Mepivacaine Hydrochloride - an Efficient Local Anesthetic Solution for the Electroresection of the Benign and Preneoplastic Lesions of the Cervix and Uterus

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We are constantly concerned about improving the diagnostic and treatment conditions we offer to our patients, and starting from the observation that the widespread use of Mepivastesin 30 mg / mL(Mepivacaine Hydrochloride) anesthesia in dental and even buccal- facial interventions has a real success and increased safety profile, inspired and encouraged by its use for the local anesthesia during diagnostic hysteroscopy, we started to use this anesthetic substance in gynecology, for the local anesthesia necessary for the electroresection of the benign and premalignant lesions of the cervix. Thus, data was collected, regarding 527 patients who received such local anesthesia between 2007 and 2017 (10 years) and worked out a study that demonstrated that the method can be used with relief and safety for this type of minimally invasive gynecological interventions.

Keywords: Gynecologic local anesthesia, mepivacaine, electroresection, cervical lesions, diathermic loop

We are constantly concerned about improving the diagnostic and treatment conditions we offer to our patients, and starting from the simple scientific observation that the widespread and safe use of Mepivastesin 30 mg / mL (Mepivacaine Hydrochloride ((±)-N-(2,6-Dimethylphenyl)-1-methylpiperidine-2-carboxamide hydrochloride) - figure 1, 1.7 mL Carpule of 30 mg Mepivacaine Hydrochloride per ml) for dental use provides an effective local anesthetic in dentistry and buccal-maxillo-facial surgery, a clinical observation that can be corroborated with the clinical and scientific reports of the gynecologists who have used this anesthetic locally (or solutions derived from the same anesthetic family) in order to treat cervical or vaginal pain associated with hysteroscopy or other endovaginal and / or endocervical maneuvers [1-6], we decided in 2007 to try using this local anesthetic for the cervical anesthesia required to electroresect the cervical lesions in the private gynecological medical units.

The molecular formula of the mepivacaine is $C_{15}H_{22}N_2O$. HCl, [7]. Its chemical structure is shown in figure 1 [7], figures 2 and 3 representing personal collection.

The product is in the form of a clear and colorless solution for injection, and is a local synthetic anesthetic which is part of the pharmacological group of amides. Its main therapeutic indication is local anesthesia by infiltration and conduction in various treatments and dental surgeries. It is

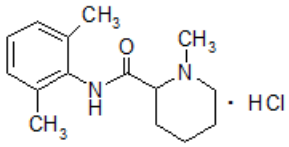

Fig. 1. Mepivacain hydrochloride chemical structure

Fig. 2. The commercial form of the Mepivastesin 30mg/mL in Romania (personal collection of images)

Fig. 3. Mepivastesin 30mg/mL commercial form in Romania (personal collection of images)

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marketed in Romania packed in a box of 50 cartridges, each containing 1.7 mL solution for injection, which must be kept at temperatures below 25°C in the original package. One milliliter of solution for injection contains 30 mg mepivacaine hydrochloride and excipients (sodium chloride, 9% sodium hydroxide and water for injections). The shelf life is 5 years [8].

Among the important clinical data regarding mepivacaine are: the therapeutic indications - local anesthesia (through infiltration and blocking of the nervous tract) in various treatments and dental interventions, the fact that the lowest possible volume of solution leading to an effective anesthesia should be administered, that the solution should be injected slowly at a rate of approximately 1 mL / min (speed not to exceed 0.5 mL / 15 s, i.e. maximum one cartridge per min) and that the recommended maximum dose is 0.1 mL mepivacaine / kg body weight, the mean dose being 0.75 mg / kg body weight. The risk of accumulation of mepivacaine increases in case of reinjection or repeated administration, in case of renal insufficiency and / or hepatic insufficiency. In the elderly, plasma concentrations of mepivacaine may increase due to decreased metabolism and decreased volume of distribution [8].

Among the contraindications of mepivacaine, the following should be noted: hypersensitivity to mepivacaine hydrochloride or to any of the excipients, hypersensitivity to local amide-type anesthetics, severe heart rhythm disorders (grade II, III, severe bradycardia - 45-50 bpm), severe heart failure, severe arterial hypotension, liver porphyria, uncontrolled epilepsy by treatment, children under 4 years or under 20 kg [8].

Among the special warnings and precautions when using mepivacaine, it has been noted that the administration should be avoided in patients who have received anticoagulants, that accidental intravenous (intravascular) injection may cause toxic reactions (e.g. hemorrhagic accidents), the fact that administration should be avoided in areas with infected or inflamed soft tissues, caution should be paid in patients with hepatic impairment, renal failure, angina pectoris, coagulation disorders, hypoxia, hyperkaliemia or acidosis, as well as those with a history of malignant hyperthermia. Also, administration of mepivacaine should be stopped at the first sign of toxicity [8].

A special caution is made by the manufacturer for administration to athletes, to which a positive reaction to anti-doping tests could be expected [8].

Regarding drug interactions and other forms of interaction, particular attention should be paid to concomitant administration of aprindine (class I b antiarrhythmic), as it causes additive toxic effects (due to the related chemical structure of aprindine with local anesthetics) and concomitant administration with central analgesics, chloroform, ether, thiopental (also synergistic toxic effect). Concomitant administration of anti-thrombotic, non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants may increase the hemorrhagic risk of administering mepivastesin (systemically and at the site of injection) [8].

There is insufficient data on the use of mepivacaine in pregnant women, which is why it is recommended that the administration of the anesthetic should be avoided during pregnancy. Caution is advised when administering it to breastfeeding patients because small amounts of mepivacaine (and other amide-based local anesthetics) pass into breast milk [8]. Mepivastesin influences the ability to drive, so the physician should warn the patient to avoid this type of activity for several hours after administration [8].

Of the pharmacodynamic properties of mepivacaine, it should be noted that its anesthetic effect is installed with a latency of 1-3 minutes and lasts for 1.5-3 h, having a median potency. The duration of the pulp (dental) anesthetic effect lasts at least 20-40 min, and soft tissue anesthesia (dental) lasts for 45-90 min. As with most local anesthetics, the anesthetic effect of mepivacaine resides in the fact that it stabilizes the neuronal membrane, increasing the threshold of excitability and thus inhibiting membrane depolarization, preventing the development of propagated action potential, with consequent blocking of the nerve impulse along the neuronal fiber. This type of action is due to diminished neuronal membrane permeability for sodium ions [8].

Regarding the pharmacokinetics of mepivastesin, it should be noted that it is rapidly and almost completely absorbed from the injection site, it binds to 60-78% of plasma proteins, with a half-life of approximately 2 h. The volume of distribution is 84 L and the plasma clearance of 0.78 L / min. It is slowly, but completely, metabolized by hepatic demethylation, the resulting metabolites being excreted by the kidney. It crosses the blood-brain barrier and the feto-placental barrier [8].

Adverse reactions should be considered as dose-dependent and are similar to adverse reactions occurring with all local anesthetics in the amide group: nervous system disorders (rare = 1/1000 - 1/10000) (tremor, nystagmus, headache), gastrointestinal disturbances (rare = 1/1000 - 1/10000), cardiac complications (rare = 1/1000-1/10000- negative inotropic effect, high doses may lead to driving disturbances, bradycardia, dyspnea, ventricular arrhythmias), vascular disorders (rare = 1/1000 - 1/10000) (hypotension, high doses may cause vasodilatation and collapse), respiratory, thoracic and mediastinal disorders (rare = 1/1000 - 10000) (tachypnea followed by apnea), immune system disorders (very rare = below 1/10000) (allergic reactions: rash, pruritus, edema or anaphylactic-type reactions) [8].

Overdosage of mepivacaine may cause central nervous system stimulation, tremor, disorientation, vertigo, increased metabolism and body temperature, and at very high doses, trismus and convulsions. Arrhythmias, hypertension, dyspnea, bronchodilation, nausea, vomiting, bradycardia, vasodilatation may also occur. At the first alarming sign, the administration should be immediately discontinued, the patient placed in a safe position and breathing should be monitored. In case of dyspnea, oxygen or artificial respiration will be administered. If seizures occur, intravenous Diazepam 10-20 mg is administered and barbiturates should be avoided. Symptomatic treatment and maintenance of vital functions represent important steps [8], which is why the presence of an anesthetist in the surgery room is extremely useful.

Based on this information, we decided to introduce into our practice (between 2007 and 2017), as a local anesthetic, mepivacaine hydrochloride (1.7 mL Mepivastesin Carpule) for the cervical anesthesia necessary for the electroresection of all types of preneoplastic cervical lesions (CIN = cervical intraepithelial neoplasia: CIN 1, CIN 2, CIN 3), benign (flat or acuminate condylomas) and even CIS (carcinoma in situ) for biopsy and curative purposes (obviously the curative aim being addressed only to benign cervical lesions and inferior or equal CIN3 premalignant lesions).

Experimental part

Materials and methods

For relatively easy to understand organizational reasons (supply with anesthetic, supply with special syringes for dental use and special atraumatic needles adaptable to the latter), as well as for the particular reasons for requesting and obtaining informed consent of the patients being cared within state hospitals, we preferred to use this type of local anesthesia exclusively within the medical practice of the private obstetrics-gynecology cabinet throughout this period (2007-2017), using a specific informed consent and interrogating all patients in advance whether they had undergone more or less recent local dental anesthesia and if they have had an adverse reaction to it. Obviously, all patients undergoing interventions and anesthesia of this type signed an individual informed consent that respected all the ethical and legal norms in force.

We prevented from using this method and anesthetics (and of course from our study) for all patients who reported adverse (or possible adverse) effects of dental anesthetics in recent or farthest history.

Thus, in the 10 years of the study (July 1, 2007 - June 30, 2017), we performed a total of 527 cervical anesthesia with mepivastesin 30 mg / mL for all electroresections of the cervical lesions (loop electrosurgical excision procedure = LEEP), cases separately described in table 1.

Postoperatively, all anatomical probes were histopathologically diagnosed, and the results of these diagnoses were grouped in table no 1 taking into consideration the most severe injury found. Thus, the co-existence of mixed lesions (CIN 1 + CIN 2 + CIN 3, for example) in the same patient was quantified in the table as the most severe lesion (ie CIN 3 for our example).

We did not include in this study the invasive cervical lesions accidentally diagnosed histopathologically after electroresection, because in most of these lesions the patients received intravenous general anesthesia or analgosedation. Also, the cervical neoplastic invasive lesions biopsied using the gynecological biotomy or by a method other than the electroresection using the diathermic loop (LEEP) have also been excluded from this study.

All patients included in the study were over 18 years of age (18-67 years of age), did not report in the past that they had a personal history of adverse reactions to local pathologically examined, these being, moreover, the criteria for the inclusion in the therapeutic-diagnostic procedure and the study.

All patients who refused or specifically required intravenous analgesia, as well as all patients who reported a history of adverse reactions to the local anesthesia and previous dental anesthesia or who took NSAIDs or anticoagulants in the last 48 h, were excluded from the study (exclusion criteria). There were also excluded from our study and statistics, 4 patients who asked, for various reasons, most often due to anxiety and fear, to convert the type of anesthesia to intravenous analgesia after prior local anesthesia with mepivacaine (before the beginning of the resection itself with the diathermic loop).

Local anesthesia was performed with a 1.7 mL carpule of Mepivastesin 30 mg / mL injected over one minute into four distinct cervix points, in its thickness, at the periphery and at a minimum of 5-6 mm from the lesion area previously demarcated by staining with acetic acid solution (3-5%) and Lugol solution (15%). Then a minute was estimated as the time necessary to install the effect. The gynecological speculum used for the cervical exposure was always a disposable, single use one, made of plastic, and the injection was made at 4 points, approximately equal, corresponding to hours 2, 5, 7 and 10 of a clock dial into the full- thickness of the cervical tissue, at about 0.7-1.0 cm depth, avoiding punction of the well-or atypically vascularized areas or intravascular injection (cervicovaginal vessels).

The injection was made with a special dental syringe (shown in fig. 4) having a twisted atraumatic needle and pre-loaded with a 1.7 mL Mepivastesin carpule (30 mg mepivacaine hydrochloride / mL).

Fig. 4. Special dental syringe with atraumatic needle and *loaded* with a 1.7 mL carpule of Mepivastesin (personal image collection of the authors)

As it can easily be seen in figures 4 and 5, the entire anesthetic device (syringe + atraumatic screwed needle) has a total length of 25 cm before use (5 cm longer than the classic device represented by a 10 mL syringe charged with a 10 mL vial of 1% lignocaine), which gives it a superior net intake and handling in the vaginal canal compared to

Year	Number	Exocervicitis	Condilomas	CIN 1	CIN 2	CIN 3	CIS
2007 (from 01.07.2007)	42	4	3	17	13	3	2
2008	59	3	6	23	21	5	1
2009	64	5	5	31	18	4	1
2010	57	2	4	23	23	5	-
2011	62	3	4	27	22	3	3
2012	55	4	5	25	16	4	1
2013	47	3	3	20	16	4	1
2014	31	2	4	13	10	2	-
2015	45	2	6	18	14	3	2
2016	38	1	3	19	11	3	1
2017 (until 30.06.2017)	27	2	2	13	8	2	-
Total	**527**	**31**	**45**	**229**	**172**	**38**	**12**

Table 1
ANNUAL AND HISTOPATHOLOGICAL DISTRIBUTION OF THE 527 CASES OF CERVICAL CANCER TREATED UNDER LOCAL ANESTHESIA WITH MEPIVASTESIN 30 mg / mL (2007-2017)

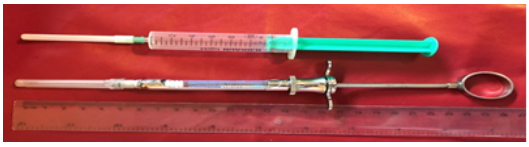

Fig. 5. Comparison between the two types of syringes / devices used in cervical anesthesia (the classic one with a 10 mL syringe loaded with a 10 mL ampoule of lignocaine 1% and the one with dental use, with a flexible screwed atraumatic needle and charged with a carpule of 1.7 mL of Mepivastesin 30 mg / mL) (personal image collection of the authors)

the classical 10 mL syringe.

Electro-resection of the cervical lesions was performed by one or more cups with a special curved or triangular diathermic loop into the *healthy tissue* (with extra-lesional margins of at least 5-7 mm) and was clearly favored by the preliminary marking of the lesional cervical area with acetic acid solution (3-5%) and Lugol solution (15%).

Postoperatively, all patients remained under observation for 60-90 min and did not describe any adverse reactions. Driving was contraindicated for these patients for the next 6 h.

Results and discussions

We did not need and did not use in any of the 527 cases more than one ampoule (reserve / carpule) of Mepivastesin 1.7 mL, so the maximum dose we used was an ampoule. All of the 527 patients included in the study successfully underwent anesthesia and electroresection of the cervical lesions and had no adverse effects, except for 5 cases of bleeding from the injection site of the anesthetic (0.94%) (bleeding which stopped when the resection and haemostasis were completed in the resection bed, that was within a few minutes), one case with a complex reno-genital and vascular malformation [9].

We did not experience any intraoperative or anesthetic accidents and we noticed a very good handling of the dental anesthesia syringe (5 cm longer and much thinner) compared to the syringe we previously used for 1% lignocaine anesthesia (10 mL syringe short and very thick, hard to handle, almost covering the operator's field of view).

We also remarked, in all cases, that a very flexible, extremely fine and long, atraumatic needle (fig. 6) of the special syringe for dental use was very handy. Moreover, due to the extremely small diameter and due to the special flexibility, the moment of injection of the anesthetic and the moment of penetration of the needle into the cervical tissue is much less perceived by the patients than in case of the traditional local anesthesia with lignocaine 1%, that we used to practice before.

Fig. 6. The extremely fine atraumatic needle of the dental anesthesia syringe (the personal collection of images of the authors)

Analyzing the data of the 527 cases included in our multicenter and multi-year study (N = 527), we found that: 31/527 of the patients included in this study (5.88%) were diagnosed histopathologically with erosive chronic exocervicitis (total benign inflammatory lesion), 45/527 patients (8.53%) had maximum lesions histopathologically classified as flat and / or acuminate condilomas (benign lesions due to HPV infections but with malignant potential), 229/527 patients (43.45% many of the group) had histopathologically been diagnosed with CIN 1 lesions (premalignant lesion of low grade), 172/527 patients (32.63%) were diagnosed with CIN 2 lesions (medium grade premalignant lesion), 38/527 patients (7.21%) with CIN 3 lesions (high grade premalignant lesion) and 12/527 patients (2.27%) with in situ carcinoma (CIS = Cervical Cancer Stage 0) .

As mentioned above, the cases diagnosed with invasive cervical neoplasia and those who underwent excision under other forms of anesthesia, than that with mepivacaine, were totally excluded from the study.

In order to assess the effectiveness of local anesthesia and the patients' comfort, we used visual analogue scale for pain [10], verbal pain scale [11] and Lickert scale for comfort and effectiveness of anesthesia. For the visual analogue scale, the patients were asked to rate the discomfort on a 100-mm visual scale.

On the verbal pain scale, the patients were scored as follows:

0 - no pain;
1 - mild pain (recognizable pain, but not discomfort);
2 - moderate pain (bearable discomfort);
3 - severe pain (discomfort difficult to bear);
4 - very severe/unbearable pain.

The Lickert scale for comfort and effectiveness of anesthesia:

1 - most uncomfortable/most ineffective;
2 - moderately uncomfortable/ineffective;
3 - minor discomfort/slightly effective;
4 - monderately comfortable/effective;
5 - very comfortable/effective.

We obtained the following results for our 527 patients: 1.83 on the visual analogue scale, 0.51 on verbal pain scale and the comfort was assessed at 4.56 on Lickert scale. The results are comparable to those cited in literature for lignocaine 2%, which is also an amide [12,-14], that proved that mepivacaine hydrochloride is an effective local anesthetic. The most of the studies for local anesthetics in literature are conducted for dentistry.

Conclusions

Mepivacaine proved thus an efficient anesthetic in curative procedures in gynecology and not only in diagnostic procedures as it was used before, in hysterosalpingography for infertility [15], proving a similar effect with that of lidocaine with epinephrine [16, 17].

Anesthesia with mepivacaine hydrochloride can be considered as particularly effective in this type of minimally invasive gynecological intervention (electroresection with the diathermy loops of the benign and premalignant cervical lesions) and can be practiced under conditions of maximum safety, under the circumstance of strict adherence to the contraindications of this type of anesthesia.

The use of special syringes, needles and special dental carpules adds value to the anesthetic method used and described by us through a special maneuverability of the anesthetic device and by a truly minimal anesthetic trauma to the injected tissues.

We have not experienced adverse effects using the anesthetic method described, except of under 1% of cases of mild hemorrhage at injection site.

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