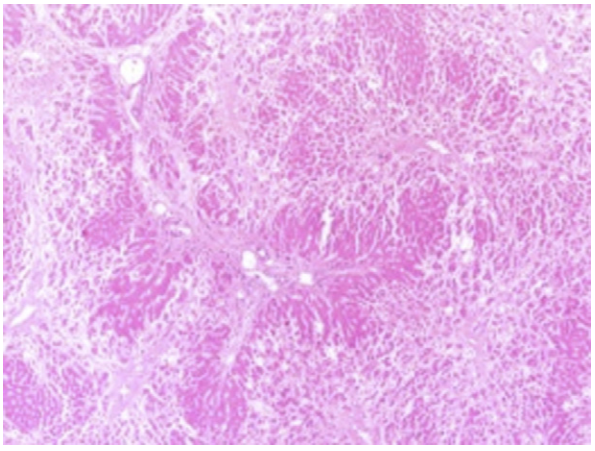

Fig. 2. The pseudolobulus formation and widespread septal fibrosis in the liver tissue treated with CCl_4. Hematoxylin and eosin stain, original magnification ×50.

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

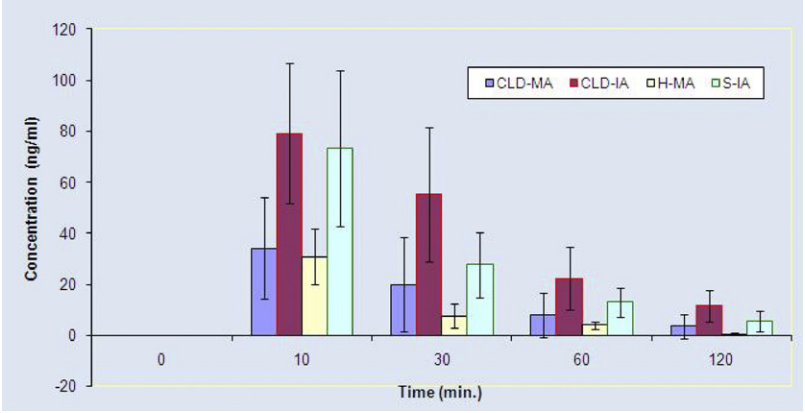

Fig. 3. Serum lidocaine concentration showed difference with time ($P < .05$).

availability of circulating drug pool for tissue uptake and pharmacodynamic effects.[14]

Many methods have been used to produce experimental liver damage in animal models.[15,16] The most common method is CCl_4 administration,[12,17] which leads to liver necrosis and apoptosis, and when administered in repeated doses may produce hepatic fibrosis and cirrhosis.[18] In the present study, 12-week treatment resulted in chronic liver damage with fibrosis in CCl4 of the animals.

Lidocaine metabolism has been shown to be reduced in liver dysfunction in various studies.[19,20] In a clinical study, Thomson et al.[19] has shown that the plasma concentration of lidocaine was increased in 8 patients with chronic hepatic dysfunction compared with healthy individuals. In rats with CCl_4-induced injury, Tanaka et al.[21] have reported that the half-life and total body clearance of lidocaine were significantly reduced. In another experimental study, Saranteas et al.[22] showed increased serum lidocaine levels in rats treated with CCl_4, after injection of lidocaine into masseter muscle. In the present study, lidocaine plasma concentrations were also found to be higher in animals treated with CCl_4, compared with healthy ones. Although maximum concentrations of lidocaine at the 10th minute were not significantly different among the healthy and diseased animals, lidocaine concentrations were higher in CCl_4-treated ones over time. The same maximum concentrations may suggest that chronic liver disease does not or only minimally effects lidocaine absorption.

Systemic toxicity of lidocaine is a function of maximum plasma concentration. Maximum concentration depends on total dosage, systemic absorption, and elimination of the drug.[12] Toxic blood concentrations of lidocaine have been examined previously. Savarese and Covino[12] reported that lidocaine blood concentrations >5 μg/mL may cause toxic reactions. However, in the present study, as a result of administration of lidocaine in very low amounts (in an equivalent dosage with a single lidocaine cartridge), the serum concentrations were much more lower than previously reported toxic blood levels of the drug. Therefore, it is possible that a single dosage of lidocaine can be administered safely to patients with chronic liver disease, using infiltration and mandibular anesthesia techniques. However, elevated serum concentrations may occur due to repeated injections or a single inadvertent intravascular administration. This is especially important in patients with liver disease and concominant cardiac and/or renal failure.[23]

Systemic absorption of local anesthetics depends on the pharmacologic features of the drug, tissue-binding capacity, the use of vasoconstrictors, and the vascularization of the injection site.[4] Absorption is increased when the anesthetic drug is administered into well vascularized tissues.[24] Little is known about the difference in blood concentrations of lidocaine after intraoral injections. In the present study, lidocaine serum concentrations were compared after IA and MA in the oral region to distinct anatomic sites in healthy and CCl_4-treated rabbits. Lido-

Table II. Relationship of serum lidocaine concentrations among the groups (ng/mL), mean (SD)

	10th min	*30th min*	*60th min*	*120th min*
CLD-MA	34.19 (20.03)[a]	20.01 (18.32)[a]	7.96 (8.97)[a]	3.60 (4.69)[ab]
CLD-IA	79.22 (27.65)[b]	55.20 (26.31)[b]	22.36 (12.37)[b]	11.60 (6.09)[c]
H-MA	30.88 (10.80)[a]	7.63 (4.77)[a]	4.00 (1.53)[a]	0.45 (0.45)[a]
H-İA	73.21 (30.49)[b]	27.73 (12.82)[a]	12.93 (5.62)[a]	5.77 (4.02)[b]

CLD, chronic liver damage; *H*, healthy; *MA*, mandibular anesthesia; *IA*, infiltration anesthesia.
[abc]Different letters within each column indicate significant statistical differences among the rates ($P < .01$; 1-way ANOVA, Duncan).

caine serum concentrations were found to be significantly higher after IA than after MA in diseased and healthy animals. This may be attributed to rich vascularization of the mandibular anterior region nourished by submental and inferior labial branches of the facial artery and mental branch of inferior alveolar artery. Besides, mental muscle plays an important role in the absorption of anesthetics in the anterior portion of the mandible. In addition, serum lidocaine concentrations were significantly increased in diseased animals after IA at and after the 30th minute, although they were not significantly different after MA in diseased and healthy animals. One explanation of this finding may be that the absorption is slower in the pterygoid space where the solution is deposited with MA.

Based on these findings in rabbits, it is possible that the risk of toxicity may be higher with repeated injections in the mandibular anterior region in patients with liver disease. Regardless of the local anesthetic technique employed, the clinician must be cautious as to the total dose of local anesthetic used in patients with liver disease.

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