We are IntechOpen,
the world's leading publisher of Open Access books
Built by scientists, for scientists

4,500
Open access books available

118,000
International authors and editors

130M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Bupivacaine Pharmacokinetics in Pregnant Women

Yazmín Guillén-Dolores

Abstract

Pregnancy, labor, and delivery are accompanied by physiological changes that impact on the use of the drugs to which they are exposed. The anesthesiologist needs to understand the principal differences in management of this particular population. The study of the main pharmacokinetic changes associated with pregnancy is relevant for the proper management of drugs to avoid adverse effects. The objective of this chapter is to review the physiological changes that impact on the pharmacokinetics of the pregnant woman with a focus on local anesthetics of the amide type, specifically bupivacaine, and the main studies that have led to a deeper understanding.

Keywords: pharmacokinetics, pregnant, bupivacaine

1. Introduction

Pregnancy and labor are accompanied by important physiological and anatomical changes. There is a modification in the metabolism of drugs and changes in their pharmacokinetics as well as their interaction with organs and systems. Anesthesia in the obstetric patient is influenced by physiological changes, concomitant diseases, and preferences for a specific drug. Local anesthetics are a special topic due to the frequent use of them during labor, the performance of cesarean section, or another non-obstetric procedure in the pregnant patient. It is necessary to know the pharmacokinetics of the local anesthetic most frequently used in our practice, bupivacaine, plain or hyperbaric, or one of its enantiomers. The objective of this review is to know the main studies that have evaluated pharmacokinetics and their interaction with systems and organs in the mother and placental passage.

2. Cardiovascular changes of pregnancy

During pregnancy many hemodynamic and hormonal changes occur like cardiovascular adaptations such as increased heart rate, plasmatic volume, cardiac output and sympathetic tone, or a reduction in peripheral resistances. The heart moves to the left and up during pregnancy, since the diaphragm progressively rises through the gravid uterus. These changes may be more important in post-term periods that are defined as pregnancies greater than 294 days ($\geq$42 weeks of gestation periods) [1]. The increase in cardiac output and blood volume may increase the distribution of some drugs; the water-soluble ones will increase in their absorption as well as the liposoluble by the augmentation of the maternal fat, and there is an increase of the

glomerular filtration and the renal sanguineous irrigation, which will produce an increase in the clearance of the drug [2].

The blood volume increases by 30–50%, and this rise begins in the first trimester and continues rising until week 30 of gestation and returns to its normal volume after pregnancy. A phenomenon is a dilutional anemia since the proportion of plasma volumes in relation to blood volume increases proportionally greater than red cells, and the hemoglobin concentrations will vary between 11 and 12 g/100 mL at the end of pregnancy. The increase in plasma volume is related to the size of the fetus; one theory is that the adrenal glands of the fetus can initiate an increase in blood volume by providing dehydroepiandrosterone (precursor of estrogen) to the placenta, stimulating the liver to produce angiotensin, which increases aldosterone production and fluid retention [3].

Increased blood volume and increased cardiac output may respond to an initial vasodilation caused by a vasodilating substance that may be prostacyclin or the endothelial-derived relaxing factor. This increase in blood volume is necessary to meet the needs of the fetus and compensate for the loss of maternal blood at delivery; the mother can lose up to 20% of their blood volume without a significant change in his hematocrit [3]. Cardiac output increases to 30–50% during pregnancy, peaks at weeks 28–32, and then decreases a little during the last weeks. The values increase to 4.5–6.5 L/min and decrease as the term of pregnancy approaches but are considerably lower in the lateral position than in the supine position. The supine position during labor is associated with an 8% incidence of hypotension, and 15–20% of patients will have aortoiliac and vena cava compression. The reduced cardiac output lowers uterine blood flow, and this adversely affects the fetus. The cardiac return is diverted from the vena cava through the vertebral and azygos systems to the superior vena cava, and this enlarges the epidural veins and provides an explanation for the reduced amount of local anesthetic needed for spinal or epidural analgesia in pregnancy, and there is an increase in sympathetic activity that results in vasoconstriction that reduced the degree of hypotension observed [4].

Uterine blood flow increases to 200 mL/min by week 28 and 500 mL/min by the end of pregnancy, the uterine musculature receives approximately 20% of the total uterine blood flow, while the area of the placenta receives 80% by what to the placenta, that is to say, 400 mL of blood per minute or approximately 80 mL of blood per 100 g of tissue per minute [4].

3. Pharmacokinetics of bupivacaine and main studies

Bupivacaine is a local anesthetic amide type, synthesized in 1957 by Ekenstam in Switzerland, and has a mechanism of action through the obstruction of sodium channels to the nerve membrane, preventing the generation of an action potential. It is used for intraoperative local anesthesia, postoperative analgesia, and chronic pain treatment. It is widely used in pregnant patients and provides excellent sensory anesthesia with reported concentrations at 0.5% [5].

The effectiveness of bupivacaine was evaluated by the toxicity, the latency, and the degree of motor block, the sympathetic block, and the sensory block, as well as the elimination time. The absorption and distribution are influenced by the vascularity of the injection site, the mode of injection, and the degree of ionization of the drug. After IV administration, its half-life is 45 min corresponding to redistribution and 2.5 h due to elimination. It is metabolized by the liver by N-dealkylation and glucuronide conjugation. Elimination is urinary. Although some metabolites are eliminated via the pulmonary and bile fluid, the portion bound to proteins is the active part, and the unbound is responsible for the toxic effects [5].

The pharmacokinetics in the mother-fetus binomial changes, the fetus and the placenta function as deposits, the placenta has the capacity to metabolize drugs, and it is possible to modulate the elimination of the drug by producing metabolites and retaining large quantities for its release back to the fetus [6].

The apparent volume of distribution increases during pregnancy with the increase in plasma volume, approximately 40–50% from the beginning of pregnancy to a maximum of 32 weeks. During the placental growth phase, the peripheral hairy surface increases from 3.7 m^2 in week 25 to 11 m^2 during the last month of gestation, and the fetal-mother exchange surface decreases from 92 to 767 m^2 due to a decrease in density of the microvilli [6].

Since the drugs that cross the placenta reach the fetus via the umbilical venous blood and 50% of it enters the liver circulation and the rest goes through the venous duct, then half of the transported drug is susceptible to hepatic metabolism and the other half enters the fetal circulation directly. The distribution of a drug in the fetus is regulated by variations in pH and protein binding [6].

The drugs once inside the organism move between the compartments, and to analyze it the changes in the concentration of the drug in a compartment as a function of time are studied, according to the following formula [7]:

$$\frac{dC}{dt} = -kCn \qquad (1)$$

where dC/dt equals the change in concentration in relation to time and −kCn refers to the decrease in the concentration of a drug which is an exponential type function [7].

When the rate of change is independent of the concentration of the drug, it is called a zero-order process, and when the process and the rate of change are proportional to the concentration of the drug, it is called a first-order process, the mother-fetus, which behaves like a model of two compartments with bidirectional distribution [7].

Bupivacaine has an asymmetric carbon atom and can take the form of two enantiomers (R + dextrobupivacaine and S-levobupivacaine), form different three-dimensional relationships in the asymmetric medium of receptors and enzymes, and result in differences in toxicity, distribution, cardiotoxicity, and neurotoxicity [8]. Levobupivacaine is soluble in water with a molecular weight of 325, a partition coefficient of 1624, and a pKa of 8.09. Both the partition coefficient and the pKa are very similar to those of bupivacaine. Its pH is 4.0–6.5. Its maximum plasma concentration reaches 30 min, and its volume of distribution is 67 L [8]. Liposomal bupivacaine is composed of multivesicular liposomes with 10–30 micrometers in diameter and has a duration of analgesia of up to 72 h [9].

Bupivacaine has a pKa of 8.1, ionized fraction of 15% at a pH of 7.4, fat/buffer coefficient of 115, protein binding 95%, molecular weight of 288 Daltons, and an effective anesthetic concentration in the rat sciatic nerve of 0.25. The main determinant of adverse systemic effects is the free fraction, which is not bound to proteins [10].

4. Studies of bupivacaine in QT interval

Spinal anesthesia involves changes in the mother's hemodynamic, including decreased venous return, decreased systemic vascular resistance, and a compensatory increase in cardiac output. These changes increase the risk of intraoperative arrhythmias in patients [1].

Local anesthetics routinely used include bupivacaine and its enantiomer levobupivacaine, the latter having a clinical profile close to bupivacaine, but it is less toxic to both the nervous system and the cardiovascular system, which makes it useful in obstetric anesthesia, where large volumes of local anesthetics may be required. It has been reported that bupivacaine and levobupivacaine cause a concentration-dependent inhibition of the amplitude of gravid myometrial contractions in rats [11].

Local anesthetics are amphiphilic and can enter a variety of cellular compartments and potentially interact with many different cell membranes, organelles (including the inhibition of mitochondrial adenosine production), and a variety of membrane junctions and charged cytosol molecules. Other mechanisms, which can contribute to myometrial inhibition, include the blocking of ionotropic signaling pathways (sodium, potassium, or calcium) and interference with protein modulation of calcium and potassium channels [11].

The practice of using low concentrations (0.125–0.25%) makes it less likely that the inhibitory concentrations in the plasma reach the clinical practice [11]. The toxic effect of local anesthetics on myocardial contractility and cardiac conduction is due to the alteration of the calcium channel [12]. In a study by Mahmut et al., 40 healthy pregnant patients were included; they evaluated QT interval, which increased significantly in the post-term group, which makes them susceptible to the development of arrhythmias; and they concluded that care must be taken during the induction of spinal anesthesia in term pregnancies as well as cardiovascular monitoring should be prolonged in this type of patients [20].

The Dogan et al. study used 12 mg of 0.5% hyperbaric bupivacaine or 0.5% of levobupivacaine for the spinal levobupivacaine group and calculated the QTc with the Bazzett formula and the QT dispersion (difference between the maximum and minimum QTc). They studied 60 patients. The mean maximum QTc was longer in levobupivacaine, and the minimum mean QTc was also longer. In the bupivacaine group, the maximum QTc was longer than levobupivacaine [17].

5. Pharmacokinetic studies in rats

It is known that the placenta does not limit the fetal transfer of local anesthetics administered to the mother; using a human placental model in rats, it is suggested that bupivacaine accumulates in the placenta [13]. The study of Morishima et al., a study in the University of Columbia with a model of rats, administered 1 mg/kg of bupivacaine followed by an infusion of 0.33 mg/kg/min, over a total period of 15 min. The maximum dose of bupivacaine was 1200–1400 ng/mL, which is similar to the concentration of plasma bupivacaine in pregnant women under cesarean section with epidural anesthesia [1].

The pharmacokinetic analysis of bupivacaine was assumed as an open two-compartment model. A transient reduction in heart rate occurred during the infusion of bupivacaine [1].

5.1 Pharmacokinetic parameters

The mean peak concentration of bupivacaine in maternal plasma was 3123 ± 370 ng/mL, the concentration decreased to 26 ± 12 ng/mL at 180 min, and after 240 min, it became undetectable. In plasma 4′-hydroxybupivacaine and 2,6-pipecoloxylidine were not detected. The half-life of distribution was 37.7 ± 2.4 min, the volume of distribution in stable state 3.86 ± 0.29 l/kg, and the total clearance 93.3 ± 8.6 mL/min^{-1}.kg^{-1}; other parameters were K_{12} 0.462 ± 0.066; K_{21} 0.081 ± 0.008 and K_{10} 0.166 ± 0.021. In fetal plasma, a bupivacaine peak of

320 ± 38 ng/mL was detected rapidly, and the drug became undetectable at 4 h. A bupivacaine concentration of 4817 ± 976 ng/g in the amnion at the end of the infusion was the highest sample of those obtained at any time [1].

While the dose of bupivacaine decreases, 3-hydroxybupivacaine remains virtually constant in the amnion and myometrium, and the 3-hydroxybupivacaine also kept increasing. Despite a high concentration of 3-hydroxybupivacaine in these tissues, the amniotic fluid concentration was not as high as expected. The 4-hydroxybupivacaine and the 2.6 pipecoloxylidide were only detected in traces in samples obtained in 2 h. The largest metabolite detected in rats was 3-hydroxybupivacaine [1].

In the fetus, the 3-hydroxybupivacaine remains detectable in the liver up to 4 h, while it virtually disappears from other tissues, because most of the umbilical venous blood perfused in fetal liver, and bupivacaine transmitted to the fetus, can directly enter the fetal liver; this may suggest that the fetal liver is capable of metabolizing bupivacaine. However, because polar metabolites do not cross the placental membrane bidirectionally, 3-hydroxybupivacaine probably accumulates in the fetus [1].

6. Studies about bupivacaine in multimodal analgesia

6.1 Blockage of the transverse abdominal muscle

In the study by Eslamian et al., a randomized, double-blind, placebo-controlled study of 50 pregnant women under elective cesarean section, transverse abdominis plane (TAP) block was used. The preparation was performed with 40 mL of 0.25% hyperbaric bupivacaine plus 2 mL of normal saline for the placebo group of 400 mL of 0.25% hyperbaric bupivacaine plus 2 mL of sufentanil for the study group. The block was guided with ultrasound; the patients who received 40 mL of hyperbaric bupivacaine 0.25% plus 10 μg of sufentanil consumed less morphine during 24 h after surgery compared to the control group (p = 0.002); the mean difference in morphine consumption was 15.6 mg in the first 24 h of the postoperative period. There were no differences in the EVA scale between one group and another with> 0.05 [13].

In the Trabelsi et al. study, a group of 17 pregnant patients were administered with spinal anesthesia with hyperbaric bupivacaine with 5 μg of sufentanil, and abdominal ultrasound-guided TAP block was placed with 20 mL 0.25% bupivacaine bilaterally. They found an accumulated average of bupivacaine of 1.4 ± 0.2 mg/kg (range of 1.05–1.79 mg/kg); the C_{MAX} was 802.36 ng/mL (231.8–3504.5 ng/mL) and was reached at 30 min (T_{MAX}). The mean area under the curve (AUC) (0–24 h) was 4505.4 ng/mL, and the elimination half-life was 8.75 h for bupivacaine, demonstrating that bilateral blockade increases the total concentration of bupivacaine in the plasma after administering spinal anesthesia with bupivacaine. Plasma concentrations occurred at 30 min after injection, all peak concentrations were reached between 10 and 90 min and a second delayed peak of 90 min [10].

In the Lacassie study, in 12 pregnant women and 11 healthy volunteers, the transverse muscle was blocked with levobupivacaine 0.25%, 20 mL with epinephrine 5 μg/ml^{-1}, venous concentrations were 2.62 mg/L^{-1}, below the level toxic, the volume of distribution of levobupivacaine was 172 L (70 kg) (IC 95% 137–207) higher than in healthy volunteers [15].

6.2 Use of patient-controlled analgesia (PCA pumps) in different combinations

The Stourac study worked with pregnant women under epidural analgesia; they used 12.5 mg of bupivacaine and 5 μg of sufentanil in 10 mL of normal saline, and boluses of half the dose every 60–90 min were administered. Another group using

PCA pumps with remifentanil connecting a 50 mL syringe with remifentanil at a concentration of 20 µg/mL studied a total of 24 patients, and there was no significant difference between the groups. The level of satisfaction of the patients was 88% with epidural analgesia and 85% with PCA pump. Among the complications, only one had hypotension, with remifentanil, and experienced drowsiness and dizziness as well as temporary anxiolysis [8].

In the Chen et al. study, they determined the lowest effective concentration of levobupivacaine and levobupivacaine with fentanyl, and one group received 1.2 mg/mL of levobupivacaine and 2 µg/mL of fentanyl. They determined that the concentrations of 0.6 mg/mL of levobupivacaine plus 2 µg/mL of fentanyl and 1 mg/mL of levobupivacaine were the lowest concentrations of the drugs required for effective analgesia, and they analyzed a total of 83 pregnant women and showed that levobupivacaine alone produces a comparable analgesia with levobupivacaine with narcotic; in addition, those who received narcotics had more adverse effects [16].

6.3 Studies in the capacity of blocking muscle fibers

In the Fanning et al. study, pregnant patients received spinal anesthesia with 10–12 mg at 0.5% hyperbaric bupivacaine with 20–25 µg of intrathecal fentanyl and 100–150 µg of intrathecal morphine. After the placental extraction, a small segment of the myometrium was removed from the incisional surface of the lower uterine segment. Each sample was dissected in four longitudinal muscles. The muscle was exposed to bupivacaine or levobupivacaine and chemical contractions were induced. Eight muscle samples were included. Bupivacaine and levobupivacaine caused a concentration-dependent decrease in the amplitude of the contractions reaching a statistical significance of $p = 0.002$ for bupivacaine and $p = 0.001$ for levobupivacaine compared to the control period before the administration of any drug [14]. There was no significant difference between bupivacaine and levobupivacaine in its effects on contraction of the myometrium, in the amplitude of the contractions, and in the interval between contractions for bupivacaine and levobupivacaine; there was no difference between the EC_{50} (effective concentration 50) and the effect of both drugs in contractility which was reversible. No increase in contractile amplitude was observed. The maximum concentrations in plasma were 1053 µg/mL (3.24×10^{-6} m) for bupivacaine and 1017 µg/mL (3.13×10^{-6} m) for levobupivacaine. They concluded that bupivacaine and its enantiomer levobupivacaine cause a similar decrease in concentration-dependent contractions. The concentrations required for their inhibitory effect on the amplitude of the contractions were much higher (33 times) than the clinically relevant plasma concentrations of these drugs after epidural administration and are unlikely to be significant in the low epidural dose scenario to analgesia in labor periods [14].

The combination with clonidine, a partial agonist of alpha 2 adrenergic receptors, interacts with the local anesthetic in the neural axis. The analgesic effect is due to its action in spinal and supraspinal α-adrenergic receptors, including the activation of postsynaptic α-2 receptors, since the noradrenergic descending pathways of cholinergic neurons and the release of nitric oxide and substances such as enkephalin reduce the absorption of local anesthetics by a vasoconstrictor effect, improving quality and increasing the duration of anesthetic blockade. It is recommended at doses of 1 µg/kg combined with bupivacaine [12]. In a Brazilian study, 66 pregnant patients were divided into two groups: a group with 8 mg of bupivacaine +75 µg of clonidine and 100 µg of morphine +0.9% saline and another group with 10 mg of bupivacaine +75 µg of clonidine +100 µg of morphine + saline 0.9%; the total volume administered was 4 ml in both groups, and there was no difference in hemodynamic parameters, adverse effects, and level of consciousness, only the

regression time of the motor block, in group 1, of 198.48 ± 47.63 min, and in group 2 of 232.84 ± 63.66 min; p = 0.00073. They concluded that morphine and clonidine at low doses produce adequate postoperative analgesia in pregnant patients [12].

In the study Zhan et al., 70 pregnant or obstetric patients were studied; 0.5% spinal isobaric bupivacaine was 4 mg; the ED50 of intrathecal bupivacaine for motor block was 3.96 mg (IC 95% 3.83–4.98) for pregnant women versus 4.51 mg (95% CI 4.27–4.76) for nonpregnant women. The potency of bupivacaine for motor block in pregnant versus non-pregnant women was 1.14 times higher (95% CI 1.05–1.24). This is because the supine position can increase the dissemination of the injected drugs due to the increase in intra-abdominal pressure, in addition to the increase in blood flow in the vasculature in the epidural veins, which distends and compresses the intraspinal space decreasing the volume of the spinal fluid cerebral [18].

7. Bupivacaine and placental transfer to fetus

The analysis of the placental intervillous space shows to be an appropriate place of investigation because this space is initially filled with blood coming from the maternal spiral arteries that interchange with the fetal venous blood, when the blood of the mother flows toward the branched villi. Although it is an important interchange interface, the intervillous space has been studied as the transport of substances between the mother, the placenta, and the fetus; obtaining blood from this compartment has provided a unique opportunity to study the maternal-fetal physiological relationship in a more physiological way [19]. The importance of this is that the reduced ability of the fetus to eliminate drugs can cause prolonged effects on the fetus, since half of the fetal circulation reaches the umbilical vein and directly reaches the fetal heart and brain by passing to the fetus. Liver immaturity contributes to the presentation of adverse effects, the fetus eliminates the drug by diffusion into the maternal compartment, although the majority of the metabolites are more polar and it is unlikely that the placental membrane crosses the placental membrane back to the compartment maternal, possibly resulting in the accumulation of metabolites in various fetal tissues [19].

In the study by Barros et al., a Brazilian study, the concentrations of bupivacaine and lidocaine as well as its metabolite (MEGX) and its placental transfer were analyzed in 10 healthy pregnant patients, under elective cesarean and epidural anesthesia. The administration of the medication was epidural of 0.1 mg of fentanyl citrate, 112.5 mg of 0.5% bupivacaine with 2:200000 epinephrine, and 200 mg of lidocaine 2% without vasoconstrictor injected into the epidural space [11]. The concentrations of bupivacaine enantiomers were high in the maternal plasma and placental intervillous space than in the umbilical vein and the umbilical artery. The concentrations of S-bupivacaine in the maternal plasma were higher than the R-bupivacaine concentrations, and the values were 195.2 and 186.0 ng/mL. There were no significant differences (P < 0.05) between their concentrations in umbilical fetal vessels [11]. The placental transfer was 33% for R-bupivacaine and 31% for the S-bupivacaine. The concentrations of the enantiomer S-bupivacaine were 3.5 and 3.82 times higher in the placental intervillous space than that of the umbilical vein and the umbilical artery, respectively [11].

The R-bupivacaine concentrations were 2.9 times higher in the placental intervillous space than the fetal umbilical vein concentrations and 3.16 times higher than the concentrations in the fetal umbilical artery. There were no cardiocirculatory changes, neonatal repercussions in the APGAR, or respiratory depression. There was no significant difference in the ratio of enantiomer concentrations between the

different compartments, maternal or fetal. This study showed that the intervillous space acts as a drug reservoir [11].

8. Conclusion

In conclusion, local anesthetics, including bupivacaine, are among the drugs most commonly used in clinical practice for the management of pregnant patients for obstetric or non-obstetric procedures. It is essential to know the pharmacokinetics of the drug in order to understand the concentrations of the drugs which we can obtain adequate analgesic and anesthetic effects, trying to diminish the toxic effects.

Acknowledgements

Conflict of interest

I declared that I do not have any conflict of interests.

Author details

Yazmín Guillén-Dolores
Instituto Nacional de Cardiología Ignacio Chávez, México City, México

*Address all correspondence to: gudyyazy@hotmail.com

IntechOpen

References

[1] Morishima HO, Ishizaki A, Zhang Y, Whittington RA, Suckow RF, Cooper TB. Disposition of bupivacaine and its metabolites in the maternal, placental, and fetal compartments in rats. Anesthesiology. 2000;**93**(4):1069-1074

[2] Babst CR, Gilling BN. Bupivacaine: A review. Anesthesia Progress. 1978;**25**(3):87-91

[3] Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald E, editor. Heart Disease. A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: WB Saunders; 2007. pp. 1843-1844

[4] González I, Armada E, Díaz J, Gallego P, García-Moll M, González A, et al. Guías de práctica clínica de la Sociedad Española de Cardiología en la gestante con cardiopatía. Revista Española de Cardiología. 2006;**53**:1474-1495

[5] Rudolph AM. Pharmacodynamics in the maternal-fetal-placental unit. NIDA Research Monograph. 1995;**154**:163-174

[6] Briggs GG, Freeman RK, Yaffe SS. Drugs in Pregnancy and Lactation. 4th ed. Baltimore: Williams and Wilkins; 1994

[7] Foster RH, Markham A. Levobupivacaine: A review of its pharmacology and use as a local anaesthetic. Drugs. 2000;**59**(3):551-579

[8] Stourac P, Suchomelova H, Stodulkova M, Huser M, Krikava I, Janku P, et al. Comparison of parturient - controlled remifentanil with epidural bupivacain and sufentanil for labour analgesia: Randomised controlled trial. Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic. 2014;**158**(2):227-232. DOI: 10.5507/bp.2012.073

[9] Lirk P, Picardi S, Hollmann MW. Local anaesthetics: 10 essentials. European Journal of Anaesthesiology. 2014;**31**(11):575-585. DOI: 10.1097/EJA.0000000000000137

[10] Trabelsi B, Charfi R, Bennasr L, Marzouk SB, Eljebari H, Jebabli N, et al. Pharmacokinetics of bupivacaine after bilateral ultrasound-guided transversus abdominis planeblock following cesarean delivery under spinal anesthesia. International Journal of Obstetric Anesthesia. 2017;**32**:17-20. DOI: 10.1016/j.ijoa.2017.04.007

[11] de Barros Duarte L, Dantas Móises EC, Cavalli RC, Lanchote VL, Duarte G, da Cunha SP. Distribution of bupivacaine enantiomers and lidocaine and its metabolite in the placental intervillous space and in the different maternal and fetal compartments in term pregnant women. Journal of Clinical Pharmacology. 2011;**51**(2):212-217. DOI: 10.1177/0091270010365551

[12] Braga Ade F, Frias JA, Braga FS, Pereira RI, Titotto SM. Spinal anesthesia for elective ceasarean section: Use of different doses of hyperbaric bupivacaine associated with morphine and clonidine. Acta Cirúrgica Brasileira. 2013;**28**(1):26-32

[13] Eslamian L, Kabiri-Nasab M, Agha-Husseini M, Azimaraghi O, Barzin G, Movafegh A. Adding sufentanil to TAP block hyperbaric bupivacaine decreases post-cesarean delivery morphine consumption. Acta Medica Iranica. 2016;**54**(3):185-190

[14] Fanning RA, Campion DP, Collins CB, Keely S, Briggs LP, O'Connor JJ, et al. A comparison of the inhibitory effects of bupivacaine and levobupivacaine on isolated human pregnant myometrium contractility. Anesthesia and Analgesia.

2008;**107**(4):1303-1307. DOI: 10.1213/ane.0b013e3181804245

[15] Lacassie HJ, Rolle A, Cortínez LI, Solari S, Corvetto MA, Altermatt FR. Pharmacokinetics of levobupivacaine with epinephrine in transversus abdominis plane block for postoperative analgesia after caesarean section. British Journal of Anaesthesia. 2018;**121**(2):469-475. DOI: 10.1016/j.bja.2018.02.070

[16] Chen SY, Liu FL, Cherng YG, Fan SZ, Leighton BL, Chang HC, et al. Patient-controlled epidural levobupivacaine with or without fentanyl for post-cesarean section pain relief. BioMed Research International. 2014;**2014**:965152. DOI: 10.1155/2014/965152

[17] Dogan Z, Yildiz H, Akcay A, Coskuner I, Arikan DC, Silay E, et al. The effect of intraspinal bupivacaine versus levobupivacaine on the QTc intervals during caesarean section: A randomized, double-blind, prospective study. Basic and Clinical Pharmacology and Toxicology. 2014;**114**(3):248-253. DOI: 10.1111/bcpt.12146

[18] Zhan Q, Huang S, Geng G, Xie Y. Comparison of relative potency of intrathecal bupivacaine for motor block in pregnant versus non-pregnant women. International Journal of Obstetric Anesthesia. 2011;**20**(3):219-223. DOI: 10.1016/j.ijoa.2011.01.001

[19] Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clinical Pharmacokinetics. 1995;**28**(3):235-269. DOI: 10.2165/00003088-199528030-00005

[20] Mahmut Alp K, Adnan I, Evren B, Nuray A, Orhan B, Besli F. Effect of spinal anesthesia on the QT interval in term and post-term pregnancies scheduled for elective cesarean section, a prospective study. The Journal of Maternal Fetal and Neonatal Medicine. 27 Jan 2019:1-5. DOI: 10.1080/14767058.2019.1569620. [Epub ahead of print]