Effect of dehydration and hyperosmolal hydration on lignocaine and metabolites disposition in conscious rabbits

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1 The present study aimed to investigate the effect of dehydration and hyperosmolal hydration on the disposition of lignocaine and two of its metabolites, monoethylglycinexylidide (MEGX) and glycine-xylidide (GX).

2 Lignocaine was infused to three groups of conscious rabbits: controls, rabbits previously deprived of water for 48 h and rabbits receiving an infusion of 2.5% NaCl.

3 In dehydrated and hyperosmolal-hydrated rabbits, plasma osmolality was 321 ± 1 and 313 ± 1 mOsm kg⁻¹, respectively ($P < 0.01$ compared to controls, 285 ± 1 mOsm kg⁻¹). In dehydrated animals, baseline values of plasma arginine vasopressin (AVP) concentrations and plasma renin activity (PRA) were higher than in controls, i.e. 12.4 ± 1.4 pg ml⁻¹ and 15.4 ± 1.7 ng AI ml⁻¹ h⁻¹ vs. 3.4 ± 0.2 pg ml⁻¹ ($P < 0.01$), and 5.1 ± 0.6 ng AI ml⁻¹ h⁻¹ ($P < 0.01$), respectively; atrial natriuretic peptide (ANP) decreased from 55 ± 11 to 32 ± 4 pg ml⁻¹ ($P < 0.05$). Compared to controls, hyperosmolal hydration only increased AVP to 15.5 ± 0.7 pg ml⁻¹ ($P < 0.01$).

4 Under both experimental conditions, lignocaine plasma concentrations were almost double ($P < 0.01$) those in controls, due to a lower systemic clearance, e.g. 54 ± 3 and 59 ± 1 vs. 96 ± 5 ml min⁻¹ kg⁻¹, respectively. Plasma levels of MEGX increased ($P < 0.01$) only in dehydrated animals, although GX plasma concentrations were augmented ($P < 0.01$) about three fold in both groups of animals. The changes in lignocaine plasma concentrations were correlated with AVP levels ($R^2 = 0.5168$, $P < 0.001$).

5 To document the effect of AVP on hepatic plasma flow, another group of rabbits received on separate occasions two doses of AVP (17 and 84 ng kg⁻¹) while receiving an infusion of indocyanine green. AVP reduced hepatic plasma flow from 38.9 ± 2.7 ml min⁻¹ to 19.6 ± 2.5 ml min⁻¹ ($P < 0.01$). The predicted maximal AVP-induced decrease in hepatic plasma flow was 19.6 ml min⁻¹ kg⁻¹ ($E_{\max}$), and AVP concentration eliciting 50% of $E_{\max}$ (ED_{50}) was 28.7 pg ml⁻¹.

6 It is concluded that both dehydration and hyperosmolal hydration alter the disposition of lignocaine and two of its metabolites.

Keywords: Lignocaine; kinetics; dehydration; hyperosmolality; arginine vasopressin

Introduction

Lignocaine, diethylglycine 2,6-xylidide, was first used as an antiarrhythmic agent almost three decades ago (Gianelly *et al.*, 1967). Soon after, it was observed that lignocaine pharmacological response was directly related to its plasma concentrations (Harrison *et al.*, 1970), and that lignocaine had a rather narrow therapeutic range (Lie *et al.*, 1974). The disposition of lignocaine is characterized by an extensive extraction by the liver (Stenson *et al.*, 1971). Because of its high rate of hepatic extraction, the clearance of lignocaine is considered blood-flow dependent (Wilkinson & Shand, 1975). Therefore, the rate of elimination of lignocaine should decrease whenever hepatic blood flow is reduced (Zito & Reid, 1978). The reduction of hepatic blood flow with aging (Abernathy & Greenblatt, 1983), and under pathological states such as congestive heart failure (Thompson *et al.*, 1973) and left heart failure secondary to myocardial infarction (Lalka *et al.*, 1980) produce a decrease in lignocaine clearance. Moreover, drugs able to diminish hepatic blood flow, such as propranolol, metoprolol or cimetidine, will decrease lignocaine clearance (Ochs *et al.*, 1980; Feely *et al.*, 1982; Conrad *et al.*, 1983).

Several endogenous substances, such as adrenaline, nor-adrenaline, angiotensin II and arginine vasopressin (AVP) interact closely to modulate peripheral resistances in order to maintain blood pressure (McNeill, 1983). These endogenous substances increase the resistances of the splanchnic vascular bed (Richardson & Withrington, 1981; Khayyal *et al.*, 1985;

Boyle & Segel, 1986). Among these products, AVP is a potent vasoconstrictor of the splanchnic vascular bed (Drapanas *et al.*, 1961), and is able to decrease the perfusion pressure of the liver at concentrations as low as 10^{-13} M (Freedman *et al.*, 1978; Altura & Altura, 1984), as well as gastric perfusion by about 56% (Gaskill *et al.*, 1983). In patients with acute or chronic heart failure of any origin, plasma concentrations of AVP are elevated (Parmley, 1985) and that may contribute to alter the kinetics of blood flow-dependent drugs.

The aims of the present study were to investigate the effect of two experimental conditions, dehydration and hyperosmolal hydration on the disposition of lignocaine and two of its metabolites. Dehydration, due to a reduction in circulating volume and an increase in plasma osmolality, enhances plasma levels of AVP and other vasoconstrictor hormones, and hyperosmolal hydration increases the circulating plasma volume and plasma osmolality, which will stimulate the secretion of AVP.

Methods

Animals

Male New Zealand rabbits, purchased from Ferme Cunicole (Mirabel, Québec, Canada), weighing 2.0 to 3.5 kg were used throughout the study. Each rabbit was installed in an individual cage, fed with Rabbit Show Feed (Purina Inc., Rals-ton) and allowed water *ad libitum*.

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Before the experiment, the rabbits were weighed and a catheter was introduced into the vesical bladder (Foley Bard No. 8-10, Laboratories Bard, Mississauga, Ontario, Canada). The animals were installed in individual restraining cages (Plas-Labs, Lansing, Michigan, U.S.A.) and a catheter (Butterfly-21, Abbott Laboratories, Ireland) was placed into the central artery of the ear for blood sampling. Another catheter (PE50, Becton Dickinson, Rutherford, NJ, U.S.A.) was introduced into the lateral vein of an ear to infuse a solution of sodium chloride 0.9% and dextrose 5% (50:50) to replace fluid loss through the lungs and urine. The rate of infusion varied between 5 and 15 ml h⁻¹ depending upon the experiment; the infusion was carried out with an infusion pump (Sage Instruments, model No. 355, Orion Research Inc., Cambridge, MA, U.S.A.). Each animal was weighed again at the end of the experiment. Once the rabbits had been prepared and installed in the restraining cages and before any experiment was started, they were left for 1 h in the cages to allow an optimum stabilization.

Experimental protocol

To document the kinetics of lignocaine and the effect of an infusion of lignocaine on baseline conditions (control experiment), six rabbits received lignocaine at the rate of 130 µg min⁻¹ kg⁻¹ given in a sodium chloride 0.9%:dextrose 5% solution (15 ml h⁻¹) for 360 min. Previous studies have demonstrated that at this rate of infusion and for 360 min, steady state was reached at the predicted levels, confirming that lignocaine kinetics were first order (Marleau *et al.*, 1987; Gariépy *et al.*, 1992). To assay AVP and atrial natriuretic peptide (ANP) plasma concentrations, as well as plasma renin activity (PRA), blood samples (5 ml) were drawn at 60 and 0 min before the infusion of lignocaine and at 300, 330 and 360 min during the infusion of lignocaine. To assay lignocaine and its two metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX), blood was drawn (1 ml) at 240, 270, 300, 330 and 360 min; in addition, in these samples, sodium and potassium plasma concentrations as well as plasma osmolality were measured.

To assess the influence of dehydration-induced increase in AVP on lignocaine disposition, a group of six rabbits was kept for 48 h without water but allowed to eat. Preliminary studies demonstrated that this protocol significantly enhanced plasma osmolality and AVP concentrations. Lignocaine was infused at the rate of 130 µg min⁻¹ kg⁻¹ for 360 min. The experimental protocol was similar to the one described for the control experiment, with the exception that the rabbits received an infusion of sodium chloride 0.9% at a rate of 5 ml h⁻¹, to compensate only for the volume of blood samples drawn.

Another group of six rabbits, instead of sodium chloride 0.9%:dextrose 5%, received an infusion of sodium chloride 2.5%, 15 ml h⁻¹ for 360 min. Lignocaine (130 µg min⁻¹ kg⁻¹) was infused with the hyperosmolar solution, and blood sampling was carried out as described earlier.

In all experiments, the rabbits' bladder was emptied and thereafter, urine was collected from -60 to 0, 0 to 120, 120 to 240, and 240 to 360 min to measure urinary osmolality. Prostaglandin E₂ (PGE₂) was assayed in urine collected from -60 to 0, pooled urine from 0 to 240 min and from 240 to 360 min.

In a final experiment, to assess the effect of increasing plasma concentrations of AVP on hepatic plasma flow, six rabbits were given intravenously 17 and 84 ng kg⁻¹ of AVP, at least at one week interval, in order to generate AVP plasma concentrations ranging between 3 and 350 pg ml⁻¹. Hepatic plasma flow was estimated by infusing indocyanine green (ICG) at a rate of 248.5 µg min⁻¹ kg⁻¹ for 30 min. AVP was given as an intravenous bolus 10 min after the initiation of the infusion, when ICG steady state was reached (Marleau *et al.*, 1987). Blood samples were drawn (3 ml) prior (time 0) and 10, 12, 16, 20 and 25 min after the

beginning of ICG infusion, to assay AVP and ICG serum concentrations.

Analytical methods

Plasma lignocaine and metabolites, as well as serum ICG, were assayed by high performance liquid chromatography (h.p.l.c.) as described by Marleau *et al.* (1987). AVP and ANP plasma concentrations were determined by radioimmunoassay as described by Larose *et al.* (1985b) and Larose *et al.* (1985a), respectively. PRA and PGE₂ were measured using the [¹²⁵I]-Angiotensin I RIA kit (NEA-022, New England Nuclear, Billerica, MA, U.S.A.) and the Prostaglandin E₂ RIA kit (NEA-020, New England Nuclear, Billerica, MA, U.S.A.), respectively. Osmolality in plasma and urine were determined with an automatic osmometer (Osmette A, Precision Systems Inc., Sudbury, MA, U.S.A.). Sodium and potassium in plasma and urine were assayed with an automatic flame photometer (Model 11943, Instrumentation Laboratory Inc., Lexington, MA, U.S.A.).

Drugs used

Lignocaine, monoethylglycinexylidide (MEGX) and glycinexylidide (GX) were donated by Astra Pharmaceuticals Canada Ltd. Arginine vasopressin (AVP) was purchased from Peninsula Laboratories (Belmont, CA, U.S.A.). Indocyanine green (ICG) was obtained from Aldrich Chemical Company (Milwaukee, Wisconsin, U.S.A.).

Analysis of data

Lignocaine systemic clearance (Cl_{Lig}) and ICG systemic clearance (Cl_{ICG}) were obtained from the ratio of the rate of infusion over the plasma concentration at steady state (Gibaldi & Perrier, 1982). To calculate Cl_{Lig} lignocaine plasma concentration at 360 min was used. Hepatic plasma flow (Q_H) was considered to be equal to ICG systemic clearance (Burczynski *et al.*, 1987; Kanstrup & Winkler, 1987; Shak & Keiding, 1987). Urinary excretion rate of PGE₂ was assessed from the product of PGE₂ urinary concentration times urine volume divided by the interval of urine collection. The predicted maximal reduction in hepatic plasma flow elicited by AVP (E_{max}) and AVP plasma concentration eliciting 50% of E_{max} (ED₅₀) were estimated using the E_{max} model (Holford & Sheiner, 1981).

Statistical tests

In the group of rabbits receiving the infusion of 2.5% NaCl, the studied parameters were always stable after 300 min and for this reason, the mean ± s.e.mean values represent the arithmetic mean of the values measured at 300, 330 and 360 min. The effect of dehydration and of hyperosmolar hydration on lignocaine disposition was assessed by a one way analysis of variance for parallel groups and Dunnett's tables were used to determine the *P* value (Winer, 1971). The minimal level of statistical significance was established at *P* = 0.05. All results are presented as mean ± standard error of the mean (s.e.mean).

Results

In control rabbits receiving only the infusion of lignocaine, plasma osmolality remained stable all through the study (Table 1). In the group of rabbits subjected to water deprivation for 48 h, plasma osmolality values were significantly higher than those in control animals. The infusion of 2.5% NaCl increased plasma osmolality gradually, to reach values of 296 ± 2 mOsm kg⁻¹ at 240 min, and higher than 300 mOsm kg⁻¹ after 270 min of infusion of NaCl 2.5% (Table 1). Compared to the control group, mean values of urine

Table 1 Plasma and urine osmolalities in control rabbits, rabbits deprived of water for 48 h and rabbits infused an hyperosmolar solution (NaCl 2.5%)

Time (min)	0 min	Plasma osmolality (mOsm kg ⁻¹)		
		270 min	330 min	360 min
Controls	283 ± 2	287 ± 2	287 ± 2	286 ± 1
Dehydrated	318 ± 4*	321 ± 1*	320 ± 1*	324 ± 2*
Hyperosmolar hydration	285 ± 3	313 ± 2†	312 ± 2†	313 ± 2†
Interval of urine collection (min)	-60 to 0 min	Urine Osmolality (mOsm kg ⁻¹)		
		0 to 120 min	120 to 240 min	240 to 360 min
Controls	778 ± 96	926 ± 68	759 ± 78	511 ± 122
Dehydrated	1667 ± 109*	1386 ± 99*	1128 ± 136*	1217 ± 148*
Hyperosmolar hydration	887 ± 102	1061 ± 155	1233 ± 155*	1093 ± 114*

Values are mean ± s.e.mean; **P* < 0.01 compared to values in control rabbits; †*P* < 0.01 compared to values at time 0 min and to values of control rabbits.

osmolality were higher in both dehydrated rabbits and hyperosmolar-hydrated rabbits (Table 1). Sodium plasma concentrations in dehydrated and hyperosmolar-hydrated rabbits were greater than those in control rabbits, i.e. 165.3 ± 1.4 and 322.0 ± 24.4 mmol l⁻¹ versus 137.4 ± 0.4 mmol l⁻¹ (*P* < 0.01), respectively.

In control rabbits, plasma concentrations of AVP ranged between 0.7 and 6.3 pg ml⁻¹ (3.4 ± 0.2 pg ml⁻¹), and remained constant throughout the experiment. In dehydrated rabbits, AVP plasma concentrations were always significantly higher than those in control animals, and in hyperosmolar-hydrated rabbits, AVP plasma concentrations increased progressively to remain stable at 300 min (Figure 1). Baseline values of PRA (-60 min) were similar in all three groups of rabbits, but in dehydrated rabbits mean PRA values increased until the end of the experiment (Figure 1). Hydration with a hyperosmolar solution tended (*P* > 0.05) to lower PRA values at 330 min. In dehydrated rabbits, at 330 min, plasma concentrations of ANP were lower than in the control group (Figure 1). Hydration with the hyperosmolar solution did not affect ANP plasma concentrations. Urinary excretion rate of PGE₂ was highly variable, and no differences in the baseline values were detected between the groups (urine collected from -60 to 0 min) (Table 2). In the control group, urinary excretion of PGE₂ increased with the infusion of lignocaine (urine collected from 0 to 240 min); however, this was not observed in dehydrated or hyperosmolar-hydrated rabbits.

In the three groups of rabbits, lignocaine plasma concentrations had already reached steady state at 240 min. In the control group, lignocaine mean steady state plasma concentrations remained constant at around 1.4 µg ml⁻¹ (Figure 2). Both in dehydrated and in hyperosmolar-hydrated rabbits, average steady state plasma levels of lignocaine were approximately 60% higher than in control animals, i.e. 2.4 and 2.2 µg ml⁻¹ (*P* < 0.01), respectively (Figure 2). The increase in steady state plasma concentrations of lignocaine was secondary to the decrease in the clearance of lignocaine, which, at 360 min, averaged 96 ± 5 ml min⁻¹ kg⁻¹ in control animals, 54 ± 3 ml min⁻¹ kg⁻¹ (*P* < 0.01) in dehydrated rabbits and 59 ± 1 ml min⁻¹ kg⁻¹ (*P* < 0.01) in hyperosmolar-hydrated rabbits.

In control rabbits, MEGX and GX plasma concentrations reached steady state at around 300 min (Figure 2), attaining an average level of 0.22 ± 0.02 and 0.23 ± 0.01 µg ml⁻¹, respectively. Plasma levels of MEGX were increased in dehydrated rabbits by approximately 300% but were not affected in hyperosmolar-hydrated rabbits. On the other hand, both experimental conditions increased plasma levels of GX (Figure 2).

ICG systemic clearance was assumed to reflect hepatic plasma flow based on two facts: (1) the ratio of ICG infusion rate to ICG steady state serum concentration yields

Figure 1 Changes in mean arginine vasopressin (a), plasma renin activity (b), and natriuretic atrial peptide (c), plasma concentrations as a function of time in control rabbits (●), animals deprived of water for 48 h (▲) and rabbits receiving an infusion of 2.5% NaCl solution (■). Mean values ± s.e.mean. **P* < 0.01.

a value of ICG clearance that is 7.4% of the value of hepatic plasma flow assessed by the transhepatic extraction ratio method (Pollack *et al.*, 1990), and (2) in the rabbit, ICG clearance values derived at steady state generate values of hepatic plasma flow that are similar to the values estimated using labelled microspheres (Neutze *et al.*, 1968). Two

Table 2 Urinary rate of excretion of prostaglandin E₂ (ng min⁻¹) in control rabbits, in rabbits deprived of water for 48 h and in rabbits infused an hyperosmolal solution (NaCl 2.5%)

Interval of urine collection (min)	-60 to 0 min	0 to 240 min	240 to 360 min
Controls	0.048 ± 0.017	0.179 ± 0.013*	0.160 ± 0.054
Dehydrated	0.368 ± 0.192	0.101 ± 0.019	0.153 ± 0.052
Hyperosmolal hydration	0.109 ± 0.057	0.220 ± 0.080	0.118 ± 0.0034

Values are mean ± s.e.mean. **P* < 0.05 compared to -60 to 0 min values.

Figure 2 Changes in mean lignocaine (a), monoethylglycinexylidide (MEGX) (b), and glycinexylidide (GX) (c), plasma concentrations as a function of time in control rabbits (●), animals deprived of water for 48 h (▲) and rabbits receiving an infusion of 2.5% NaCl solution (■). Mean values ± s.e.mean. **P* < 0.01.

minutes after the intravenous injection of 17 or 84 ng kg⁻¹ of AVP, plasma peak concentrations of AVP were of the order of 26 ± 2 or 279 ± 22 pg ml⁻¹, which decreased with a half life of approximately 4 min. Baseline hepatic plasma flow was 38.9 ± 2.7 ml min⁻¹ kg⁻¹ and at peak concentrations of AVP (dose 17 ng kg⁻¹), this value decreased to 29.4 ± 2.3 ml min⁻¹ kg⁻¹; however, this difference did not reach statistical significance. After the 84 ng kg⁻¹ dose of AVP, hepatic plasma flow was reduced to 19.6 ± 2.5 ml min⁻¹ kg⁻¹ (*P* < 0.01). When the changes in hepatic plasma flow are represented graphically as a function of AVP plasma concentrations, a hyperbola is apparent (Figure 3), suggesting a direct relationship between changes in hepatic blood flow and

Figure 3 Relationship between the changes in hepatic plasma flow as a function of plasma concentrations of arginine vasopressin (AVP). The relationship is defined by the following equation: $E = E_{\text{bas}} + [E_{\text{max}} \times C_{\text{AVP}} / (E_{\text{max}} + ED_{50})]$, where *E* are the changes in hepatic plasma flow, *E*_{bas} is the baseline value of hepatic plasma flow, *E*_{max} is the predicted maximal effect of AVP on hepatic plasma flow, and *ED*₅₀ is the concentration of AVP eliciting 50% of *E*_{max}, and *C*_{AVP} are plasma concentrations of AVP. *E*_{max} = 19.6 ml min⁻¹ kg⁻¹; *ED*₅₀ = 28.7 pg ml⁻¹.

AVP plasma concentrations. Based on the *E*_{max} model, it was possible to predict the maximal effect of AVP (*E*_{max}) on hepatic plasma flow, i.e. it was reduced to values of 19.6 ml min⁻¹ kg⁻¹. In addition, the concentration of AVP eliciting 50% of *E*_{max} (*ED*₅₀) was 28.7 pg ml⁻¹ (*R* = 0.93 and sum of squared residuals = 33.1).

Discussion

The aim of the present study was to assess the effect of endogenous peptides eliciting a potent constriction of the splanchnic vascular bed, i.e. AVP and angiotensin (McNeill, 1976; Richardson & Withrington, 1981; Schrauwen & Houvenaghel, 1982; Altura & Altura, 1984) on the disposition of lignocaine, a flow-dependent drug. To elevate plasma concentrations of AVP and PRA, plasma osmolality was increased by depriving rabbits of water for 48 h. To increase only AVP, another group of rabbits received by infusion a hyperosmolal solution. In addition to osmolal changes, dehydration should reduce the circulating volume and ANP (Trapani *et al.*, 1988), and conversely, hyperosmolal hydration should increase both of them (Kinsey, 1981; Lang *et al.*, 1985; Yandle *et al.*, 1986). Lignocaine plasma levels were augmented in dehydrated rabbits and in hyperosmolal-hydrated rabbits. MEGX levels were increased only in dehydrated animals, although GX levels were enhanced under both experimental conditions.

In man, lignocaine is dealkylated and hydroxylated to generate MEGX, 3-hydroxy- and N-hydroxy-lignocaine, respectively, dealkylation being the major route of degradation, i.e. around 80% of the dose. Dealkylation occurs at very rapid rates and is responsible for the blood flow-

dependent clearance of lignocaine (Stenson *et al.*, 1971; Wilkinson & Shand, 1975). MEGX is also dealkylated and hydroxylated to produce GX, 3-hydroxy- and N-hydroxy-MEGX; however, the major route of MEGX elimination is hydrolysis, to yield 2,6-xylydine. GX biotransformation includes essentially hydrolysis to yield 2,6-xylydine (Drayer *et al.*, 1983). MEGX clearance may be influenced by changes in hepatic blood flow since its rate of elimination parallels that of lignocaine (Bennett *et al.*, 1982); however, GX clearance is around 165 ml min⁻¹ of which almost half is renal, thus GX metabolic clearance should be minimally affected by changes in blood flow (Strong *et al.*, 1975). In the rabbit, as in other species (Keenaghan & Boyes, 1972), the metabolism of lignocaine yields the same metabolites (Hollunger, 1960). However, the relative importance of each pathway varies; for instance, in man, steady state MEGX and GX concentrations are around 50 and 20% of lignocaine plasma levels (Prescott *et al.*, 1976; Bennett *et al.*, 1982); in the dog, these figures are 20 and 50% (du Souich *et al.*, 1992) and in the rabbit, in the present study, MEGX and GX concentrations were 15 and 17% of lignocaine plasma concentrations.

In control rabbits, lignocaine clearance was 96 ± 5 ml min⁻¹ kg⁻¹. However, since lignocaine binds to erythrocytes (ratio of plasma to erythrocyte concentration 1.66), the value of blood lignocaine clearance is around 40% lower, i.e. 60 ml min⁻¹ kg⁻¹ (Tucker *et al.*, 1970). Hepatic plasma flow estimated in the present and other studies is about 40 ml min⁻¹ kg⁻¹ (Marleau *et al.*, 1987; Gariépy *et al.*, 1992) therefore, hepatic blood flow should be about 67 ml min⁻¹ kg⁻¹ assuming an average haematocrit of 0.4. As a consequence, it is possible to assume that most lignocaine biotransformation could happen in the liver.

In dehydrated rabbits, several factors should contribute to reduce hepatic blood flow, such as reduced circulating volume, increased AVP and angiotensin II plasma levels (Brough *et al.*, 1975; McNeill *et al.*, 1976; Richardson & Withrington, 1981), and elevated plasma levels of catecholamines (Richardson & Withrington, 1977). This reduction in hepatic blood flow may explain in part the increase in lignocaine and MEGX plasma concentrations. To explain the increase in GX plasma levels, assuming MEGX de-ethylation was reduced, we may speculate that dehydration decreased the rate of GX elimination.

In the group of animals receiving the infusion of the hyperosmolar solution, the clearance of lignocaine decreased by 39%, and as discussed earlier, a reduction of this magnitude implies a decrease in its dealkylation. The repercussions of a rise in plasma osmolality of the order of 30 mOsm kg⁻¹ on mesenteric resistance and intrahepatic blood distribution are unknown. It has been reported that moderate increases in plasma osmolality, of the order of 5 mOsm kg⁻¹, enhance hepatic blood flow by about 10% (Levine *et al.*, 1978; Richardson & Withrington, 1980). On the other hand, Ballet *et al.* (1988) reported that increasing concentrations of AVP were able to augment portal resistances even in the presence of enhanced hepatic blood flow. Since in the present study AVP plasma concentrations increased, we may speculate that high AVP plasma concentrations may override the effect of a hyperosmolar-induced increase in liver blood flow. We may postulate that under the present experimental conditions, hepatic plasma flow was

decreased by elevated AVP plasma concentrations and as a consequence, the clearance of lignocaine was diminished. The possibility that AVP decreases lignocaine clearance by reducing splanchnic blood flow is supported by the fact that the changes in lignocaine plasma concentrations were correlated with the changes in AVP ($R^2 = 0.5168$, $P < 0.001$). In hyperosmolar-hydrated rabbits, MEGX plasma levels were not modified. However, since lignocaine clearance was reduced, MEGX formation was probably decreased and therefore, its elimination must also be lessened. To explain the increase in GX concentrations, an increase in MEGX dealkylation cannot be invoked, but rather a decrease in GX elimination.

As discussed earlier, both dehydration and the infusion of a solution of 2.5% NaCl promote multiple homeostatic reactions; since AVP was increased under both experimental conditions, AVP may account, at least in part, for the decrease in MEGX and GX elimination. AVP binds to V₁ and V₂ receptors, the former being on smooth muscle cells, hepatocytes, platelets and kidneys; V₁ receptors are coupled to phospholipase C, responsible for the formation of diacylglycerol and inositol-1,4,5-trisphosphate that will increase intracellular calcium. V₂ receptors are located mainly in the kidneys, where AVP activates adenylate cyclase that will promote the synthesis of adenosine 3':5'-cyclic monophosphate (cyclic AMP) (Hays, 1990). The influence of intracellular increases in diacylglycerol, inositol-1,4,5-trisphosphate or calcium on phase I reactions of biotransformation is unknown. It is possible that stimulation of V₂ receptors may influence the metabolism of lignocaine and its metabolites since it has been shown that cyclic AMP inhibits hepatic phase I reactions (Weiner *et al.*, 1972a,b; Weiner, 1973), and in addition, it appears that the kidneys of rabbits have the ability to metabolize lignocaine (Åkerman *et al.*, 1966). We may speculate that increases in AVP not only reduce splanchnic blood flow, but also decrease the rate of metabolism of selected drugs. Indeed, further studies are needed to verify such a hypothesis.

The observations reported in the current study may be helpful in predicting situations where lignocaine or its metabolites can accumulate and as a consequence, toxicity could be observed. The pathological states where effective plasma volume is reduced, such as patients with left heart failure, hypotension of any cause, congestive heart failure, dehydration and in the elderly, entail an elevation of AVP, angiotensin II and other peptides plasma levels, which can be the cause of accumulation of lignocaine and its metabolites. As a consequence, the risks of toxicity will be augmented. It is interesting to note that Prescott *et al.* (1976) reported that in patients with congestive heart failure, lignocaine plasma concentrations were greatly increased, secondary to a low cardiac output and increased peripheral resistances, but in addition, as observed in the present study, MEGX plasma concentrations were also increased.

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