TITLE: INTRAPLEURAL ANALGESIA WITH BUPIVACAINE FOLLOWING THORACOTOMY IS INEFFICIENT : RESULTS OF A CONTROLLED STUDY AND PHARMACOKINETICS.

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Recently intrapleural analgesia, a new technique of postoperative pain relief, has widely spread (1,2). Although efficacy of this technique is a much debated question (3), no controlled study was conducted in the field and patients underwent various anesthesia and surgical procedures.The aim of this study is to evaluate the efficacy of intrapleural analgesia with bupivacaïne following pulmonary partial resection.

18 patients were included after ethical approval and informed consent. All patients were anesthetized using a standardized technique and had lateral and posterior thoracotomy for lobectomy or wedge resections. Before closure, an epidural catheter was surgicaly introduced posteriorly into the pleural cavity. Patients were selected at random in two groups : group 1 (n = 10) received 40 ml .25 % bupivacaïne with epinephrine, group 2 (n = 8) received 20 ml .5 % bupivacaïne with epinephrine. The first injection was performed 1 or 2 hours after anesthesia recovery. Following injections were done up to 3 time a day, for a maximum time of 4 days.

Subjective evaluation of pain was performed using a 0 to 10 visual analogic scale before and after each injection by response to spontaneous pain, coughing, deep breathing and incision palpation. Simultaneously, heart rate, respiratory rate, mean arterial pressure and vital capacity were measured. Blood gas analysis was done daily. Maximum peak concentration and maximum time to reach the peak were estimated after the first and the last injections. Statistical comparisons of clinical data and pharmacokinetic parameters were done using a Mann - Witney and a Wilcoxon test.

In 18 patients, 97 injections were performed. No significant pain relief was obtained in both groups attested either by pain score with visual analogic scale or hemodynamic, respiratory, spirometric and blood gas parameters variations. C MAX and T MAX after the first and the last injection were not significantly different between the two groups. In each group, C MAX following the last injection was significantly higher than after the first injection ($p < .05$) ( table 1).

In this controlled study, intrapleural analgesia conducted either with 40 ml .25 % bupivacaïne with epinephrine or 20 ml .5 % bupivacaïne with epinephrine was inefficient on thoracotomy despite high plasma bupivacaïne concentration.

REFERENCES : 1 - Regional anesthesia 11 : 89-91, 1986
2 - Anesthesiology 69 : 261-264, 1988
3 - Anesthesiology 67 : 811-813, 1987

| | | 1° injection | last injection |
|---|---|---|---|
| C MAX | G1 | .75 ± .57 | 2.11 ± .71 * |
| | G2 | .42 ± .29 | 1.53 ± .60 * |
| T MAX | G1 | 24.5 ± 11 | 39 ± 9 |
| | G2 | 23 ± 14 | 33 ± 8 |

Table 1 : Pharmacokinetic parameters of bupivacaïne ( mean ± SD)
C MAX : maximum peak concentration (µg/ml)
T MAX : maximum time to reach the peak (min)
* $p < .05$ 1° injection value taken as reference



**TITLE: NICARDIPINE PROTECTS FROM BUPIVACAINE INDUCED CARDIORESPIRATORY TOXICITY (BICT) IN RATS**

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**INTRODUCTION:** Calcium channel antagonists (CCA) are frequently being used in the treatment of a variety of medical conditions, including perioperative hypertension, ischemic coronary artery disease, and cardiac dysrhythmias. A number of these patients undergo surgery under bupivacaine regional anesthesia. Bupivacaine is considered more cardiotoxic, when given accidentally into a blood vessel or when administered in excessive amounts, than any other local anesthetic in use today. In spite of its cardiotoxicity bupivacaine is still the most widely used local anesthetic both in pregnant and non-pregnant patients because of its unique physicochemical properties. Investigators have shown that bupivacaine not only inhibits fast sodium dependent channels but also slow calcium dependent channels. Nicardipine, a new dihydropyridine calcium channel antagonist structurally related to nifedipine, has been shown to produce coronary vasodilation and reduce systemic vascular resistance. The purpose of the present study is to investigate the effect of nicardipine on BICT.

**METHODS:** Fifty adult male Sprague Dawley rats were divided into four groups and anesthetized with i.p. pentobarbital 40-60 mg/kg. EKG lead II (heart rate and rhythm), precardial pulsations, and respirations were monitored. A femoral vein was cannulated with a 24g i.v. catheter and 20 ul were taken for blood gas analysis. Based on our preliminary dose-response studies with 0.5% bupivacaine, we have chosen 3.5 mg/kg (LD10) and 5mg/kg (LD90) for the study of cardiorespiratory toxicity. Groups I and III were pretreated with normal saline, and Groups II and IV were pretreated with nicardipine 30 ug/kg. Three min after pretreatment, rats were given either 3.5mg/kg (Groups I & II) or 5mg/kg (Groups III & IV) bolus iv bupivacaine. Rats were classified as survivors or fatalities at five minutes following the administration of bupivacaine. Rats that sustained adequate ventilation, color, and heart rate were classified as survivors and rats that developed apnea, cyanosis, and agonal rhythm with no cardiac impulse were classified as dead.

**RESULTS:** All rats receiving low dose bupivacaine (Groups I & II) survived (100%). In the high dose bupivacaine groups (Groups III & IV) more rats that received nicardipine pretreatment (74%) survived compared to the rats that received saline pretreatment (7%) ($P<0.001$ by chi-square with Yate's correction). All rats developed apnea at 8-10 sec following the injection of bupivacaine. The rats that survived resumed spontaneous breathing within 10-12 sec and maintained regular heart rate and rhythm, and good color. The rats that did not survive remained apneic, became cyanotic, and developed agonal cardiac rhythm and cardiac arrest. There were no differences in the blood gases or weights or pentobarbital doses among the groups (ANOVA).

**DISCUSSION:** The mechanism of bupivacaine induced cardiorespiratory toxicity is not clear. At high blood concentrations, bupivacaine is known to increase systemic, pulmonary, and coronary vascular resistances. We speculate that nicardipine decreases the vascular resistance and thus decreases bupivacaine induced cardiorespiratory toxicity in rats. In conclusion, our results show that nicardipine significantly reduced the fatalities from BICT.

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