THE USE OF ROPIVACAINE AND BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK
ANY DIFFERENCE?

by;

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ABSTRAK

PEGGUNAAN ROPIVACAIN DAN BUPIVACAIN DIDALAM BIUS SUPRAKLAVIKULAR BRAKIAL PLEKSUS

APAKAH PERBEZAANNYA?

Satu kajian intervensi yang memakan masa satu tahun dua bulan telah diadakan kepada pesakit-pesakit yang menjalani pembedahan anggota atas di Hospital Sains Malaysia, Kubang Kerian. Ia adalah satu kajian perbandingan antara dua ubat bius setempat, ropivacain dan bupivacain untuk blok supraklavikular brakial pleksus.

Bius penuh sebenarnya tidak sunyi dari komplikasi. Kajian yang berterusan untuk mencari ubat bius setempat yang terbaik adalah sangat penting bagi mengelakkan masalah kehilangan darah, vena dalaman yang tersumbat, komplikasi paru-paru sesudah pembedahan dan keadaan konfusi bagi orang tua.

Kajian in pada mulanya mengandungi 64 pesakit. 4 pesakit terpaksa dibuang dari kajian kerana gagal diblok dan juga masalah keresahan. Pesakit-pesakit ini telah menjalani pelbagai jenis pembedahan anggota atas dari 1hb November 1999 hingga 31hb Disember 2000. mereka telah dimasukkan samada di wad ortopedik atau wad pembedahan.

Kesemua mereka telah menjalani bius supraklavikular brakial pleksus yang telah distandadkan menggunakan kaedah klasik dengan bantuan stimulasi saraf. Mereka kemudian

diperhatikan, permulaan sensasi dan motor hilang, jangkamasa bius serta perubahan tanda-tanda vital. Komplikasi yang lain juga diperhatikan.

Kajian telah mendapati bahawa, permulaan rasa sakit hilang, permulaan rasa tidak sakit sepenuhnya dan permulaan rasa kebas adalah lebih cepat bagi ropivacain dan adalah signifikan dari segi statistik. Permulaan rasa sakit hilang adalah juga lebih cepat dari permulaan pemblokan motor. Ini membuktikan bahawa ajen ini lebih suka memasuki saraf sakit dari saraf motor. Tetapi kajian ini gagal mendapati perbezaan didalam permulaan pemblokan motor diantara kedua ajen jangkamasa bius. Walaubagaimanapun, jangkamasa bius (permulaan rasa sakit, permulaan rasa sakit yang teruk, permulaan rasa kebas hilang dan jangkamasa kepada rasa yang normal) adalah lebih lama dan signifikan dengan bupivacain berbanding ropivacain. Jangkamasa bius motor walaubagaimanapun adalah lebih cepat dengan ropivacain berbanding bupivacain. Kajian mendapati terdapat perbezaan didalam perubahan tanda-tanda vital tetapi perubahan bukanlah konklusif. Kesimpulannya, kajian ini telah berjay membuktikan yang penggunaan ropivacaine lebih baik dari bupivacain dari segi ia lebih cepat bertindak, jangkamasa pemblokan motor yang lebih pendek walaupun rasa kebasnya adalah lebih pendek dari bupivacain dengan ini ia tidaklah boleh menjadi ajen yang lebih baik dari bupivacain sebagai ubat penahan sakit selepas pembehan yang baik. Tidak ada sebarang komplikasi serius berlaku semasa kajian dijalankan.

ABSTRACT

THE USE OF ROPIVACAINE AND BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK ANY DIFFERENCE?

An interventional study of one year and two months duration of patients undergoing upper limb surgery in University Science Hospital, Kubang Kerian. A comparative study of local anaesthetic, ropivacaine and bupivacaine used for regional block, supraclavicular brachial plexus block.

General anaesthesia is not free from complications. The continuous search for a better regional anaesthesia agent is important because of issues such as blood loss, deep vein thrombosis, postoperative lung complications and confusion in elderly are avoided.

This study initially involved 64 patients. 4 patients were dropped out because of fail block and anxiety. These patients undergone various operations of the upper extremity from 1st November 1999 to 31st December 2000. They were admitted either in orthopaedic or surgical ward. All of them were elective cases with medical status ASA 1-2, age ranged from 14 to 50 years old.

All the patients received a standard technique of supraclavicular brachial plexus block using the classic technique with the aid of nerve stimulator. They were then assess for the

onset of sensory and motor block, the duration of the block and the changes in the vital sign. Other complications was also noted.

This study found that the onset of sensory block, particularly the onset of complete pain relief and numbness is much faster and statistically significant for ropivacaine. The onset of sensory block was also found to be much faster than the onset of motor block for ropivacaine. This prove the claims that this agent has more preference to the sensory nerve fibber than the motor fibber. However the study fail to find any difference in the onset of motor block between both agents. The duration of analgesia (onset of first pain felt, onset of severe pain, duration to first loss of numbness and the duration to complete normal sensation) is significantly longer with bupivacaine than with ropivacaine. The duration of motor block was shorter with ropivacaine than with bupivacaine. There were difference in the change of the vital signs but the finding is not conclusive. In conclusion, this study prove the advantage of using ropivacaine for faster onset and shorter duration of motor block even though faster offset will not be a better postoperative pain relief than bupivacaine. No serious complication happened during the study.

INTRODUCTION 1

1.1 PERIPHERAL NERVE BLOCK

Regional anesthesia for surgery of the extremities is not a new idea. Extremity amputations were performed after surgical exposure of the brachial plexus or femoral sciatic nerves and application of cocaine before the turn of the century. During those days not few complications occurred due to systemic as well as local effect of the drug. With the great advances in general anesthesia during the first half of this century enthusiasm for regional anesthesia decreased. It subsequent resurgence is due to effective new local anesthetic, improvement in block equipment, and the proliferation of anesthesia residency program. The gruesome realities of war were actually responsible for reestablishment of the safety and efficacy of regional anesthesia for combat casualties. Recently introduced techniques for combined operative anesthesia and post-operative analgesia, new local anesthetic present an exiting scenario for 21st century anesthesiologist. The continuous search for a better regional agent is very important because of issues such as blood loss, deep vein thrombosis, post operative lung complication and confusion in elderly patient outweigh the regional block as compared to general anesthesia.

Many research has been done before on the new enantiomer of bupivacaine but mostly about the epidural route administration. The hyperbaric ropivacaine is found to be as half potent and equipotent doses has similar profile to hyperbaric

bupivacaine but with a higher incidence of side effect e.g. back pain. The relative potency of ropivacaine is less than bupivacane and about 0.6 as potent as bupivacaine .

The motor block appears to be shorter with ropivacaine which allows early mobilization but with a good control of postoperative intravenous patient –controlled analgesia with morphine. This is very important as an ideal anesthetic agent because the risk of developing deep vein thrombosis can be avoided. The use in intravenous anesthesia was found to be comparable with lignocaine but has longer lasting effect.

The search of the suitable dose for regional block has been done. Hickey et. al. 1991a demonstrate that ropivacaine 0.5% and bupivacaine 0.5% appeared equally effective in providing brachial plexus anesthesia. Klein et. al. 1998 compare 0.5% bupivacaine , 0.5% ropivacaine and 0.75% ropivacaine for interscalene brachial plexus block demonsrate a similar efficacy between equal concentration of ropivacaine and bupivacaine and increasing concentration of ropivacaine from 0.5% to 0.75% fails to improve the onset or duration of the block.

1.2 OBJECTIVES

1.2.1 General objective :

To determine the difference between bupivacaine 0.5% and ropivacaine 0.75%, the onset, duration and quality of brachial plexus block.

1.2.2 Specific Objective:

To determine the difference between bupivacaine 0.5% and ropivacaine 0.75% in brachial plexus block concerning :

1. The onset of sensory and motor block
2. The duration of the block
3. The quality of the regional block given
4. The effect on the vital sign i.e. heart rate and blood pressure
5. The effect of sedation
6. Other associated side effect

1.3 HYPOTHESIS

Null hypothesis – There is no difference between ropivacaine 0.75% and bupivacaine 0.5% in supraclavicular block in terms of ;

1. The onset of sensory and motor block
2. The duration of regional block
3. The change in vital sign i.e heart rate(HR) and blood pressure(BP)
4. Other complication

1.3.1 VARIABLES:

Independent variables:

1. Different group of agent for brachial plexus block.
2. Time to onset of sensory and motor block
3. Duration of sensory or motor block.
4. Percentage of patient.

Dependent variables:

1. Change in the vital sign, heart rate (HR) and blood pressure (BP) after block given.

LITERATURE REVIEW 2

2.1. HISTORY

Ropivacaine and bupivacaine like other local anaesthetic agents are drugs that are used clinically to produce reversible inhibition of excitation-conduction process in peripheral nerve fibers and nerve endings, and thus produce the loss of sensation in a circumscribed area of the body.

2.1.1 BUPIVACAINE

Like etidocaine, bupivacaine was created by a modification of an existing local anesthetic (mepivacaine) with the intent to create a more potent, longer duration local anesthetic. The duration of action of bupivacaine exceeds lidocaine by two to three times or more, and duration is even longer if analgesia is considered as an end point. These properties immediately established a niche for bupivacaine in surgical anesthesia. The high pKa and lipid solubility limit transfer of the agent across the placenta to the fetus. The limitation in the placental transfer, combined with the selective increased potency for sensory block and also relatively decreased potential for motor block at lower concentrations, established efficacy of bupivacaine for obstetric anesthesia. Ironically, selective cardiac toxicity associated with bupivacaine has led to 0.75% bupivacaine being specifically disapproved for obstetric use by the U.S.Food and Drug Administration.

2.1.2 ROPIVACAINE

The concern about the potential of bupivacaine to produce cardio toxicity after accidental intravenous injection, has led to a search for an alternative long acting local anaesthetic drug. Ropivacaine has undergone considerable laboratory and clinical evaluation and has recently become improved for clinical use by the regulatory process in many parts of the world. Ropivacaine is the newest addition to the clinical options for the regional anesthesia. As with many of the newer amino amides, ropivacaine was designed by modification of the existing local anesthetic to achieve a clinical objective. Ropivacaine is a member of pipecolyl xylide (PPX) family and is chemically very similar to bupivacaine and mepivacaine. This is due to it belongs to the same chemical series as mepivacaine and bupivacaine, being intermediate between the two agents. All the compounds in the series contain an asymmetrical carbon atom which means that they may exist (and are usually presented) as a racemic mixture of two, optically active isomers. The motivation for designing ropivacaine came from the observation that toxicity with mepivacaine was most often central nervous system (CNS) toxicity and though rarely caused morbidity, whereas the toxicity with bupivacaine was often serious cardiac toxicity.

Although ropivacaine was first synthesized at approximately the same time as bupivacaine, it did not receive attention as a potential clinical agent until cardiac toxicity of bupivacaine became apparent, and the objective of a possible replacement for bupivacaine became appealing (Carpenter 1996). The goal was to create an agent with the favorable properties of bupivacaine (long acting block, motor sparing at lower concentrations) with a toxicity profile that was more similar to mepivacaine. Because the difference between mepivacaine and bupivacaine is one-carbon substitution (methyl) on the tertiary amine for mepivacaine and four-carbon substitution (butyl) at the same site for bupivacaine, attempting to achieve this goal by shortening this aliphatic chain was logical. The three-carbon substitution (isopropyl) is the substitution that creates ropivacaine (figure 2.1). An experimental molecule with five carbons was created and further established the impetus for development of ropivacaine, because the result was much more potent and considerably more cardiotoxic than bupivacaine.

Much of the early work during the clinical trials leading to the release of ropivacaine for general clinical use focused on achieving a clinical profile similar to bupivacaine with less cardiac toxicity. The results of the clinical trials were promising and the U.S.Food and Drug Administration released ropivacaine for sale in 1996. Ropivacaine is a chiral drug; in its production ropivacaine is unique in that it is marketed as an almost pure solution of the S isomer. This isomer was chosen because it is the longer acting of the two when used as a nerve blockade in animals.

2.1.3 PREPARATIONS

Most local anesthetics including ropivacaine and bupivacaine are bases that are almost insoluble in water. Consequently, their hydrochloric salts, which are extremely water soluble, are usually dissolved in modified isotonic Ringer's solution. The preservative helps to maintain the stability of local anaesthetic solution, while the fungicide (usually a small concentration of thymol) prevents the growth of contaminating fungi. Plain bupivacaine is mildly bactericidal at room temperature (Sakuragi et al. 1997). Solutions of local anaesthetic are extremely stable and are usually have an effective shelf life of more than 2 years. Bupivacaine is prepared in the hydrochloride liquid state, from 0.25-0.75%, with a pH of 5.5-6.0 and pKa of 8.1. Whereas ropivacaine is prepared in liquid, hydrochloride salt, pH 5.5-6.0, with pKa of 8.1 and commercially available concentrations are between 0.25% and 1.00%.

2.1.4 CHEMICAL AND PHYSICOCHEMICAL PROPERTIES

In common, all local anesthetics consist of lipophylic aromatic group (R_1), an intermediate ester (-CO.O-) or amide (-NH.CO-) chain, and a hydrophilic secondary or tertiary amine group (R_2). The intermediate chain is an important determinant of the duration of action; it also allows local anesthetics to be classified as esters or amides. Our local anesthetics of concerned come from amide group. From this group are other local anesthetics such as;

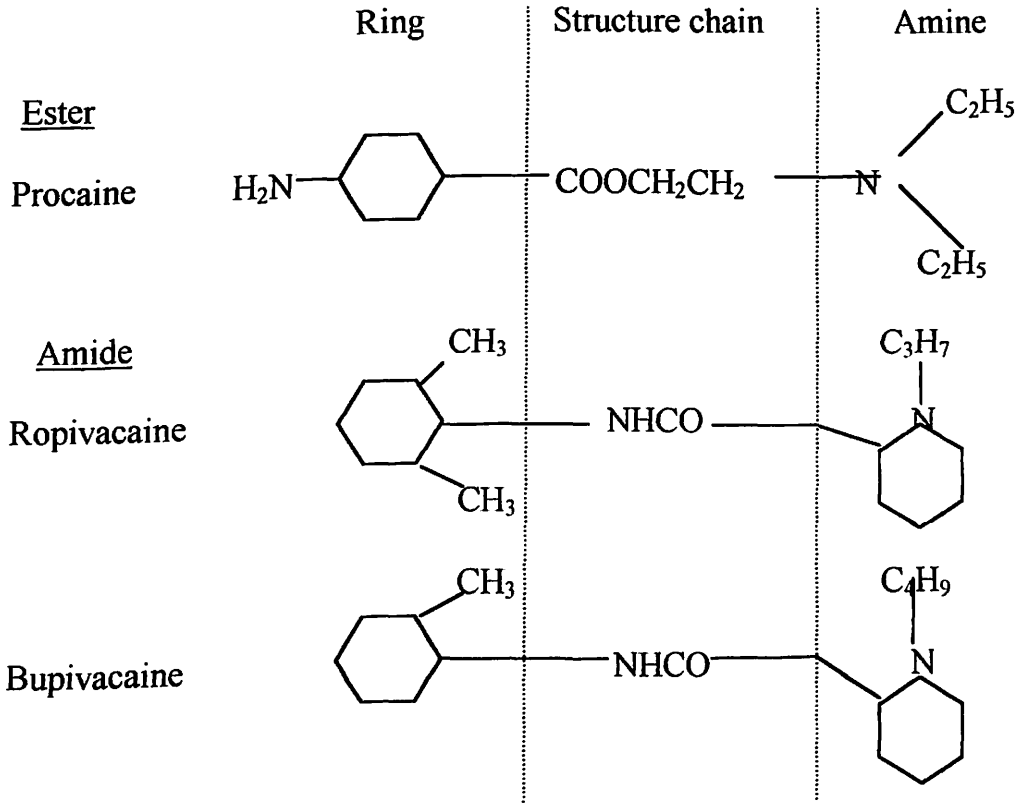
Amide local anesthetics include;

1. Lignocaine
2. Mepivacaine

Whereas ester local anaesthetic include;

1. Cocaine
2. Procaine
3. Chloroprocaine
4. Amethocaine

Figure 2.1 The chemical structure ester and amide local anaesthetic concerned are as below.



The difference between these two groups are esters are relatively unstable in solution, and are rapidly hydrolyzed in the body by plasma cholinesterase, as well as some other esterases. By contrast, our local anesthetics of interest come from amide group which is relatively stable in solution, and slowly broken down by amidases in the liver. In addition, hypersensitivity reactions to amide local anaesthetic are almost unknown.

Modification of the chemical structure may have a profound effect on their physicochemical characteristics. In particular, anaesthetic properties may be modified by changes in: 1) lipid solubility; 2) plasma and tissue protein binding; and 3) the dissociation constant (pKa) value. Values for these constants in ester and amide local anesthetics are shown below.

The close correlation between lipid solubility and anaesthetic potency presumably due to lipid solubility reflect the ability of local anaesthetic to penetrate perineural tissues and the neuronal membrane, and reach their site of action in the axoplasm. For instance, in most clinical situations bupivacaine is approximately four times as potent as lignocaine and ropivacaine probably ¾ as potent as bupivacaine.

Plasma and tissue protein binding primarily affect the duration of action. For example, procaine (which is not extensively bound to plasma protein) has a short duration of action; by contrast, bupivacaine and ropivacaine are extensively bound and have prolonged effects, whereas lignocaine are moderately bound to plasma and tissue proteins and have intermediate duration of action.

The dissociation constant (pKa value) is the important factor affecting their rapidity and onset of action. In order to produce their effect, local anaesthetic must diffuse across the nerve sheath and the neuronal membrane in the form of non-ionized and uncharged freebase. By using the equation:

$$pKa\text{-}pH = \log_{10} \frac{(BH+)}{(B)}$$

For example, lignocaine has pKa value of approximately 7.7; at pH 7.4, 33% is present in solution as the non-ionized base B, and is available to diffuse across the nerve sheath. In contrast, bupivacaine and ropivacaine have a pKa value of 8.1; at pH 7.4, only 17% of these drugs are present in solution as non-ionized base B, and are available for diffusion. This means that the onset of action is slower for ropivacaine and bupivacaine and more rapid for lignocaine.

Table 2.1 Physicochemical properties and pharmacological effects

	PKa value	relative Lipid solubility	relative potency	protein binding	onset of action	duration of action
Lignocaine	7.7	150	2	65	fast	moderate
Ropivacaine	8.1	400	6	94	moderate	long
Bupivacaine	8.1	1000	8	95	moderate	long

Most of the ester local anesthetics (e.g. procaine, chloroprocaine, and amethocaine) as well as lignocaine are achiral compounds; in contrast, most of the amides are chiral drugs. Many chiral drugs (e.g. prilocaine, mepivacaine, bupivacaine and etidocaine) are commonly administered clinically as a racemic mixture of two stereoisomers. Ropivacaine that is more recently developed is used as an s (-) enantiomer. Although individual enantiomers of chiral compounds have approximately equal local anaesthetic activity, the s-enantiomers may have important advantages in other respects. For example, they may produce enhanced vasoconstriction and thus prolong local anaesthetic activity; they may reduce the intensity and duration of blockade and may be associated with reduced risk of cardio toxicity.

2.1.5 MODE OF ACTION

Most local anaesthetic agents including ropivacaine and bupivacaine are tertiary amine bases (B) and administered as water-soluble hydrochlorides (B-HCL). After injection, the tertiary amine base is liberated by the relatively alkaline pH of tissue fluid:

$$B.HCl + HCO_3^- \longrightarrow B + H_2CO_3 + Cl^-$$

Consequently, in tissue fluid the local anaesthetic is present in both a non-ionized (B) an ionized (BH+) form; their relative proportions will depend on the pH of the solution and the pKa of the individual compound, as determined by the modified Handerson-Hasselbalch equation.

$$pKa - pH = \log 10 \frac{(BH+)}{(B)}$$

The non-ionized base B then diffuses through the nerve sheath, perineural tissues and neuronal membrane to reach the axoplasm, where it partially ionizes;

$$B + H+ \rightarrow BH+$$

In the ionized form BH+, local anaesthetic enters the sodium channel from the axoplasm (i.e from the interior of the nerve fiber); it either occludes the channel, or combines with the receptor that results in channel closure. The sodium channel itself may be the receptor for local anesthetics, or there may be multiple binding sites for drugs in the sodium channel. The diffusion of the drugs through open ion channels is required for local anesthetics to reach their site of action.

2.1.6 PHARMACOKINETIKS

Significant absorption of local anesthetics occurs from their site of injection. For each individual drug, the amount of local anaesthetic absorbed and the peak plasma concentration will be dependant on the dose, and may be modified by the presence or absence of a vasoconstrictor (particularly during infiltration or conduction anaesthesia). The site of injection is also important; for example, higher blood levels are attained after intercostals and caudal blockade. Thus every 100mg lignocaine injected in an adult, the peak venous plasma concentration ranges from 1.5 mcg/ml (intercostals blockade), 1.2 mcg/ml (caudal and paracervical blockade), 1.0 mcg/ml (epidural blockade), 0.6 mcg/ml (brachial plexus blockade) to 0.4 mcg/ml (intrathecal blockade). The range of concentrations is mainly due to differences in vascularity, although other factors (e.g. uptake by tissue lipids) may also be involved. Therefore adherence to dose limits for local anesthetics may obscure potential differences in systemic toxicity, depending on the site of injection.

The rate of uptake is related to the surface area available for absorption (e.g. extremely rapid when topical local anaesthetic sprays are applied to the tracheobronchial tract). The inherent effect on vascular smooth muscle-tone also affects the rate of absorption. In the concentrations present clinically, they may all produce some degree of vasodilatation, usually in the order procaine > prilocaine > lignocaine > mepivacaine > bupivacaine > ropivacaine.

After intravenous injection, the plasma concentration of all local anaesthetic usually declines in biexponential manner. There is an initial rapid distribution phase (half-life = 1-3 min) associated with their rapid uptake by highly perfuse organs (e.g. lung, liver and kidney, as well as skeletal muscle). Subsequently, there is a slower decline in plasma concentration; this phase represents the removal of local anaesthetic by metabolism and excretion. The elimination half-life of amides ranges from 100 min (lignocaine) to 160 min (bupivacaine) as compared to relatively short (approximately 10 min) for most esters due to rapid hydrolysis by plasma esterases. The volume of distribution of ropivacaine and bupivacaine or in general, amide local anaesthetic is rather greater than total body water, while plasma clearance is comparable with liver blood flow.

The binding of local anaesthetic by plasma proteins may also affect their pharmacokinetic behavior and pharmacodynamic effects. In general, ester local anesthetics are not significantly bound by plasma proteins (i.e. 5-10% or less). In contrast, amide local anaesthetic are mainly bound by α_1-acid glycoprotein, in the order bupivacaine > ropivacaine > mepivacaine > lignocaine > prilocaine. The extent of plasma protein binding ranges from 55% to 95%; it is usually reversible, and does not appear to limit or restrict the uptake of local anaesthetic by most tissue or organs. In certain physiological and pathological condition e.g. pregnancy, infancy, old age, myocardial infarction, renal failure, malignant disease and after the operation, this protein is increased therefore plasma protein binding is increased, free (unbound) concentration of drugs is reduced, and the total plasma concentration of local anesthetics may not be related to their effective concentration.

2.1.6.1) PHARMACOKINETICS OF BUPIVACAINE COMPARE WITH ROPIVACAINE FROM PREVIOUS STUDIES

The pharmacokinetics of ropivacaine and bupivacaine were determined in dogs after IV and epidural administration by Arthur et.al 1988. After 15-minute IV infusions of 30 mg/kg ropivacaine (n=6) and 3.4 mg/kg bupivacaine (n=4), the maximum arterial concentrations (C_{max}) of ropivacaine 2.41 +/- 0.52 micrograms/ml compared with 3.35 +/- 0.16 microgram/ml of bupivacaine. The elimination half-life ($t_{1/2}$ beta) of ropivacaine (25.9 +/- 1.7 min) was significantly shorter than for bupivacaine (39.1 +/- 13.3 min) after IV infusion. This was reflected by mean clearance values (Cl) for ropivacaine of 41.1 +/- 8.2 ml/min/kg compared with 32.3 +/- 4.8 ml/min/kg for bupivacaine, although the difference was not statistically significant. After epidural injections (ropivacaine n=6, bupivacaine n=5), a dose-related increase in Cmax was observed with both drugs. Although Cmax tended to be higher for ropivacaine, a significant difference was only attained when comparing Cmax after administration of 0.25% plain solution of both agents. The addition of epinephrine did not consistently decrease the Cmax of either agent. The apparent $t_{½}$ beta of both agents was significantly longer after epidural administration than after IV administration. No differences existed between $t_{½}$ beta values for ropivacaine and bupivacaine after epidural administration. Total body clearance of both agents tended to be lower after epidural administration, particularly with epinephrine-containing solutions was employed. Little difference existed between the two drugs when equivalent solutions were administered.

Ekstrom et.al. 1996 found that ropivacaine is predominantly eliminated by extensive metabolism in the liver, with only 1% of the dose being excreted unchanged in the urine of humans. They identified four metabolites formed in human liver microsomes, which are 3-OH-ropivacaine, 4-OH-ropivacaine, 2-OH-methyl-ropivacaine, and 2',6'-pipecoloxylidide (PPX). The enzymes involved in the human metabolism of ropivacaine have not been identified. To ascertain which forms of cytochrome P450 are involved, they incubate ropivacaine with human microsomes from 10 different livers having different cytochrome P450 activities. A strong correlation was found between the formation of 3-OH-ropivacaine and CYP1A and between the formation of 4-OH-ropivacaine, 2-OH-ropivacaine, and PPX and CYP3A. Therefore cytochrome P450 1A and 3A are found to be responsible in the metabolism of ropivacaine in human liver microsomes.

2.1.7 METABOLISM AND ELIMINATION

The metabolism of local anaesthetic is determined by their chemical structure. Plasma cholinesterase and other esterase enzymes in certain tissues break down ester local anesthetics.

2.1.7.1) BUPIVACAINE

Bupivacaine is the most complex of the pipecolyl xylide (PPX) family. Because of the size of the two sides of this amphipathic molecule, hydrolysis of the amide linkage does not occur. Because of the large molecular weight and high level of lipid solubility, very little bupivacaine is excreted intact in urine, unless the urine is aggressively acidified.

The first step in elimination of bupivacaine is biotransformation of the piperidine ring. Dealkylation creates PPX, the same by-product that results from dealkylation of the piperidine ring of mepivacaine. The rate of biotransformation is much slower than with mepivacaine. Much of PPX is excreted unchanged in the urine, and the remainder is slowly biotransformed by hydroxylation. The toxicity of PPX is less than 10% of the parent molecule, and accumulation of the primary metabolite is not a major component of toxicity. With large, repeated doses of bupivacaine, metabolites increases, and half-life of bupivacaine can increase, with net effect of accumulation (Dauphin et al. 1997). During sustained infusions, the total amount and the free fraction in the plasma increase in a linear manner with total dose (Emaneulsson et al. 1995). Because plasma clearance is not changed, accumulation does not increase in comparison to lidocaine or mepivacaine (Mather et al, 1971). Continuous infusion into interscalene brachial plexus by catheter can be achieved with sustained analgesia, without linear increases in the free plasma levels for up to 48 hours (Kirkpatrick et al. 1985).

Because of the high lipid solubility and protein binding of bupivacaine, drugs that are also highly protein bound, such as diazepam, have the potential to displace bupivacaine from binding sites. This increases the free plasma levels and slightly increases the rate of hepatic extraction, but, the larger unbound fraction increases the rate of entry into organ in which toxicity can occur (i.e., central nervous system (CNS), myocardium). The converse is equally true. Because bupivacaine has such a strong potential for protein binding, plasma levels of bupivacaine displace other, less protein-bound agents from binding sites, increasing their plasma level. This must be considered when mixtures of local anesthetics are used, because bupivacaine protein binding decreases the protein binding of other local anesthetics, such as mepivacaine, increasing their plasma levels (Hartrick et al. 1984). Drugs that prolong the metabolism or decrease hepatic clearance of bupivacaine also increase plasma levels. H2 blocker do not decrease the plasma clearance of bupivacaine, even though they have an effect on lidocaine, perhaps because of the high lipid solubility and low hepatic extraction rate with bupivacaine (O'Sullivan et al. 1988). When clonidine was given to mice before administration of bupivacaine, decreased hepatic metabolism occurred (Bruguerolle et al. 1995).

2.1.7.2 ROPIVACAINE

Like bupivacaine, the large aromatic and amine poles of ropivacaine protect the amide bond from hydrolysis. Because of high level of lipid solubility and molecular weight, almost no ropivacaine is excreted intact in the urine is aggressively acidified. Virtually the entire metabolism occurs in the liver (Rutten et al.1990). Biotransformation begins with dealkylation by mixed-function liver oxidases of the

piperidine ring to PPX, and subsequently follows a path to elimination similar to the path that PPX takes during metabolism of mepivacaine and bupivacaine (Oda et al. 1995). The rate of this first step is intermediate between ropivacaine two relatives (mepivacaine and bupivacaine), but closer to bupivacaine (Lee et al. 1989). Hence, the metabolic half-lives of bupivacaine and ropivacaine are very similar. Like bupivacaine, ropivacaine has potential for cumulative effect when infusion rate exceeds the rate of biotransformation and elimination. Although the total plasma concentration of ropivacaine increased with time during postoperative infusion for analgesia after orthopaedic surgery, the free plasma fraction stabilized within the initial 24 hours at level well below toxic (Burm et al. 1997;Erichsen et al. 1996). After an established epidural level, continued analgesia with ropivacaine is not associated with increases in free plasma fraction of the agent or with levels that reach the toxic range (Scott et al. 1997). The increased plasma fraction may be related to the weaker binding of ropivacaine to plasma proteins (compared to bupivacaine), which is also responsible for the higher level of free plasma fraction ropivacaine found in the fetus shortly after injection into pregnant sheep (Santos et al. 1990).

2.2 PROPERTIES FOR CONDUCTION BLOCK

2.2.1 BUPIVACAINE

With a high pKa and high level of protein binding, the latency to onset of conduction block for bupivacaine is the longest of all available local anesthetics. Early evidence of onset is usually apparent 20 minutes after injection into the epidural space or peripheral nerve site. Complete block is usually present by 30 minutes. Sensory block is usually excellent with bupivacaine, even at lower concentrations. Duration of complete anesthesia is long, with motor function returning first. At full doses, bupivacaine can occasionally produce conduction block with 24 hours duration or greater, without neural injury as the mechanism (Madej et al. 1987). At very low concentrations (less than 0.25%), sensory anesthesia and analgesia separate, and achieving analgesia without complete motor block if possible.

The sympathetic block that is achieved with bupivacaine is related to central axis activity and not plasma levels, because comparable sympathetic changes do not occur at the same plasma levels achieved by parenteral administration (Malmqvist et al. 1989). During scoliosis surgery, somatosensory evoked potential can be recorded from the posterior tibia nerve as long as the concentration of epidural bupivacaine is 0.25% or lower (Loughnan et al.1995). Differential block with bupivacaine for different fiber types (Gisses et al. 1982; Palmer et al.1983), either within the spinal column (Dietz and Affe 1997a). The effect also occurs in vitro (Rosenberg et al. 1980).

The clinical observations are supported by in vitro work with isolated rabbit vagus nerve, which shows sensory block comparable to that of bupivacaine with a decreased potency for motor fibers after administration of ropivacaine (Bader et al. 1989; Reynolds 1991). Ropivacaine is less soluble in fat than bupivacaine. This may explain why less potency for A-fiber block exists (motor) in intact nerve preparations, whereas potency for C fibers (sensory) is identical, because A fibers are contained within intact nerves, which contain a considerable amount of fatty tissue (Rosenberg et al. 1986). The high level of lipid solubility and protein binding limit the movement of ropivacaine through tissues (as with bupivacaine), increasing the need for anatomic accuracy of injection with regional anesthetic procedures. In rats, ropivacaine produced a longer duration of sciatic block with less toxicity than bupivacaine (Kohane et al.1998)

.2.3 EFFECT OF ADDITION OF EPINEPHRINE TO PHARMACOKINETIC PROPERTY

Epinephrine has very little effect on the duration of action of ropivacaine (Cederholm et al. 1994b). Epinephrine does not delay the interval to maximum plasma level or decrease the absolute level achieved (Hickey et al.1990b) . They did a study to determine the pharmacokinetic properties of ropivacaine used with or without epinephrine for perivascular brachial plexus block. They measured the plasma concentration of ropivacaine in peripheral venous blood samples taken for 12 hours after drug administration. The mean peak plasma concentration (Cmax) was 1.6 +/- 0.6 mg/L and 1.3 +/- 0.4 mg/L after administration of ropivacaine with and without epinephrine. The median time to peak plasma concentration (t_{max}) was 0.75 hr and 0.88 hr and the mean area under the plasma concentration curve AUCO-12h w as 7.7 +/- 3.6 and 7.0 +/- 3.4 mg.l/hr. The differences were found not statistically significant. Therefore they concluded that the addition of epinephrine does not alter the pharmacokinetic properties of ropivacaine when used for subclavian perivascular brachial plexus block. Motor block duration is not increased by addition of epinephrine (Feldman and Covino 1988). Increasing the concentration of ropivacaine (from 0.5% to 1.0%) increased the duration of sensory block as well as of motor block, when the agent administered in the epidural space (Finucane et al. 1996).

2.4 TOXICITY

2.4.1 BUPIVACAINE

The maximum recommended dose for bupivacaine is the lowest of all the available local anesthetics at 1-2 mg/kg. Epinephrine added to bupivacaine decreases the plasma levels achieved and increases the time interval to maximum level (Burm et al.1986). One unique aspect of bupivacaine is diminished or absent clinical signs of accumulation of bupivacaine in the plasma that occurs until plasma protein-binding sites are fully occupied. In many patients, the aura of CNS toxicity does not occur at all with bupivacaine (Friedman et al. 1982; Yamashiro 1977). Although convulsion proceeded cardiovascular collapse with intravenous bupivacaine in dogs (Liu et al. 1983) and monkeys (Munson et al. 1975) studied, this may not be the case in all humans, especially if premedicated. The systemic signs are related to the free plasma fraction, which remains extremely low until the binding sites are fully occupied. When no more sites for protein binding are available, the free fraction in the plasma rises rapidly, and the toxicity can occur. The time interval between rapid rise and abrupt onset of major toxicity is narrow, which decreases the aura of CNS toxicity that occurs with other local anesthetics. Among the most lipid-soluble agents, rapid administration of bupivacaine caused CNS changes later than a comparable rate of administration of etidocaine (Malagodi et al. 1977). The value of benzodiazepines in the prevention of convulsion with bupivacaine is not clear; their use in the prompt treatment of early signs of generalized convulsions is more unequivocal. When benzodiazepines are used to raise the seizure threshold or for anxiolysis, they can displace bupivacaine from protein-binding sites and abruptly increase the free plasma fraction, suddenly