TITLE: PHARMACOKINETICS OF INTRATHECAL MORPHINE IN CESAREAN SECTION PATIENTS

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INTRODUCTION: Intrathecal administration of morphine for post-cesarean section analgesia is popular. The pharmacokinetics of intrathecal morphine is not well defined. This study examines the pharmacokinetics of intrathecal morphine administration during spinal anesthesia for cesarean section.

Methods: Review board approval and informed consent were obtained from ASA I patients (n=13) for cesarean section. Following hydration with 2000ml Ringer's lactate, a mixture of 12 mg bupivacaine in 8.5% dextroxe and 0.6 mg morphine were injected intrathecally to produce a T3-T4 sensory level. Blood and urine samples were collected at .25, .5, 1, 2, 3, 6, 12, and 24 hours. Unconjugated morphine (UM) from serum and urine was measured with a RIA (range 0.17-200 ng/ml, with a cross reactivity to morphine-3-glucuronide of 0.3%). Total morphine was measured after incubating samples with glusalase (glucuronidase and sulfatase) to hydrolyze conjugates. Conjugated morphine (CM) was calculated as total morphine minus UM. Area under the curve (AUC), terminal elimination half life ($t_{1/2}$beta), plasma clearance (Cl), and volume of distribution (VDss) were calculated[1]. Results are expressed as mean ± 1SE.

Results: (Fig and Table) Serum profiles of UM and CM best follow a bi-exponential model. UM rapidly appears in the serum, but does not peak until 3 hours. Maximal urinary UM level occurs at 6 hours. Serum and urine CM peak at 6 hours but persist in significant quantities until 24 hours.

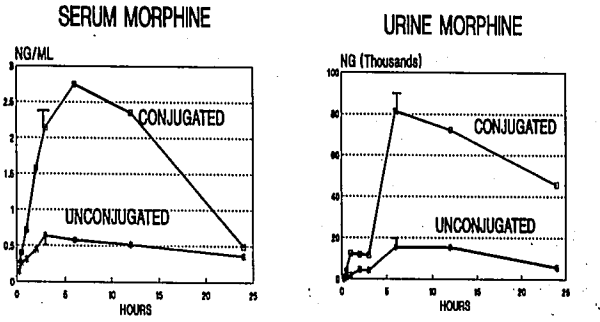
Discussion: The data show that morphine absorption from the intrathecal space continues for several hours. Morphine elimination follows a bi-exponential distribution. Morphine conjugates rapidly appear in urine. Urinary excretion continues at least for 24 hours.

References: 1) Shumaker RC, Drug Metab Rev 1986:17:331.

Table: INTRATHECAL MORPHINE PHARMACOKINETCS

	AUC ng-hr/ml	$t_{1/2}$beta hrs	Cl L/hr	VDss L
Unconj	14.9±3.1	14.8±2.7	50.8±11	827.6±65
Conjug	44.6±21	8.8±1.3	20.6±5.5	210.6±31

Values are mean ± 1SE



TITLE: ENDOTHELIN LEVELS IN PATIENTS WITH PREECLAMPSIA

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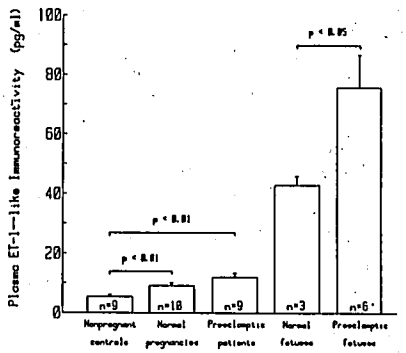
Endothelin is a recently discovered peptide that is produced by endothelial cells and elicits a potent and long lasting vasoconstriction.[1] Elevated concentrations of endothelin have been detected in patients with essential hypertension.[2] Therefore, it is quite possible that this peptide plays a significant role in blood pressure regulation.

Because disruption of endothelial cells, a process that may cause a release of endothelin, is a common event in preeclampsia,[3] we hypothesized that the hypertension of preeclampsia is caused by elevated levels of circulating endothelin.

After Institutional Review Board approval, plasma endothelin-1 was determined by radioimmunoassay in 9 patients with preeclampsia, 10 patients with normal pregnancy, and 9 non-pregnant female control subjects. In addition, fetal samples from the umbilical vein were obtained from 6 preeclamptic pregnancies and 3 normal pregnancies. Maternal and control plasma were compared using analysis of variance followed by Neuman-Keuls test; fetal blood values were compared using Student's t-test.

Plasma endothelin (mean ± SEM) in preeclamptic patients (11.9 ± 1.4 pg/ml) and normal pregnancy patients (9.1 ± 1.0 pg/ml) did not differ from each other, but each was significantly elevated as compared to non-pregnant control subjects (5.4 ± 0.7 pg/ml, Figure 1). Endothelin in fetal plasma (43.1 ± 3.1 pg/ml) was significantly greater than in maternal plasma. Fetal blood in the preeclamptic pregnancies had even higher values (76.1 ± 10.9 pg/ml) and was significantly greater than that of normal fetuses.

We conclude that plasma endothelin in maternal plasma is increased in late pregnancy. Because circulating endothelin in women with preeclampsia did not differ from that in women with normal pregnancies, the elevation of this peptide is insufficient to explain the hypertension of preeclampsia. However, the nearly 5-fold elevation of fetal over maternal endothelin values prompts us to speculate that this peptide plays a regulatory role in fetal circulation. Furthermore, the even greater concentration of endothelin in the preeclamptic fetus conceivably could contribute to the increase in feto-placental vascular resistance, the fetal growth retardation, and the oligohydramnios associated with this syndrome.



References

1. Nature 332: 411-415, 1988
2. N Engl J Med 322: 205, 1989
3. Am J Obstet Gynecol 161: 1200-1204, 1989