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Partitioning of intravenous lidocaine into gastric juice

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ABSTRACT Lidocaine concentration in gastric juice and serum, following a single bolus iv injection of lidocaine hydrochloride 1.4 mg · kg^{-1} was examined in 6 healthy male volunteers under basal conditions and / or after pentagastrin secretory stimulation. Lidocaine concentration found in the gastric secretion exceeded by several times that found in serum. The partitioning of iv lidocaine into stomach lumen ranged between 5.2 and 13.0 % of the total lidocaine dose given.

KEY WORDS lidocaine; gastric juice; pentagastrin

Lidocaine hydrochloride is a weak basic compound with the p*K*a value of 7.86[1]. Therefore, due to slightly acidic pH of saliva (pH < 7.0) as compared to plasma, the concentration of lidocaine in saliva was found to be higher than in plasma after iv injection of this drug[2–4]. Taking into account the strong acidic milieu within the stomach, one would expect a washing out of iv lidocaine also into the gastric lumen. The problem raised seems to have a potential clinical relevance because of the widespread use of iv lidocaine in the treatment of cardiac arrhythmias. Thus in order to test the hypothesis mentioned, concentrations of lidocaine in gastric juice and in serum were measured in healthy volunteeres after a single bolus iv injection of this drug.

MATERIALS AND METHODS

The project of this study was reviewed and accepted by the Human Research Ethical Committee of the Silesian School of Medicine. Having given their written informed consent, 6 men volunteered to take part in the examinations. On the basis of history questioning, physical examination, routine laboratory tests, and endoscopy they were all stated to be in good health, and accordingly they did not take any medication. Their mean values of age 23.2 (19–29) yr, body weight 70.5 (60–82) kg, height 178 (170–182) cm, and body mass index 22.2 (18.9–26.6) kg · m^{-2}.

The subjects were examined after an overnight fast at 08:30. A rubber sampling tube was inserted into the stomach and its position was checked by the water recovery technique. The volunteers lay then in the left semilateral position and gastric juice was collected by continuous aspiration. An additional syringe suction and air injection down the tube, if necessary, was performed to ensure constant patency. After removal of the residual secretion from the stomach, the following procedures were performed:

1. Four volunteers were given an iv bolus injection of lidocaine hydrochloride (Xylocaine^{R}, Astra Pharmaceutical Products, Inc) 1.4 mg · kg^{-1} and immediately thereafter samples of basal gastric secretion were obtained for 1 h after the iv (four 15–min collections). Then pentagastrin 6 μg · kg^{-1} was injected sc and 4 subsequent 15–min fractions of the stimulated gastric secretion were collected.

2. In two volunteers an iv bolus injection of lidocaine hydrochloride 1.4 mg · kg^{-1} was given concurrently with the sc injection of pentagstrin 6 μg · kg^{-1} and immediately thereafter samples of stimulated gastric secretion were obtained for 2 h (eight 15–min collections).

The volunteers were asked not to swallow but to expectorate their saliva throughout the examination. Blood samples were obtained from an iv cannula fixed on the subject's other

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arm at 10 and 20 min after the lidocaine injection. The gastric juice samples were centrifuged to remove any debris and their volumes were measured carefully. The gastric acid concentration was determined by titration with NaOH 0.1 mol / L to pH 7.0.

The concentration of lidocaine in serum and gastric juice was measured by gas–liquid chromatography according to the method of Mather-of Tucker[5]. In brief: To a test tube containing a 1 ml sample of serum or gastric juice, 0.5 ml KOH 5 mol / L and 10 μl of an internal standard (a methanol solution of diphenylamine at a concentration of 2 mg • L^{-1}) was addêd and the solution was extracted with 6 ml of diethylether. The phases were separated by centrifugation (2000 rpm for 15 min), the ether layer was removed, evaporated to dryness at 35℃ and resuspended in 50 μl of methanol. Aliquots (3 μl) of the methanol phase were withdrawn with a microliter syringe and injected into the chromatograph. The analytic instrument was a gas chromatograph equipped with a nitrogen–phosphorus detector (Chrom–5, Laboratorni Pristroje Praha, Czechoslovakia) and an electronic integrator (CL–100, Laboratorni Pristroje Praha, Czechoslovakia). A glass column 1.25 m × 2 mm (ID) was packed with 3% OV–17 on 80–100 mesh Chromosorb G (Applied Science Laboratories Inc, USA). The operating temperature were: injector port 250 ℃, detector 250 ℃, column – programme: 180 ℃ for 2 min, then raised at 20 ℃ per min to 230 ℃ for 2 min, and then raised at 20 ℃ per min to 241 ℃ for 10 min. Gas flow rates were: 140 kPa for nitrogen, whereas 35 ml • min^{-1} and 650 ml • min^{-1} for hydrogen and air, respectively. A new column was conditioned for 24 h at 250 ℃ with a carrier flow rate of 140 kPa. Lidocaine concentrations were calculated from previously constructed standard curves based on the area under the peak ratio of lidocaine (pure standard purchased from the Applied Science Laboratories Inc, USA) to internal standard *vs* the known concentration of lidocaine. The intra– and inter–assay variability was found to be 8.6% and 6.4%, respectively.

RESULTS

Immediately after a bolus injection of lidocaine 1.4 mg • kg^{-1} the volunteers usually reported one or more of the following complaints: headache, a feeling of squeezing the head, dizziness, tinnitus, a feeling of tumble. These symptoms disappeared within 3–5 min and the subjects felt well throughout the rest of the examination.

Lidocaine was found in gastric juice at concentrations (Tab 1) that exceeded clearly those that could be expected in serum[6,7] after iv injection of this drug. This presumption

Tab 1. Lidocaine concentrations in gastric juice (mg • L^{-1}) after iv lidocaine–HCl 1.4 mg • kg^{-1} in healthy male volunteers.

Subject	Gastric secretory status*	Timing of gastric juice collection (minutes) 0–15	15–30	30–45	45–60	60–75	75–90	90–105	105–120
A	B+S	96.4	113.2	55.8	37.3	24.9	14.7	13.5	12.6
B	B+S	16.0	47.2	40.7	31.7	20.4	11.2	8.3	8.2
C	B+S	72.0	83.0	59.2	25.0	32.0	17.0	15.0	14.0
D	B+S	75.0	42.8	25.5	13.8	14.6	12.9	7.4	7.2
E	S	77.6	28.6	14.7	11.2	8.7	8.7	8.2	3.7
F	S	121.8	56.6	20.6	15.8	15.0	14.1	19.1	—

* B+S = 1–h basal + 1–h pentagastrin–stimulated gastric secretion.
S = pentagstrin–stimulated gastric secretion was collected 2–h.

was supported by the calculation of the ratios of gastric juice to serum concentrations of lidocaine (Tab 2). Lidocaine partitioning into the gastric secretion ranged between 5.2% and 13.0% of the total dose given iv in healthy men found to be either normo– or hypersecretors of gastric acid (Tab 3.)

Tab 2. Ratios of lidocaine concentration in gastric juice to that in serum after iv lidocaine–HCl 1.4 mg · kg^{-1} in healthy male subjects.

Subject	Gastric secretory status	Ratio[a] at 10 min	Ratio[a] at 20 min
A	basal	68.8	106.8
B	basal	11.1	37.5
C	basal	76.6	87.4
D	basal	42.8	34.9
E	stimulated[b]	47.0	—
F	stimulated	174.0	85.8

a) Ratio = serum lidocaine concentration at 10 min and lidocaine concentration in the gastric juice sample collected 0–15 min, or serum lidocaine concentration at 20 min and lidocaine concentration in gastric juice collected 15–30 min.
b) Gastric acid secretion was stimulated with sc pentagastric 6 μg · kg^{-1}

DISCUSSION

Taking into account the magnitude of the difference in pH between plasma and gastric juice, the finding of high concentrations of a weak base, such as lidocaine, in the gastric secretion after iv injection is not surprising. On the other hand, an active secretion of lidocaine into the stomach lumen can not be excluded as a possible cause for high gastric juice concentrations of this drug. This study used subjects with normal or above normal gastric acid secretion and therefore it does not answer whether lower lidocaine gastric juice concentrations would be expected in patients suffering from achlorhydria or undergoing treatment with potent inhibitors of gastric secretion, such as H_2–receptor antagonists or inhibitors of K^+H^+–ATPase.

Lidocaine partitioning into the gastric juice was assessed to amount between 5.2% and 13.0% of the total lidocaine dose injected iv. This quantity might even be higher because without the use of an exogenous marker infused and sucked from the stomach (eg, [^{14}C] polyethylene glycol) a complete recovery of the gastric secretion could not be ensured.

Available pharmacokinetic data, indicating a rapid absorption from the gut and high metabolic clearance of lidocaine in the liver[6,7] suggest that the fraction of iv injected lidocaine partitioned into the stomach lumen would be lost for its anti–arrhythmic effect. A possibility should also be poited out that a continuous lidocaine infusion may result in considerably higher amounts of lidocaine entering the stomach than estimated in this study on the basis of a single dose injection. Consequently, a considerable rise in plasma

Tab 3. Lidocaine partitioning into the gastric juice after iv lidocaine–HCl 1.4 mg · kg^{-1} as well as gastric acid secretion determined in healthy male volunteers.

Subject	Gastric secretory status[a]	Total lidocaine recovery (mg)	% of the iv dose	Basal acid output (mmol · h^{-1})	Pentagastrin–stimulated acid output (mmol · h^{-1})
A	B+S	6.4	5.7	7.1	21.6
B	B+S	6.4	6.1	2.3	24.7
C	B+S	9.7	9.1	5.2	33.7
D	B+S	5.8	5.2	18.1	58.0
E	S	9.9	11.8	—	29.5
F	S	11.3	13.0	—	25.7

a) Same as in Tab 1.

levels of toxic deethylated lidocaine metabolites is to be expected in such circumstances[6,7].

Summing up, the present study points out a possibility of a leakage of basic drugs into the gastric juice after iv injection. However, in the case of a single bolus iv injection of lidocaine this phenomenon seems not to have a major clinical sequel.

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