Correlations of Parotid Saliva and Plasma Lidocaine Concentrations in Rats

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Abstract □ The concentration ratios of parotid saliva to plasma lidocaine were determined in rats after a single dose (10 mg of lidocaine/kg) and constant infusion (60 μg of lidocaine/kg/min). Parotid saliva and plasma samples were obtained at 10, 20, and 30 min after single-dose lidocaine administration and at 70, 80, and 90 min after the initiation of a lidocaine infusion. The saliva/plasma concentration ratios for lidocaine after single-dose administration decreased from 1.13 ± 0.03 at 10 min to 0.51 ± 0.06 at 30 min, whereas the ratios determined during the lidocaine infusion remained constant (0.43 ± 0.03, 0.45 ± 0.03, and 0.43 ± 0.04) over the time period tested. The variable saliva/plasma concentration ratios obtained after single-dose administration may be associated with rapid drug distribution between the plasma and peripheral compartments and variation in lidocaine binding to plasma proteins. However, during constant lidocaine infusion, a steady-state concentration was achieved within 70 min, as demonstrated by the constant saliva/plasma concentration ratios.

Keyphrases □ Lidocaine—concentration in parotid saliva and in blood, single dose and continuous infusion, rats □ Anesthetics, local—lidocaine, concentration in parotid saliva and in blood, single dose and continuous infusion, rats □ Saliva—lidocaine concentration after single dose and continuous infusion, compared to serum □ Serum—lidocaine concentration after single dose and continuous infusion, compared to saliva

The secretion of pharmacological agents into saliva has been the subject of several investigations in animals and humans. Drugs such as synthetic opium derivatives (1), barbiturates (2, 3), ethanol (4), and procainamide (5) have been detected and quantitated in saliva. Little or no information is available, however, concerning the salivary excretion patterns of other antiarrhythmic agents including lidocaine. The work presented here reports the detection and quantitation of lidocaine in parotid saliva and plasma samples simultaneously collected from rats. Experiments were divided into two phases: single-dose lidocaine administration and constant lidocaine infusion.

The saliva/plasma lidocaine concentration ratios were calculated in each experiment, and comparisons were made to determine whether parotid salivary secretion of lidocaine directly reflects plasma concentrations.

EXPERIMENTAL

Male Wistar rats, 200–230 g, were surgically prepared for drug administration and parotid saliva collection by a reported method (6). The rats were anesthetized with pentobarbital (50 mg/kg ip), and tracheotomies were performed. With a dissecting microscope, both parotid ducts, the left femoral vein, the femoral artery, and the brachial artery were surgically exposed for cannulation.

The parotid duct was opened by puncturing the duct membrane with the tip of a 23-gauge needle; a polyethylene cannula (~275–0.015 mm i.d. × ~0.600–0.150 mm o.d.) was inserted into the duct. A calibrated collecting cannula (PE 60) was placed over the free end of the parotid cannula for measurement of salivary flow rates. The collecting cannula was interchangeable so that sequential collections could be obtained.

The brachial artery, the femoral artery, and the femoral vein were cannulated with polyethylene tubes (PE 50). The brachial artery was used primarily for the constant pilocarpine infusion (0.06 mg/min), and the femoral vein was available as the administration route for a single bolus dose or constant infusion of lidocaine. The femoral artery was used for blood sample collection.

Saliva samples collected in this manner were transferred to appropriate vessels by flushing the calibrated collecting cannula with a syringe containing distilled water. In the first experiment (single lidocaine dose), pilocarpine (0.2 mg/ml) was infused over 30 min to induce salivary secretion into the brachial artery at a rate of 0.3 ml/min. At the beginning of the pilocarpine infusion, a single lidocaine dose (10 mg/kg) was administered intravenously into the femoral vein. Samples were collected 10, 20, and 30 min after lidocaine administration. Blood was collected simultaneously with saliva collection into heparinized capillary tubes and centrifuged, and the plasma was removed. Saliva was collected into precalibrated capillary tubes and stored for analysis (Fig. 1a).

In the second experiment, lidocaine was infused at a rate of 60 μg/kg/min through the femoral vein. After 1 hr of lidocaine infusion, a pilocarpine infusion (0.2 mg/ml) was started at a rate of 0.3 ml/min. Both the pilocarpine infusion and the lidocaine infusion proceeded coincidentally without interruption for the remaining 30 min of this experi-

Table I—Rat Plasma and Parotid Saliva Concentration Ratios of Lidocaine after a Single Dose and after Constant Infusion

Minutes[a]	Saliva/Plasma Concentration Ratios: Constant Infusion[b]	Saliva/Plasma Concentration Ratios: Single Dose[c]
10 (70)	0.43 ± 0.03	1.13 ± 0.03
20 (80)	0.45 ± 0.03	0.68 ± 0.07
30 (90)	0.43 ± 0.04	0.51 ± 0.06

[a] Time intervals in parentheses refer to the collection periods employed in the constant 90-min lidocaine infusion; $n = 9$. [b] During administration of a constant lidocaine infusion (60 μg/kg/min). [c] After the administration of a single bolus dose of lidocaine (10 mg/kg).

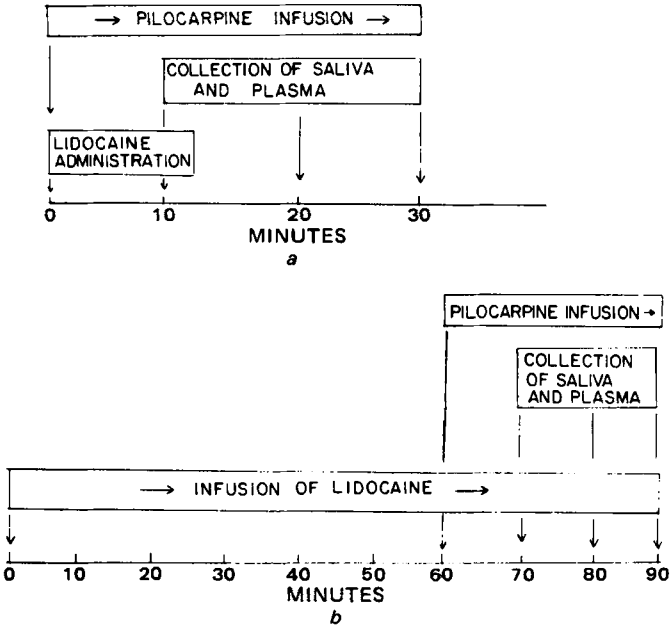

Figure 1—*Experimental approach in determining blood and parotid saliva lidocaine concentrations utilizing single-dose lidocaine administration (10 mg/kg) (a) and constant lidocaine infusion (60 μg/kg/min) (b) in the rat model.*

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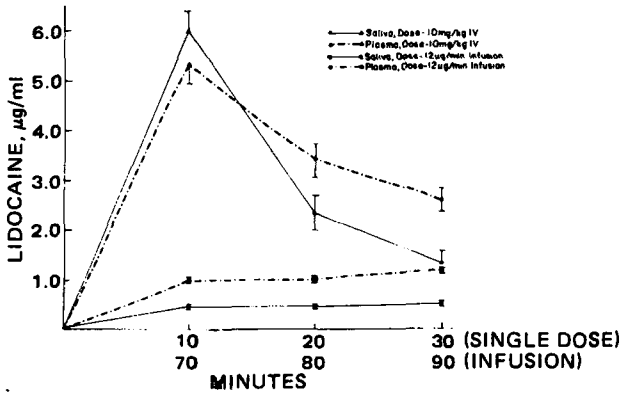

Figure 2—*Mean rat plasma and saliva concentrations (±SEM) of lidocaine. Each concentration is the mean of nine individual rat experiments. Key: ▲, plasma and saliva concentrations after single dose; and ●, plasma and saliva concentrations after constant infusion.*

ment. Total lidocaine infusion did not exceed 2.7 ml over 90 min. Saliva and blood samples were collected at 70, 80, and 90 min after the initiation of lidocaine infusion (Fig. 1*b*).

Lidocaine analysis was accomplished utilizing a commercially available enzyme multiplier immunoassay technique kit[1].

RESULTS AND DISCUSSION

Following a single lidocaine dose (10 mg/kg), the 10-, 20-, and 30-min mean (±*SEM*) plasma concentrations were 5.30 ± 0.42, 3.40 ± 0.35, and 2.57 ± 0.28 μg/ml, respectively (Fig. 2). The corresponding parotid saliva concentrations were 6.00 ± 0.40, 2.30 ± 0.37, and 1.34 ± 0.25 μg/ml. The mean saliva/plasma concentration ratios were 1.13 ± 0.03, 0.68 ± 0.07, and 0.51 ± 0.06 at these three time periods (Table I).

During a constant lidocaine infusion (60 μg/kg/min), the mean (±*SEM*) plasma concentrations obtained at 70, 80, and 90 min were 0.99 ± 0.08, 1.00 ± 0.08, and 1.18 ± 0.15 μg/ml, respectively (Fig. 2). The corresponding parotid saliva concentrations were 0.43 ± 0.03, 0.45 ± 0.03, and 0.51 ± 0.03 μg/ml, respectively. The mean saliva/plasma concentration ratios were 0.43 ± 0.03, 0.45 ± 0.03, and 0.43 ± 0.04 at these times (Table I).

In single-dose lidocaine experiments, the saliva/plasma ratios were not constant over 30 min. At the initial 10-min sample collection, the saliva lidocaine concentration was significantly higher than that in plasma. The saliva lidocaine concentrations fell below the plasma concentrations, however, during subsequent sample collection periods. These results indicate that salivary lidocaine secretion was markedly greater during the first 10 min than at the later two collection periods.

This particular finding is best explained by this drug's rapid distribution and redistribution among various tissues in the body. This hypothesis is supported by distribution studies using ^{14}C-lidocaine (7). Following administration, lidocaine distributed quickly within the first 10 min to the liver, gut, kidney, muscle, and adipose tissue (7). In the first 10 min of the present study, the parotid salivary concentration exceeded plasma levels and then decreased. Because of the dynamic changes occurring during this period, the saliva/plasma concentration ratios were not constant. However, the saliva/plasma concentration ratio at 30 min was 0.51 ± 0.06. Concentration ratios for the single lidocaine dose were not estimated beyond this 30-min period. If samples had been obtained at later times (in the postdistributive phase), the saliva/plasma ratio might have tended to be constant and might have approached values of 0.43–0.45 as occurred during the constant infusion.

During a constant (90-min) lidocaine infusion, the saliva/plasma concentration ratios remained unchanged at 70-, 80-, and 90-min sample collection periods, indicating that a steady state was achieved. The mean saliva/plasma concentration ratio was 0.44. Thus, about 44% of the plasma lidocaine concentration could be found in the parotid saliva at any time during the 30-min sample collection period.

Tucker *et al.* (8) performed *in vitro* studies indicating that lidocaine is protein bound and that the degree of binding to human plasma proteins is dependent on the plasma lidocaine concentration. At a 5-μg/ml plasma concentration, only 45% was present as unbound drug and the remainder was bound to plasma proteins. In the present study during constant lidocaine infusion, a plasma concentration of ~1.0 μg/ml yielded a parotid saliva concentration that corresponded to 44% of the total plasma concentration. If one accepts the premise that the parotid salivary drug concentration reflects the free form of a drug in plasma, then the percentage of lidocaine unbound in rat plasma, at 1 μg/ml of plasma, appears to be about 44%. This value compares favorably with the results of Tucker *et al.* (8) and suggests that saliva reflects the free (nonprotein-bound) drug concentration in the plasma.

[1] EMIT system, Syva Co., Palo Alto, Calif.

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