ACID-BASE BALANCE DISTURBANCES FOLLOWING TOXIC DOSES OF LOCAL ANESTHETICS

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SUMMARY

The effect of equitoxic doses of three carbamate local anesthetics (pentacaine, carbisocaine and heptacaine), and a derivative of lidocaine (trimecaine) on the acid-base balance of blood was studied in conscious rabbits. In addition, changes in arterial blood pH induced by local anesthetics in relation to lipophilicity of the respective drugs were evaluated. All the drugs administered at the dose of half of LD_{50} induced a significant decrease in the arterial blood pH as well as in the plasma bicarbonate level and in the blood base excess. The observed acidosis was compensated within a 60 minute period by hyperventilation. The local anesthetic-induced decrease in the blood pH, expressed as AUC, correlated to some extent with the partition coefficient of these agents. These findings suggest that the acidifying effect of local anesthetics may be dependent on their lipophilicity.

KEY WORDS

local anesthetics, acid base balance, toxic effects, acidosis, lipophilicity

INTRODUCTION

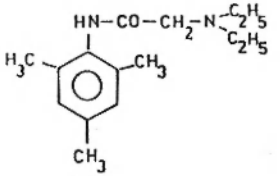
Severe acidosis, hypoxia and hypercapnia occur concomitantly with the convulsions induced by a rapid accidental intravascular injection of a local anesthetic agent in some patients /1/. Animal studies have shown that a decrease in arterial pH and an increase in P_{CO_2} are accompanied by an increase of the CNS toxicity of local anesthetics /2/. Acidosis, hypercapnia and hypoxia decrease the convulsive threshold and increase the cardiodepressant effects of local anesthetics.

Within the past twenty years, carbamate local anesthetics have been extensively studied because of their high local anesthetic potency and low toxicity /3-6/. No data, however, concerning the effect of these agents on the acid-base status of the blood are available. The purpose of the present investigation was to evaluate the toxic effects of three carbamate local anesthetics (pentacaine, carbisocaine, and heptacaine) on the acid-base balance and to compare them with the toxic effects of trimecaine during preclinical studies. In addition, the experiments sought to elucidate whether any relationship exists between the physico-chemical properties of the local anesthetics and their ability to cause acidification of arterial blood.

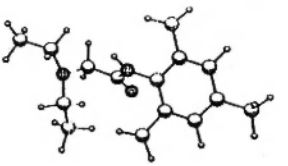
MATERIALS AND METHODS

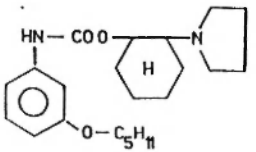
Drugs

Pentacaine (pentacainium chloratum), carbisocaine (carbisocainium chloratum), and heptacaine (heptacainium chloratum) were prepared at the Faculty of Pharmacy, Komensky University, Bratislava, Czechoslovakia. Trimecaine (Mesocain®, Spofa - 1% solution trimecainium chloratum), a derivative of lidocaine, was from Léciva, Praha, Czechoslovakia. Carbamate agents were dissolved in aqua pro inj. (Spofa) to obtain a 1% solution. The chemical structures of the anesthetics tested are shown in Fig. 1.

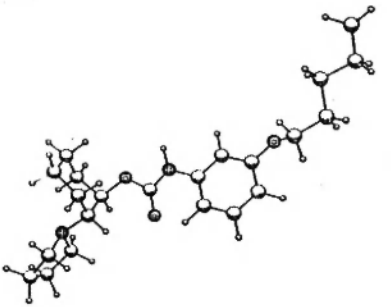


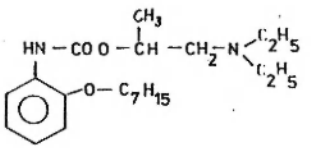
TRIMECAINE



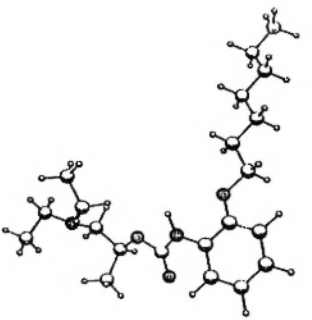


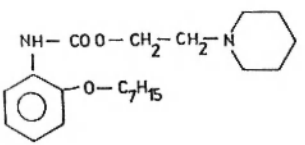
PENTACAINE





CARBISOCAINE





HEPTACAINE

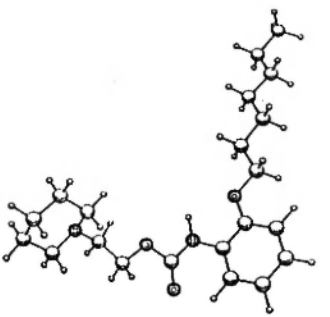


Fig. 1: Chemical formulae and structural models of trimecaine, pentacaine, carbisocaine and heptacaine.

Experimental protocol

Animal experiments complied with the ethical standards for the care and use of laboratory animals. Seventy-two Chinchilla rabbits used in this study (2.3-3.0 kg) were divided into four drug groups, and each group into three dose subgroups, consisting of six animals. All drugs were administered intraperitoneally at three equitoxic sublethal doses (LD_{50}, see Table 4) - 1/2, 1/4 and 1/8 of LD_{50} - to conscious rabbits.

The arterial blood samples for analysis were withdrawn from arteria centralis auricularis into heparinized capillaries (Radiometer) five minutes before and 5, 20, 40, 60 and 120 minutes after the administration of the anesthetic agent.

Analysis and statistics

Arterial blood pH and Pco_2 were measured directly using an acid-base analyzer (PHM, Radiometer). Other acid-base parameters (i.e., plasma actual bicarbonate level and whole blood base excess level) were determined by means of the Siggaard-Andersen alignment nomogram. The decrease of blood pH expressed as AUC was calculated from the time course of blood pH between time zero and 120 minutes using the trapezoidal rule. The changes of arterial pH expressed as AUC were studied in relation to physico-chemical properties (pK_a values and log P') of local anesthetics as well as to the relative local anesthetic potency of these drugs.

The results were statistically evaluated using Student's t-test and linear regressions were determined via least-square analysis.

RESULTS

All the drugs administered at a dose of half LD_{50} induced a significant decrease in the arterial pH as well as in the plasma bicarbonate level and in the blood base excess, five minutes after administration (Table 1). Pco_2 in arterial blood was decreased only slightly, with the exception of the heptacaine-induced decrease. The above-mentioned changes in the acid-base parameters were compensated within a 60 minute period by hyperventilation. Drugs tested at

TABLE 1

Effect of trimecaine (T), pentacaine (P), carbisocaine (C) and heptacaine (H), at a dose of half LD_{50}, on the acid-base status of blood in rabbits (mean±S.D.). *p < 0.05, **p < 0.01 vs. control group

Acid-Base Parameter	Drug	Min Following i.p. Injection					
		0 (Control)	5	20	40	60	120
Arterial pH	T	7.441±0.008	7.420±0.012**	7.427±0.013	7.438±0.012	7.442±0.008	7.444±0.013
	P	7.434±0.015	7.395±0.025**	7.420±0.013	7.425±0.026	7.427±0.032	7.431±0.023
	C	7.431±0.017	7.393±0.014**	7.410±0.018*	7.422±0.017	7.433±0.017	7.435±0.015
	H	7.429±0.054	7.352±0.071*	7.419±0.052	7.409±0.057	7.428±0.024	7.408±0.052
P_{CO_2} (kPa)	T	3.97±0.12	3.88±0.19	3.79±0.17	3.83±0.22	3.75±0.21	3.77±0.22
	P	4.06±0.31	3.77±0.42	3.68±0.37	3.59±0.10	3.61±0.53	3.50±0.31
	C	3.97±0.16	3.77±0.21	3.88±0.21	3.92±0.16	4.01±0.21	4.08±0.16
	H	4.12±0.60	3.51±0.36	3.70±0.36	3.61±0.50	3.57±0.55	3.56±0.48
Plasma HCO_3^- (mmol/l)	T	20.2±0.7	18.8±0.9*	18.6±1.2*	19.4±1.7	19.1±1.6	19.3±1.8
	P	20.3±1.7	17.3±2.3*	17.8±1.3*	18.0±1.9	17.9±2.9	16.6±2.5
	C	19.8±1.5	17.7±0.7*	18.1±1.1	19.9±0.8	19.9±1.1	20.3±1.0
	H	20.2±3.6	14.6±3.0**	17.8±2.9	17.0±3.2	17.5±3.8	16.9±2.9*
Base excess (mmol/l)	T	-2.9±0.7	-4.7±0.9**	-4.5±1.3*	-3.8±1.6	-3.9±1.5	-3.8±1.8
	P	-2.9±1.6	-6.5±2.3*	-5.4±1.3*	-5.5±2.4	-5.3±2.0	-5.7±3.2
	C	-3.5±1.6	-6.6±0.8*	-5.1±1.1	-4.2±0.9	-3.2±1.1	-2.9±0.9
	H	-3.1±3.6	-9.6±3.9*	-5.2±3.3	-6.2±3.7	-5.4±3.7	-6.5±2.2

a dose of one quarter LD_{50} caused similar changes in all the acid-base parameters, but to a lesser extent (Table 2). At the lowest dose (1/8 of LD_{50}) the local anesthetics caused no significant changes in any of the acid-base parameters (Table 3).

The decrease of the arterial pH, expressed as AUC, was dose and drug dependent (Table 4). The anilide anesthetic trimecaine affected the blood pH to a lesser extent that the carbamate anesthetics, pentacaine, carbisocaine and heptacaine. No correlation was found between the local anesthetic-induced decrease of blood pH and pK_a. On the other hand, a correlation was found between induced changes of pH (AUC) and log of the octanol:water partition coefficients (log P') (Fig. 2). In addition, there was a correlation between the index of relative local anesthetic potency and decrease of arterial pH, expressed as AUC. The linear regression equation was as follows: $\log y = 1.71x - 0.70$ and the correlation coefficient, $r = 0.974$ ($p < 0.05$).

DISCUSSION

The observed changes in acid-base parameters indicate a development of metabolic acidosis induced by toxic doses (1/2 and 1/4 of LD_{50}) of local anesthetics. These acid-base disturbances were compensated within a 60 minute time interval by hyperventilation. The above disturbances of the acid-base balance were similar to bupivacaine-induced acidosis reported in patients /1, 7/. Similar results have been found in different experiments in animals as well as *in vitro* /2, 8, 9/.

The local anesthetic-induced decrease of arterial blood pH correlated to some extent with the partition coefficients of these agents (Fig. 2), i.e., local anesthetic-induced acidosis was dependant, to some extent, upon local anesthetic hydrophobicity. Similarly, the decrease of blood pH induced by the local anesthetics under study depended on the relative local anesthetic potency of these drugs (Table 4).

CNS toxicity of local anesthetics depends largely upon their membrane stabilizing effect /11/. Animal studies confirm that the cardiovascular system is considerably more resistant than the CNS to toxicity from all agents in all species tested /11/. However, bupiva-

TABLE 2

Effect of trimecaine (T), pentacaine (P), carbisocaine (C) and heptacaine (H), at a dose of one quarter LD_{50}, on the acid-base status of blood in rabbits (mean±S.D.). *p < 0.05, **p < 0.01 vs. control group

Acid-Base Parameter	Drug	Min Following i.p. Injection					
		0(Control)	5	20	40	60	120
Arterial pH	T	7.441±0.008	7.427±0.012	7.438±0.012	7.442±0.015	7.444±0.013	7.444±0.011
	P	7.441±0.012	7.398±0.028**	7.425±0.015	7.441±0.019	7.443±0.015	7.445±0.010
	C	7.418±0.020	7.415±0.020	7.419±0.013	7.418±0.020	7.419±0.019	7.421±0.020
	H	7.440±0.046	7.366±0.041*	7.415±0.059	7.431±0.059	7.439±0.037	7.442±0.052
P_{CO_2} (kPa)	T	3.99±0.32	3.81±0.26	3.77±0.21	3.88±0.26	3.90±0.21	3.92±0.26
	P	3.97±0.10	3.72±0.26	3.55±0.37*	3.50±0.42*	3.44±0.56	3.46±0.58
	C	3.97±0.11	3.86±0.21	3.77±0.21	3.75±0.11	3.75±0.10	3.99±0.21
	H	4.45±0.47	4.12±0.40	3.99±0.75	4.39±0.38	4.46±0.49	3.97±0.45
Plasma HCO_3^- (mmol/l)	T	20.4±1.7	18.7±1.4	18.9±0.9	19.8±1.3	20.0±1.0	20.1±1.2
	P	20.1±0.6	17.1±1.7**	17.2±1.8**	17.7±2.2**	17.5±3.2	17.7±2.8
	C	19.2±1.1	18.5±1.9	18.2±1.9	17.9±1.1	17.9±1.2	19.4±1.9
	H	22.2±3.6	17.1±1.4**	19.7±4.0	21.7±3.3	21.5±2.3	19.6±1.8
Base excess (mmol/l)	T	-2.8±1.7	-4.4±1.4	-4.1±0.8	-3.3±1.1	-3.0±0.9	-2.9±1.3
	P	-3.0±0.8	-6.3±2.0**	-5.9±1.8**	-5.0±2.2	-5.2±3.2	-5.1±2.8
	C	-4.3±1.5	-4.8±2.0	-5.1±2.0	-5.3±1.3	-5.3±1.3	-4.0±2.1
	H	-1.1±4.0	-6.7±2.3*	-4.2±3.6	-2.8±3.3	-1.6±2.5	-2.9±2.1

TABLE 3

Effect of trimecaine (T), pentacaine (P), carbisocaine (C) and heptacaine (H), at a dose of 1/8 LD_{50}, on the acid-base status of blood in rabbits (mean±S.D.). $^{*}p<0.05$, $^{**}p<0.01$ vs. control group

Acid-Base Parameter	Drug	Min Following i.p. Injection					
		0(Control)	5	20	40	60	120
Arterial pH	T	7.440±0.007	7.438±0.007	7.443±0.012	7.444±0.015	7.441±0.017	7.443±0.013
	P	7.426±0.018	7.425±0.017	7.433±0.016	7.433±0.012	7.437±0.017	7.438±0.011
	C	7.434±0.010	7.437±0.012	7.438±0.010	7.433±0.014	7.436±0.011	7.434±0.012
	H	7.414±0.063	7.424±0.049	7.437±0.017	7.409±0.032	7.414±0.012	7.419±0.017
P_{CO_2} (kPa)	T	3.99±0.32	3.81±0.26	3.77±0.21	3.88±0.26	3.99±0.21	3.92±0.25
	P	3.79±0.37	3.57±0.42	3.44±0.58	3.48±0.63	3.41±0.68	3.53±0.63
	C	4.08±0.21	3.95±0.23	4.10±0.16	4.12±0.21	3.95±0.10	4.03±0.15
	H	4.44±0.47	4.19±0.47	4.77±0.35	5.23±0.38	5.19±0.29	3.90±0.45
Plasma HCO_3^- (mmol/l)	T	20.4±1.7	19.1±1.4	19.2±0.9	19.8±1.3	19.9±0.9	20.1±1.2
	P	18.7±2.5	17.5±2.8	17.1±3.0	17.3±3.3	17.1±3.2	17.8±3.1
	C	20.3±1.1	19.9±1.0	20.7±1.1	20.8±1.0	19.9±0.6	20.7±0.4
	H	21.4±5.8	20.4±5.2	23.7±4.6	24.7±4.0	24.8±3.3	18.8±4.5
Base excess (mmol/l)	T	-2.8±1.6	-3.8±1.3	-3.7±0.8	-3.2±1.1	-3.3±0.9	-3.0±1.3
	P	-4.5±2.7	-5.6±2.9	-5.8±3.0	-5.6±3.3	-5.7±3.2	-5.0±3.0
	C	-2.9±1.1	-3.3±0.9	-2.6±1.0	-2.7±1.0	-3.3±0.6	-2.8±0.7
	H	-2.3±4.8	-3.0±4.6	-0.1±3.8	+0.2±4.1	+0.3±2.6	-4.5±3.7

TABLE 4

Acute toxicity (LD_{50}) in rabbits /10/, pK_a values, relative intradermal local anesthetic potency (RIDLAP), and the acidifying effect of used local anesthetics on arterial blood expressed as $\Delta pH\ [AUC]_0^{120}$

Drug	pK_a	LD_{50}	1/2 LD_{50}	RIDLAP (procaine = 1)	Δblood pH as AUC (pH.min)	
		(mg/kg, i.p.)			1/2 LD_{50}	1/4 LD_{50}
Trimecaine	7.99	95	47.5	3	0.609	0.278
Pentacaine	8.80	47	23.5	76	1.649	0.736
Carbisocaine	8.78	48	24	461	1.975	0.266
Heptacaine	7.60	204	102	171	1.530	1.250

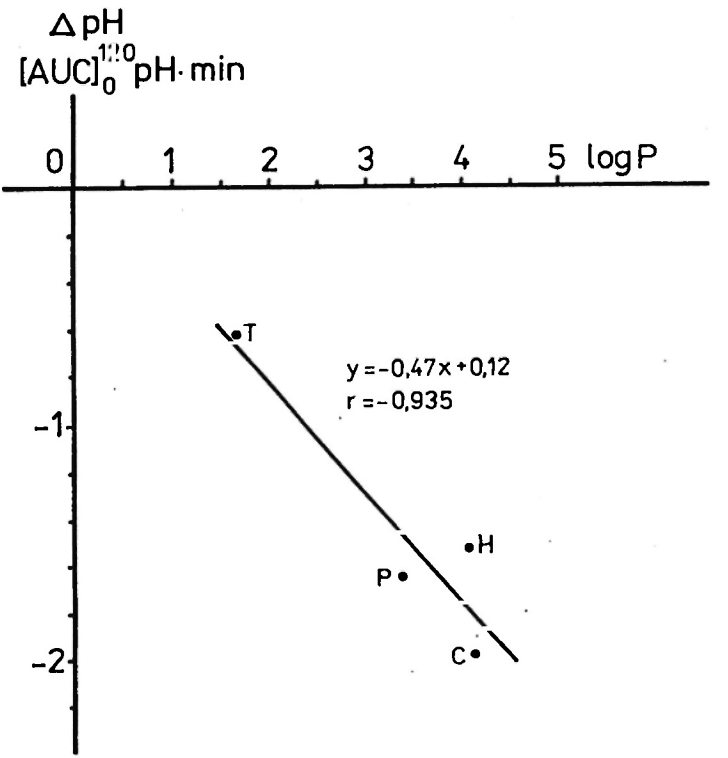


Fig. 2: Relationship between local anesthetic-induced decrease in arterial blood pH, expressed as AUC, and log of the octanol:water partition coefficients (log P') of trimecaine (T), pentacaine (P), carbisocaine (C) and heptacaine (H). All drugs tested were administered at a dose of half the LD_{50}.

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