

# Importance of the Chemistry of Local Anesthetic in Modulation of Cardio-vascular Response

OANA ELENA CIURCANU<sup>1</sup>, OVIDIU STEFANESCU<sup>1</sup>, MONICA MIHAELA SCUTARIU<sup>2\*</sup>, CARMEN GABRIELA STELEA<sup>1</sup>

<sup>1</sup> Gr. T. Popa University of Medicine and Pharmacy Iasi, Dental Medical Faculty, Department of Dento-Alveolar Surgery, Anesthesiology in Dental Medicine, Oral Medicine, 16 Universitatii Str., 700115, Iasi, Romania

<sup>2</sup> Gr. T. Popa University of Medicine and Pharmacy Iasi, Dental Medical Faculty, Department Implantology, Removable Restorations, Technology, Oro-Dental-Diagnosis and Gerontostomatology, 16 Universitatii Str., 700115, Iasi, Romania

*Local anesthetics are chemical substances which depress reversibly, temporary and specifically the sensibility and transmission of nervous impulses of pain. To reach the nervous fiber, the local anesthetic must propagate from the administration point to the area where it will exercise the specific effect. After the deposit, a part of it will bind to nonspecific tissue (conjunctive tissue, fat, muscular fibers), another part is absorbed into the blood and just a small fraction is transported to the nervous tissue. Once it has entered circulation, the local anesthetic binds partially (5 to 95%) to plasma proteins, in particular to acid alpha 1-glycoprotein (and less to albumin) and a part circulates freely. Because alpha 1-glycoprotein transports other drugs: betablockers (propranolol), blockers of calcium ions (verapamil), antiarrhythmics (quinidine), the fraction unbound by local anesthetic in cardiovascular patients will increase in circulation and it can determine serious general accidents of overdose, interpreted as accidents of intolerance, allergic.*

*Keywords: ALR, epinephrine, cardiovascular constants, vasoconstrictor*

Local anesthetics when used in pain management differ from the majority of other medications used in medicine and dentistry in an important manner. Virtually all other drugs, relative to administration rate, must first enter the circulatory system in sufficient concentration (or therapeutic blood level) to begin activity [1]. Local anesthetics cease therapeutic effect when absorbed in circulation, in the injection site. One of the first factors involved in termination of anesthetic activity is the absorption in cardiovascular system. The presence of local anesthetic in the circulatory system means transportation to each cell of the body. Local anesthetics have the potential to influence the functioning of these cells [2]. The variation of the individual response to anesthetic is quite common and is split between "alarm" and normal. The majority of patients respond predictably; some however, without including the mentioned factors, will have specific reactions of different duration to anesthetic response, which is considered normal. All local injectable anesthetics have varied vasodilator effect, from maximum (procaine) to minimum (prilocaine, mepivacaine) [3]. After injection of anesthetic, arterioles and especially capillaries expand, leading to increase of local blood flow, with the following reactions: increase absorption rate of local anesthetic in cardiovascular system (redistribution); increase of local anesthetic concentration in plasma with increased risk of toxicity (overdose); decrease of duration and quality of anesthesia caused by rapid diffusion of anesthetic; increased local bleeding as a result of increased blood flow [4]. In contrast to other drugs which operate after their entrance in circulation, local anesthetics become ineffective as they are absorbed in the blood flow.

The absorption rate of local anesthetics depends on the dose and the pharmacological profile of the administered

drug, the volume of the solution and the presence of vasoconstrictive agent. Therefore, the more quantity of local anesthetic is injected, the higher the blood concentration [5]. For equal quantities of local anesthetic, the more concentrated solutions achieve superior plasma levels, therefore presenting increased toxic risk. After absorption anesthetics are metabolised and subsequently released through the kidneys. The metabolism is performed depending on the chemical structure and the differences in biotransformation of local anesthetics are sometimes clinically relevant [6].

The compounds with ester structure (procaine and articaine) are hydrolysed rapidly by cholinesterase or pseudo-cholinesterase, but also by hepatic esters. This determines short duration of systemic effects and relatively low toxicity. On individuals with genetic defects in activity of pseudo-cholinesterase the usual doses of ester anesthetic produce toxic reactions. The compounds with amide structure (lidocaine, mepivacaine, prilocaine) are metabolised slowly in the liver [7]. The hepatic blood flow influences the rate of metabolism, which explains the toxic risk of amide local anesthetic on hepatic patients. The lipid solubility is the first determiner of anesthetic potential and is expressed through coefficient ratio lipids/water. The protean binding influences the activity rate. The pKa of local anesthetics determines the activity form [8].

The addition of vasoconstrictives, like epinephrine, phenylephrine can prolong the activity duration of local anesthetic, may decrease their absorption (and the level of plasma proteins) and thereby involve the block [9] (table 1).

Lidocaine is the most widely used local anesthetic utilized for the inherent potential, the fast installation effect, tissue diffusion and efficiency. The absorption of lidocaine after subcutaneous infiltration is relatively low. The activity

\* email: monascutaru@yahoo.com

AGENT	Pot.	Onset	pKa	%PB	P. coef
Procaine 0.5-1% (Novocain)	1	Rap	8.9	5.8	0.02
Chloroprocaine 2-3% (Nesacain)	4	Rap	8.7	?	0.14
Tetracaine 0.1-0.5% (Pontocain)	16	Lent	8.5	75.6	4.1
Lidocaine 1-5% (Xylocaine)	1	Rap	7.9	64.3	2.9
Mepivacaine 1.5% (Carbocaine)	1	Mod	7.6	77.5	0.8
Bupivacaine 0.25-0.75% (Marcainesensorcaine)	4	Lent	8.1	95.6	27.5
Etidocaine 0.5-1.5% (Duraneat)	4	Rap	7.7	94	141
Prilocaine	1		7.9	55	0.9
Ropivacaine 0.75% (Naropin)	4	Mod	8.1	94	2.9

**Table 1**  
THE PHYSICO-CHEMICAL PROPERTIES OF  
MAIN LOCAL ANESTHETICS IN USE

duration of subcutaneous administration is 1-3 h. The adding of epinephrine 1:200,000 or 1:100,000 of lidocaine slows vascular absorption and prolongs its effects [10].

Bupivacaine is a lasting local anesthetic of amide type, recommended for peripheral infiltrations, nervous block, spinal and epidural anesthesia. The activity is rapid (1-5 minutes) if utilized for spinal anesthesia, but slower for peripheral nerves block effect. [11] The activity duration is significantly longer than the activity of other local anesthetics. The usual concentration area is 0.125%-0.75%. The major disadvantage of bupivacaine is severe cardiotoxicity which can appear at large plasma levels [12].

Ropivacaine is an amid of lasting local anesthetic type. It is structured and has a pharmacokinetics similar to bupivacaine, although it has better exposure than bupivacaine to cardiotoxicity. The activity duration is between 2.5-5.9 h for epidural block, 8-13 h for peripheral nerves block [13]. It is less soluble in lipids and it is eliminated through the liver faster than bupivacaine. Some studies show lower motor block. Because of this safety profile and a better sensory-motor differentiation ropivacaine is an anesthetic of choice in practice [14].

Levobupivacaine is an amido-amide with local anesthetic effect. Levobupivacaine is the enantiomer S(-) of bupivacaine [15]. Levobupivacaine produces sensory-motor block similar to bupivacaine. The activity is fast spreading for sensory block, intense motor block for lumbar epidural anesthesia, comparable in effect to bupivacaine. Levobupivacaine exposes less to cardiotoxicity than bupivacaine [16].

Mepivacaine is a local anesthetic of amide type with intermediary duration of activity. Mepivacaine is used in infiltrations and transtracheal anesthesia, peripheral anesthesia of sympathetic, regional (Bier block) [17] and epidural nervous block. Compared to lidocaine, mepivacaine produces reduced vasodilation and has a faster installation activity and a longer activity duration. In practice, it is the first local intermediary-anesthetic of activity for peripheral nerve block [18].

### Experimental part

The scope of the study consists in the evaluation of efficiency of proposed anesthetic agents corroborated with the value of the cardiovascular response specific to each patient. Therefore we conducted a study on a representative human sample formed of 228 patients resolved in the Oral and Maxillo-Facial Surgery Clinic Iasi. The anesthetic agents used in our research were:

- UBISTEZIN FORTE 4% - 4% Articaine; with Adrenaline 1/200,000 as vasoconstrictive
- MEPIVASTEZIN 3% - Mepivacaine hydrochloride 30mg, no Adrenaline
- SCANDONEST 3% PLAIN - Mepivacaine hydrochloride 30 mg/ml. Scandonest 3% plain no vasoconstrictives.
- LIDOCAINĂ 2% cu epinephrine 1:100000
- XILINĂ 2% plain

The monitoring of cardiac constants for the objective cardiovascular response of the patient relative to the

anesthetic agent used was obtained with the Patient Monitor Drager device.

### Results and discussions

The benefits of utilizing a vasoconstrictive associated with local anesthetic must be weighed relative to the risk of presence in the circulatory stream. The epinephrine is absorbed from the point of injection as a local anesthetic. The measurable levels of epinephrine in the blood can have a harmful effect on the heart and vessels.

The release of endogenous epinephrine is more harmful than the exogenous one. Recent studies prove that plasma levels of epinephrine equivalent between those who exercise heavy and those who are administered intraoral anesthetic. The intravascular administration of the vasoconstrictive, the administration to sensitives (hyperactives), the apparition of unanticipated interactions can lead to significant clinic manifestations.

The mixture of epinephrine and norepinephrine must be absolutely avoided. Epinephrine still remains the most effective and utilized vasoconstrictive in oral practice.

Analyzing the processing of statistical data after quantization of anesthesia duration depending on the time needed yielded the following results (fig. 1):

- 3 min (44.25%)
- 2 min (24.42%)
- 1 min (17.14%)
- 5 min (14.19%)

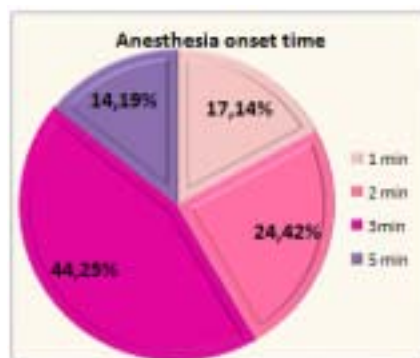


Fig. 1.

Depending on the installation duration of anesthesia of 1 minute the most used were: anesthesia type - Intraosseous anesthesia, anesthetic substance - articaine 4% - epinephrine 1:200000 and the apicectomy treatment (fig. 2)

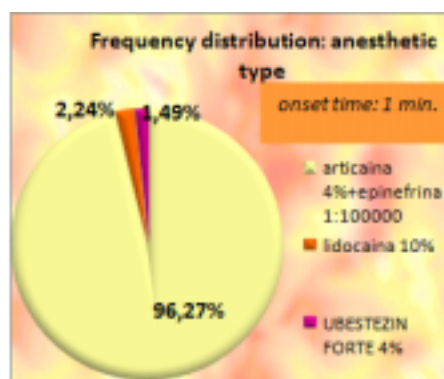


Fig. 2.

Anesthetic Type		Absolute frequency	Frequency percentage	Cumulative percentage frequency
Valid	articaine 4%+epinephrine 1:200000 - 2 min	118	61.8	61.8
	mepivacaine 3% - 2 min	73	38.2	100.0
Total		191	100.0	

Table 2

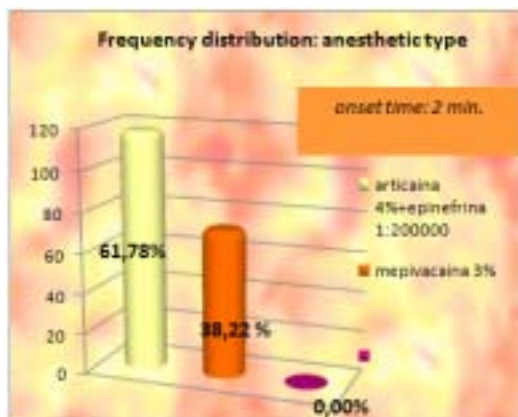


Fig. 3.

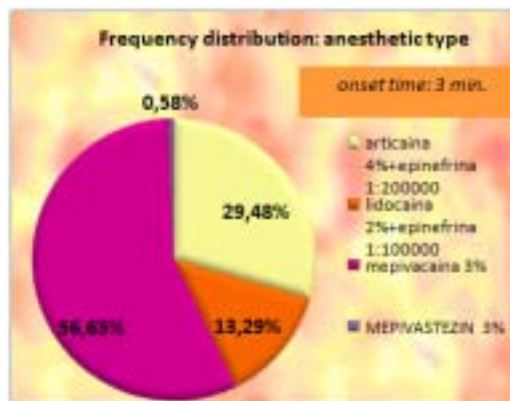


Fig. 4.

Anesthetic Type		Absolute frequency	Frequency percentage	Cumulated frequency percentage
Valid	Articaine 4% + epinephrine 1:200000 - 3 min	102	29.5	29.5
	Lidocaine 2% + epinephrine 1:100000 - 3 min	46	13.3	42.8
	mepivacaine 3% - 3 min	196	56.6	99.4
	MEPIVASTEZIN 3% - 3 min	2	.6	100.0
Total		346	100.0	

Table 3

Analyzing the process of statistical data after anesthetic type depending on the anesthetic duration of 2 min the following results were obtained: articaine 4% - epinephrine 1:200000 were effected most frequently (61.78%), mepivacaine 3% (38.22%).

The frequency of substances used when anesthesia is installed in 2 min has showed us the following results (table 2).

Analyzing the process of statistical data after anesthetic depending on anesthesia duration of 2 min yielded the following results: articaine 4% - epinephrine 1:200000 were administered most frequently (61.78%), mepivacaine 3% (38.22%) (fig. 3).

The frequency of anesthetic substances when installation duration of anesthetic is 3 min (table 3, fig. 4)

Depending on the anesthetic installation duration of 2 min the most utilized were: anesthetic type - intraosseous anesthetic, anesthetic substance - articaine 4% - epinephrine 1:200000 and treatment - apicectomy. Depending on anesthetic installation duration of 3 min the most utilized were: anesthetic type - ATP on Spix spine, anesthetic substance - mepivacaine 3% and treatment - apicectomy.

The anesthetic agents utilized in research were: ubistezin forte 4 - 4% articaine with adrenaline 1/200000 as vasoconstrictive, mepivastezin 3% - mepivacaine hydrochloride 30 mg/mL, scandonest 3% plain does not contain vasoconstrictives, lidocaine 2% with epinephrine 1:100000 and xiline 2% plain. We notice the predominance

of anesthetics without vasoconstrictive, the reason being to reduce at a minimum the cardiotoxicity risks especially associated with the intervention on the apparently healthy patient.

The analysis of data on variable anesthetic agent vs medical emergency installation (altered cardiovascular response) has revealed the following preliminary data:

- ubistezin forte 4% ..... 33 %
- mepivastezin 3% ..... 10 %
- scandonest 3% plain ..... 11 %
- lidocaine 2% with epinephrine 1:100000..... 30%
- xilinã 2% ..... 15% (fig.5)

The quartile range Q25, average and Q75 is represented by different values of cardiovascular emergency incidence, which demonstrates a significant difference between average values, with a significant maximum for ALR index.

The nonparametric Spearman correlation test, based on the analysis of EMERGENCY values variation, verifies if between the average index values corresponding to the studied groups there are significant statistical differences. The statistic value Chi-square ( $\chi^2=21.2$ ,  $\chi^2>12.59$ ) corresponding to ANESTHETIC index (df = 6), as well as the value of the level of significance indicates a significant difference for emergency incidence depending of anesthetic indication (p=0.00167) (table 4).

We can therefore conclude that in the course of dental therapy or dental alveolar surgery, the installation of a cardiovascular emergency is influenced by the anesthetic

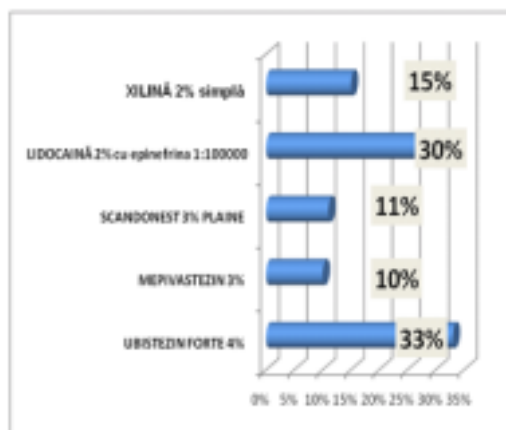


Fig. 5.

agent used, the vasoconstrictive presence being a risk factor.

The anesthetic agent utilized, however actual would be is far from offering protection against the risks associated with the intervention. If the general health of the patient is eluded and also the mental state at the time of the operation, even a complex method and a complete anesthetic do not succeed to eliminate the risk of a unforeseen cardiovascular accident.

### Conclusions

In modern stomatology the adequate control of pain is difficult without the help of vasoconstrictives in anesthetic solution. Only if the general health condition of the patient contraindicates the inclusion of vasoconstrictive or the intervention is brief this vasoconstrictive is discarded. Regardless of the usage it is recommended to avoid accidental intravascular of anesthetic with/without vasoconstrictive through a careful aspiration and slow administration of minimum dilutions. It is mandatory to determine the severity degree of the general disease to choose if the vasoconstrictive must be excluded or included in the anesthetic solution.

### References

1. AGGARWAL V., JAIN A., KABI D., 2009: Anesthetic Efficacy of Supplemental Buccal and Lingual Infiltrations of Articaine and Lidocaine after an Inferior. *Journ. of Endodontics*, 2009, 35(7): 925-929
2. COVINO BG, VASSALLO HG: Local anesthetics: mechanisms of action and clinical use New York, 1976, Grune & Stratton
3. MIZOGAMI M., TSUCHIYA H., Stereospecific interaction of bupivacaine enantiomers with lipid membranes, 2008, *Reg. Anesth. Pain Med.*, 33(4): 304-311

Table 4

Anesthetic agent	vs.	Chi-square $\chi^2$	df	p
EMERGENCY				
M-L Chi-square test		21.22785	df=6	0.00167
Contingency coefficient		0.4028908		
Correlation coefficient Spearman Rank		0.5532772		0.00002

4. AMERICAN SOCIETY OF ANESTHESIOLOGISTS : Manual for anesthesia department organization and management. A.S.A, 2003, Park Ridge, IL
5. JASTAK JT, YAGIELA IJA, Donaldson D: Local anesthesia of the oral cavity, Philadelphia, 1995, WB Saunders.
6. D'ERAMO E.M., BONTEMPI W.J., HOWARD J.B., Anesthesia Morbidity and Mortality Experience Among Massachusetts Oral and Maxillofacial Surgeons, 2008, *Journ. Oral and Maxillofacial Surg.*, 66(12): 2421-2433
7. AXELSSON S., ISACSSON G., The efficacy of ropivacaine as a dental local anaesthetic, 2004, *Swed Dent J.*, 28(2):85-91
8. MALAMED SF., What's new in local anesthesia ?, 2009, *SAAD digest*, 25: 4-14
9. BAUMGAERTEL S., Compound topical anesthetics in orthodontics: Putting the facts into perspective, 2009, *American Journ. of Orthodont. & Dentofacial Orthoped.*, 135(5):556-557
10. \*\*\* Evidence-Based Review of Clinical Studies on Local Anesthetics, 2009, *Journ. of Endodont.*, 35(8) : 1130-1134
11. GOLDBERG S., READER A., DRUM M., Comparison of the Anesthetic Efficacy of the Conventional Inferior Alveolar, Gow-Gates, and Vazirani-Akinosi Techniques, 2008, *Journ. of Endodont.*, 34(11): 1306-1310
12. BRICKHOUSE H., WEBB M.D., Articaine use in children among dental practitioners, *Ped. Dent.*, 2008, 30(6) : 516-521
13. KRASOWSKI M.D., : Using molecular similarity to highlight the challenges of routine immunoassay-based drug of abuse/toxicology screening in emergency medicine, 2009, *BMC Emergency Medicine*, 9: 1-5
14. BUCUR A., VILA C.N., LOWRY J., ACERO J.,: Compendiu de chirurgie oro-maxilo-facială. 2009, Edit. Q Med Publishing, București
15. GRATZ I., DEAL E., LARJANI G.E., 2, Articaine and epinephrine for lower third molar extraction, 2008, *Dental Abstracts*, 53(4): 194-201
16. CAVIEDES-BUCHELI J., The effect of different vasoconstrictors and local anesthetic solutions on substance P expression in human dental pulp, 2009, *Journ. of Endodont.*, 35(5) : 631-633
17. HILA EPSTEIN-BARASH I., KWON A.H., Prolonged duration local anesthesia with minimal toxicity, 2009, *Proceedings of the National Academy of Sciences*
18. COSTA C.G., ROCHA, R.G., Onset and duration periods of articaine and mepivacaine on maxillary infiltration, *Quint. Intern.*, 2005, 36(3) : 197-201

Manuscript received: 9.03.2015