DIFFERENCES IN LOCAL ANESTHETIC EFFECTS OF OPTICALLY ACTIVE ISOMERS OF LOCAL ANESTHETIC COMPOUNDS

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ABSTRACT
Amino-amide type local anesthetics, which have been most frequently used in clinical anesthesia are lidocaine, prilocaine, bupivacaine, ropivacaine and mepivacaine. These drugs show different clinical properties depending on their structures. In clinical praxis bupivacaine and mepivacaine are used as racemic mixtures. The stereochemistry of these two local anesthetic affects considerably the pharmacological action and toxicity. R(+) bupivacaine is 7 times more potent in blocking the sodium channels than the S(-)-enantiomer. Levobupivacaine and ropivacaine provide nerve blocking characteristics similar to those of racemic bupivacaine in almost all regional anesthesia techniques. The potency of bupivacaine is proportional to the toxic effects on cardiovascular system and central nervous system. Since these local anesthetic compounds are toxic, causing cardiovascular and central-nervous disorders, the therapeutic blood-plasma/serum concentrations should not exceed certain limits.

Introduction
Local anesthetics (LA) are agents which cause local temporary intensitivity with fully preserved consciousness due to reversible paralysis of peripheral sensory nerves. They affect the cellular membrane in which they block the sodium channels and inhibit the creation and transmission of the nervous impulse along the nervous fiber. The application method of local anesthetics and the way of their action depend on their physicochemical properties (stability, solubility, pKa), which are in connection with the protein-binding properties (1, 2, 3).

Although given locally, local anesthetics may exert a systemic effect, as they are transferred through blood to other areas (kidneys, liver). These systemic effects which are dependent on the concentration of local anesthetics in the blood usually cause sedation, nausea, vertigo and anxiety. Local anesthetics are used in surgery, dentistry, ophthalmology and cardio-therapy. They are also used for the temporary relief of pain from insect bites, burns, and other types of surface wounds (4, 5, 6).

Physical and chemical properties of local anesthetics
According to chemical structure, local anesthetics can be: alkaline esters, ethers, ketones, amides and anilides (Table 1). A molecule of a local anesthetic consists of a hydrophilic part which is connected to the lipophilic part via the alkyl interchain and an amide or ester group (Fig. 1) (1, 4, 6).

Physicochemical properties of local anesthetics affect the potency, speed of origination, depth and lasting of local anesthetic action (Table 2). The chemical characteristics of local anesthetics’ molecules affect their clinical characteristics directly. Drugs which contain an ester group metabolize easier and are less toxic (procaine and chloroprocaine) (7). The lipophility determines the relative potency, while binding to blood plasma proteins has an influence on the lasting of the effect. pKa, i.e. pKb values directly correlate with the beginning of the local anesthetic effect. According to abovementioned properties, we can classify the local anesthetics which are used clinically into three groups:
TABLE 1

<table>
<thead>
<tr>
<th>Structures of local anesthetic of alkaline anilides type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lidocaine</strong></td>
</tr>
<tr>
<td><img src="image1" alt="Lidocaine structure" /></td>
</tr>
<tr>
<td><strong>Bupivacaine</strong></td>
</tr>
<tr>
<td><img src="image2" alt="Bupivacaine structure" /></td>
</tr>
<tr>
<td><img src="image3" alt="Bupivacaine structure" /></td>
</tr>
<tr>
<td><strong>Mepivacaine</strong></td>
</tr>
<tr>
<td><img src="image4" alt="Mepivacaine structure" /></td>
</tr>
<tr>
<td><img src="image5" alt="Mepivacaine structure" /></td>
</tr>
</tbody>
</table>

Fig. 1. The schematic review of the structure of the alkaline ester-type local anesthetic

1. moderate-potent anesthetics with short-lasting effects (procaine and chloroprocaine)
2. moderate-potent anesthetics with moderate-lasting effects (lidocaine, carticaine and prilocaine)
3. high-potent anesthetics with long-lasting effects (bupivacaine, ropivacaine, tetracaine and etidocaine) (8, 9).

Absorption and distribution of amide-type local anesthetics depend above all on the degree of binding to plasma proteins, plasma pH and the physical properties of the anesthetic (4).

Amide-type local anesthetics which have been most frequently used in clinical anesthesia are lidocaine, prilocaine, bupivacaine, ropivacaine and mepivacaine. These drugs show different clinical properties depending on their molecular weight (MW) and structures. The anesthetic potency increases in the order of mepivacaine, ropivacaine and bupivacaine with lengthening the alkyl chains. Lidocaine and prilocaine are less potent than bupivacaine. A high percentage of protein-binding as well as high lipid solubility, give bupivacaine a longer effect in comparison to other aminoamide local anesthetics.

Table 1. Both the size of the molecule (bupivacaine – MW 288) and the value of the octanol/water partition coefficient affect the length of the effect (bupivacaine has the highest partition coefficient (~346) while the ropivacaine value is ~115.3 (2, 8) (Table 2). The structure - dependence of pharmacological effects is accounted for not only by
TABLE 2

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Trade name</th>
<th>MW</th>
<th>Partition coefficient octanol/water 25ºC, pH=7.4</th>
<th>Relative lipid solubility</th>
<th>Protein binding (%)</th>
<th>Beginning of effect (min)</th>
<th>Lasting of effect (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Xylocain</td>
<td>234</td>
<td>43</td>
<td>4</td>
<td>64</td>
<td>&lt;2</td>
<td>1-1.5</td>
</tr>
<tr>
<td></td>
<td>Lignocain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duncain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Carbocain</td>
<td>246</td>
<td>−</td>
<td>1</td>
<td>78</td>
<td>3-5</td>
<td>0.75-1.5</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Naropin</td>
<td>274</td>
<td>115</td>
<td>2.8</td>
<td>94</td>
<td>1-30</td>
<td>2-6</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Marcain</td>
<td>288</td>
<td>346</td>
<td>30</td>
<td>96</td>
<td>5</td>
<td>2-4</td>
</tr>
</tbody>
</table>

The feature of local anesthetic of amides type

the selective affinity of drugs to membrane receptors and enzymes but also by the specific hydrophobic interaction of drugs with membrane lipids. The intensity of anesthetic and membrane interaction is usually related to the partitioning of drugs between non-polar (lipid) and polar (aqueous) phase (7, 9).

Alkaline anilide-type local anesthetics are weak bases with pKb values ranging from 5.8 to 6.4, which makes them incompletely ionized at physiological pH values, which is important for their ability to pass through the nerve shell and the membrane of the nerve cell (5). The unionized form of the local anesthetic is insoluble in water, and soluble in ethanol, ether and methylene chloride. Alkaline local anesthetics react with hydrochloric acid and form salts soluble in water. The ionized anesthetic in the form of a hydrochloride is mostly well soluble in water and ethanol, but almost insoluble in ether. With local infections, tissues under inflammations are often acid, which additionally increases the concentration of the ionized form of the local anesthetic (6). That is why the hydrosoluble salt of the local anesthetic dissolves in a sodium-hydrogencarbonate solution, so as to increase the availability of unionized molecules which penetrate through inflammatory tissues faster and lessen the pain through subcutaneous infiltration. For example, 1 ml 8.4% sodium-hydrogencarbonate solution is added to 10 ml 1% lidocaine (1, 7).

Ionized molecules of local anesthetics additionally deionize in contact with blood plasma and under the influence of the physiological pH of the tissue, which causes the releasing of a base which passes lipophilic membranes (5).

Both bupivacaine and mepivacaine have one chiral carbon atom. In clinical praxis they are used as racemic mixtures which contain equal quantities of the R and S-enantiomers. The stereochemistry of these two local anesthetics affects considerably the pharmacological action and toxicity. R (+) bupivacaine is 7 times more potent in blocking the sodium channels than the S (-) enantiomer. The potency of bupivacaine is proportional to the toxic effects on cardiovascular system (CVS) and central nervous system (CNS) [S (-) bupivacaine < racemic bupivacine < R (+) bupivacaine] (10) (Table 3).

The mechanism of action

The mechanism of action of local anesthetics is achieved by a reversible block of the sodium channels in the cellular membrane of the nerve cell and the influx of sodium ions into the cell. The block of sodium channels prevents creation and spreading of the nervous impulse (action potential) (6).

Hydrophilic pathway. Local anesthetics with a tertiary amine group (unionized form) pass through the nerve cell membrane and...
Fig. 2. The schematic review of the mechanism of action of local anesthetics.

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Pharmacological activity of the enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine*</td>
<td>S-enantiomer is less toxic and has a longer-lasting effect than the R-enantiomer</td>
</tr>
<tr>
<td>Bupivacaine*</td>
<td>R(+) enantiomer has a longer-lasting effect and is more toxic on CVS and CNS than the S-enantiomer</td>
</tr>
</tbody>
</table>

*local anesthetics which have one chiral C-atom in their structure

enter the intracellular space of the cell where they react with hydrogen ions, which causes the local anesthetic molecule to ionize (BH⁺). From the intracellular space, the ionized molecule can only move to the open sodium channel and block it i.e. deactivate it (Fig. 2). (6).

**Hydrophobic pathway.** Local anesthetic-blocker (the unionized form) enters the cellular membrane and directly makes its way to the ion channel, which can be open or closed. The molecule-blocker passes through the glycoprotein structure of the ion channel and ionizes (BH⁺) in its interior. The local anesthetic molecule will block an open or closed sodium channel (Fig. 2) (4, 6).

Lidocaine is very often used in treatment of ventricular arrhythmia which is related with an acute myocard ischemia. It is a potential blocker of Na⁺ and K⁺ channels. The openness of these channels is a prerequisite for the mechanism which leads to ischemia (5, 8).

By deactivating the sodium channels, the distribution of sodium ions into the interior of the cell is inhibited. By preventing the influx of sodium ions into the nerve cell the creation of nerve impulses is disabled and thus the feeling of pain is blocked, which represents the major goal of the local anesthetic effect (11, 12).

**Dependence of pharmacological activity on the structure of local anesthetics**

The hydro solubility is conditioned by secondary and tertiary amine groups, which is important for the transport of the drug to the cellular membrane and the receptor (5). The substitution of the hydrophilic amine centre with ethyl-propyl groups increases the activity. The introducing of 1-alkylpiperidine-2-il groups leads to faster beginning of the effect and longer effect than lidocaine. With lengthening the alkyl chains of the piperidine group local anesthetics are several times more efficient, but also the toxicity and unwanted effects increase drastically. Bupivacaine is four times more powerful but also more toxic than mepivacaine, because it has a 1-butylopiiperidine-2-il group, while mepivacaine has a 1-methylpiperidine-2-il group. Ropi-vacaine is slightly weaker in effect than bupivacaine.
because instead of a butyl it has a propyl group in position 1 of the piperidine-2-il remnant. Ropivacaine is less toxic than bupivacaine (6).

Local anesthetics which contain a secondary amine group in their structure are more polar than local anesthetics which have a tertiary amine as a hydrophilic centre. Regarding the polarity of the secondary amine, local anesthetics which contain a secondary amine group will pass harder through lipophilic (hydrophobic) membranes of tissues and nerve cells (4, 6). Nevertheless, it is significantly reduced, because local anesthetics diffuse into other non-specific tissues (adipose, muscular). The substitution of an ethyl group with a propyl group on the hydrophilic centre of lidocaine drastically affects the reduction of polarity of the tertiary amine. Also, an introduction of a methylene group into the middle bridge of lidocaine affects the activity positively. The reduction of polarity of the tertiary amine will affect the increase of relative lipid solubility of etidocaine (35 times higher compared to lidocaine). A considerable increase in the duration of effect of etidocaine compared to lidocaine is conditioned by changes in chemical structure (6, 7).

The lipophilic centre is represented by a carbocyclic or heterocyclic system. Carbocyclic systems include a phenyl group while heterocyclic systems include either thiophene or chinoline (5, 9). The lipophilic center is largely responsible for the solubility of local anesthetics in lipids. The solubility in lipids is very important because it is established that the activity of local anesthetics depends on their ability to pass through cellular membranes of the nerve cell. The best local anesthetic effect is achieved when the lipophilic and the hydrophilic center are in balance. If the lipophilic centre is more dominant in the structure, the local anesthetic effect is reduced because passing through membranes is very weak. On the other hand, if the lipophilic centre dominates, the effect of the local anesthetic will also be weak. In this case, the local anesthetic can pass through membranes of a nerve cell, but the solubility in extra- and intracellular space is low (9, 13).

A dimethyl substitution of the lipophilic-phenyl group in positions 2 and 6 affects the steric protection of the molecule. A sterically protected molecule considerably hinders the degrader – microsomal liver enzymes from approaching. The hardened approach of microsomal enzymes to the anesthetic increases the duration of the effect. Prilocaine is a local anesthetic that has a hydrogen atom instead of a methyl group in the position 2 of the phenyl group. The insufficient steric protection of the prilocaine molecule affects the reduction of the effect duration compared to other local anesthetics – alkaline anilides which are substituted with methyl groups in positions 2 and 6 (12).

The presence of an amide group in the structure affects the higher stability of these local anesthetics compared to local anesthetics which contain an ester in their structure, because the ester is very susceptible to hydrolysis (6).

**Metabolism and toxicity**

Esters (e.g. cocaine, procaine, tetracaine, benzocaine) are metabolized by plasma and liver cholinesterase with the formation of potential allergen para-aminobenzoic acid (PABA). In contrast, amides (e.g. ropivacaine, bupivacaine, mepivacaine, etidocaine and prilocaine) are more slowly metabolized in the liver, under the influence of microsomal enzymes and rarely evoke allergic reactions (6).

The speed of detoxification in the liver depends on the chemical character of the local anesthetic. Some local anesthetics hydrolyze gradually, and the secondary products are secreted by urine. Other agents are partially detoxified, and partially eliminated unchanged through urine. The local anesthetics that are more slowly metabolized and detoxified are more toxic (12).

The most dangerous unwanted toxic effects originate as a result of action on CVS and CNS. Toxic effects of LA’s are manifested through anxiety and convulsions which are accompanied by respiratory depression, hypotension and even stopping of the heartbeat (6). Convulsions usually appear suddenly. They can be stopped by using antiepileptics-sedatives like diazepam or barbiturates (9).

Cardiovascular effects of LA’s are a result of myocardium depression and vasodilatation.
TABLE 4

The recommended doses and clinical use of local anesthetics

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Recommended doses (mg)</th>
<th>Toxic doses (mg/kg)</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>~ 200</td>
<td>6.4</td>
<td>Peripheral nerve block, infiltration, topical, spinal and epidural anesthesia</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>~450</td>
<td>9.8</td>
<td>Epidural anesthesia of peripheral nerve blocks and infiltration anesthesia</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>250</td>
<td></td>
<td>Epidural anesthesia during birth</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>~150</td>
<td>1.6</td>
<td>Peripheral nerve block, infiltration and epidural anesthesia</td>
</tr>
</tbody>
</table>

A combination of these two effects leads to hypotension, which can happen abruptly and be life-threatening (6). Bupivacaine poisoning is manifested through musculature spasms, sleepiness and convulsions (2). The toxic effects of LA’s on CVS and CNS are a consequence of a threshold excess – i.e. an excess of prescribed therapeutic doses (7) (Table 4).

With all LA’s, the relative cardiotoxic potency correlates with relative anesthetic potency. More potent agents (e.g. bupivacaine, levobupivacaine, ropivacaine) produce cardiotoxic effects at lower blood concentrations and doses than less potent LA’s (e.g. lidocaine). Factors that are associated with increased propensity for LA cardiac toxicity include increases in lipid solubility, protein binding, and size of side chain (length and bulkiness). Stereospecificity of LA solution may also change the toxicity profile of an LA. The R (+) enantiomers bind cardiac Na⁺ channels with greater affinity than the S (-) enantiomers. However, S (-) enantiomers have affinity for neuronal Na⁺ channels comparable with R (+) enantiomers (14).

Ropivacaine, lidocaine and bupivacaine are amide-type local anesthetic drugs which contain protonizable tertiary amine functions. Their pKa values are 8.1, 7.7 and 8.1 respectively. Local anesthetic drugs act by blocking both nociceptive and cardiac sodium ion channels and are therefore commonly used for regional anesthesia and antiarrhythmia (12, 14).

The toxic doses of mepivacaine exceed 500 mg. Toxic effects on the embryo have been documented (3). Bupivacaine has a cardiotoxic effect that can be demonstrated after overdosing or after an accidental intravenous application so it is not recommended for intravenous regional anesthesia. The unwanted effects of lidocaine at increased doses include sleepiness, humming in the ears, vertigo and twitches. At toxic doses (<200 mg) the symptoms are: CVS depression, coma and respiratory depressions (2).

REFERENCES