

## EFFECTS OF KETAMINE ON THE PREGNANT UTERUS

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### SUMMARY

Intra-uterine pressure was recorded by placing a Foley catheter in the extra-amniotic space before the termination of pregnancy in 25 patients, and Caesarean section in 12 patients. The effects of administration of i.v. ketamine 2 mg/kg body weight, sodium thiopentone 4 mg/kg body weight and ergometrine 0.5 mg, and intra-cervical 0.5% lignocaine 20 ml were measured in the first trimester of pregnancy, and i.v. ketamine and sodium thiopentone in late pregnancy. Ketamine was found to cause uterine contraction (mean increase 16.1 mm Hg) equal to ergometrine (mean increase 14.8 mm Hg) in early pregnancy, but exert no effect (mean decrease -1.33 mm Hg) in late pregnancy. Lignocaine in early pregnancy given as a paracervical block had no significant effect on intra-uterine pressure (mean increase 0.33 mm Hg). Sodium thiopentone (mean decrease -4.28 mm Hg first trimester and -2.22 mm Hg at term) in late pregnancy had no significant effect on intra-uterine pressure.

Ketamine hydrochloride (Ketalar) has been used widely in anaesthetic practice since the initial paper by Domino, Chodoff and Corssen (1965). In 1971 Galloon reported on its use as an induction agent for the termination of pregnancy by suction curettage, noting that blood loss was minimal during the procedure and that the uterus was well contracted at the conclusion of the operation. Later, Galloon (1973) measured the effect of ketamine on uterine muscle at hysterotomy and found an increase in both uterine tone and the intensity of contractility. Such effects had not been observed by Peltz and Sinclair (1973) on a pregnant uterus at term at Caesarean section, and thus it was decided to investigate further the action of ketamine and compare it with that of thiopentone in the first and last trimester of pregnancy and with ergometrine and lignocaine in early pregnancy.

### PATIENTS AND METHODS

The procedure was explained to and informed consent obtained from 19 women undergoing therapeutic termination of pregnancy under general anaesthesia who were allocated randomly to three groups. The first group (I) received ketamine, the second (II)

thiopentone and the third (III) ergometrine followed by ketamine. An oral premedication of lorazepam 3 mg and droperidol 5 mg was given 1 h before the induction of anaesthesia. A further six women (group IV) chose to have termination of pregnancy under local anaesthesia; no premedication was given to these patients.

In a second study, 12 women prepared for elective Caesarean section on account of cephalopelvic disproportion were allocated randomly to two groups. The first (group V) were given ketamine and the other (group VI) thiopentone for the induction of anaesthesia. In keeping with our routine practice for elective Caesarean section, the patients were not premedicated, and breathed 100% oxygen until the trachea was intubated. As soon as the intra-uterine pressure had been measured (*vide infra*) the patients were given suxamethonium i.v., an endotracheal tube was inserted and the lungs were ventilated in the normal manner. The anaesthetic was continued using conventional techniques and the intra-uterine catheter removed.

Before the induction of anaesthesia each patient was placed in the lithotomy position, the vulva and vagina were cleaned with chlorhexidine solution 0.5% and, after draping with sterile towels, a bivalve speculum was inserted into the vagina to display the cervix. A size 12 Foley catheter was fed through the cervix into the extra-amniotic space and the self-retaining balloon distended with 5 ml of saline. The catheter filled with saline was connected to a Bell and Howell transducer and the pressure recorded on a Devices recorder after calibration.

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TABLE I. Mean changes (SEM) in intra-uterine pressure with drug administration

	Termination of pregnancy				Caesarean section		
	Ketamine (Group I)	Thiopentone (Group II)	Ergometrine then ketamine (Group III)	(Total increase)	Lignocaine 0.5% (Group IV)	Ketamine (Group V)	Thiopentone (Group VI)
Resting pressure	11.1 (1.0)	15.6 (2.3)	8.8 (2.4)	23.6 (6.3)	11.7 (2.2)	15.2 (2.7)	22.0 (2.6)
Final pressure	26.4 (5.3)	11.3 (1.5)	23.6 (6.3)	34.8 (7.5)	12.0 (2.5)	13.8 (1.9)	19.8 (2.2)
Mean change	16.1 (4.9)	-4.3 (2.0)	14.8 (4.5)	26.0 (5.5)	0.3 (0.8)	-1.3 (1.5)	-2.2 (0.5)

Once a steady baseline pressure had been obtained for 3 min, ketamine 2 mg kg<sup>-1</sup> body weight i.v. was given to groups I and V, thiopentone 4 mg kg<sup>-1</sup> body weight i.v. to groups II and VI, and ergometrine 0.5 mg i.v. to group III. In group IV, lignocaine 0.5% 20 ml was injected in four divided doses at "12, 3, 6, and 9 o'clock" at the junction of the inner  $\frac{2}{3}$  and the outer  $\frac{1}{3}$  of the cervix. The intra-uterine pressure was recorded continuously until a steady state had been reached for a further 3 min. In group III ketamine 2 ml kg<sup>-1</sup> body weight i.v. was administered and the recording of intra-uterine pressure continued until a new steady state had been obtained. The catheter was removed and the planned operation performed. No anaesthetic or surgical complications occurred. There was no case of post-abortion or puerperal infection.

The period of gestation at termination of pregnancy ranged from 8 to 12 week and at Caesarean section from 37 to 40 week. The *F* test was used to test for equality of variance before comparison of means. If the *F* test was positive, Student's *t* test was used; if not, a modified Student's *t* was applied.

#### RESULTS

The changes in intra-uterine pressure in the six groups are shown in figure 1 and the mean changes and SEM are listed in table I. The significance of the comparison of these means is detailed in table II. From these data it can be seen that the action of ketamine was quite different in early and in late pregnancy. In the first trimester it produced an increase in intra-uterine pressure comparable to that produced by ergometrine, whilst at term a decrease in intra-uterine tone was recorded, although this was not statistically significant. Thiopentone and lignocaine induced little change in intra-uterine pressure; the decrease noted in group II, although consistent, was not statistically significant.

Blood loss was measured at termination of pregnancy. The means for each group were 125, 150, 182

TABLE II. Significance of comparison of changes in intra-uterine pressure. TOP = Termination of pregnancy; l.s.c.s. = lower uterine Caesarean section; n.s. = not significant

Groups	<i>t</i>	<i>P</i>
TOP Ketamine v. TOP thiopentone	3.57	<0.01
TOP Ketamine v. ergometrine	1.77	n.s.
TOP Ketamine v. lignocaine	2.72	<0.02
TOP Ketamine v. l.s.c.s. ketamine	2.94	<0.02
TOP Thiopentone v. lignocaine	1.84	n.s.
TOP Thiopentone v. l.s.c.s. thiopentone	0.81	n.s.
TOP Thiopentone v. ergometrine	3.90	<0.01
TOP Thiopentone v. ergometrine + ketamine	5.26	<0.001
L.s.c.s. ketamine v. l.s.c.s. thiopentone	0.50	n.s.

and 75 ml respectively. Because of inaccuracies inherent in estimations not employing a "washing machine" technique and the difficulties in allowing for fetal and liquor volume, these differences were not subjected to statistical analysis.

No patient reported unpleasant dreams or exhibited disturbed behaviour patterns in the recovery period. This is in keeping with our experience when using lorazepam plus droperidol as a premedicant.

#### DISCUSSION

Simpson and colleagues (1974) reported no increase in peripheral oxytocin concentrations during the administration of ketamine, which suggests that its action is not mediated by oxytocin. Furthermore, they found that pharmacological concentrations of ketamine were not associated with contraction of the isolated pregnant uterine muscle strips, although these did respond to noradrenaline. In this study we found that, after a pressure plateau had been attained following the administration of ergometrine, there was a further, and equal, increase in intra-uterine pressure with the subsequent injection of ketamine. Therefore, uterine muscle was not stimulated maximally by ergometrine 0.5 mg and was capable of further contraction.

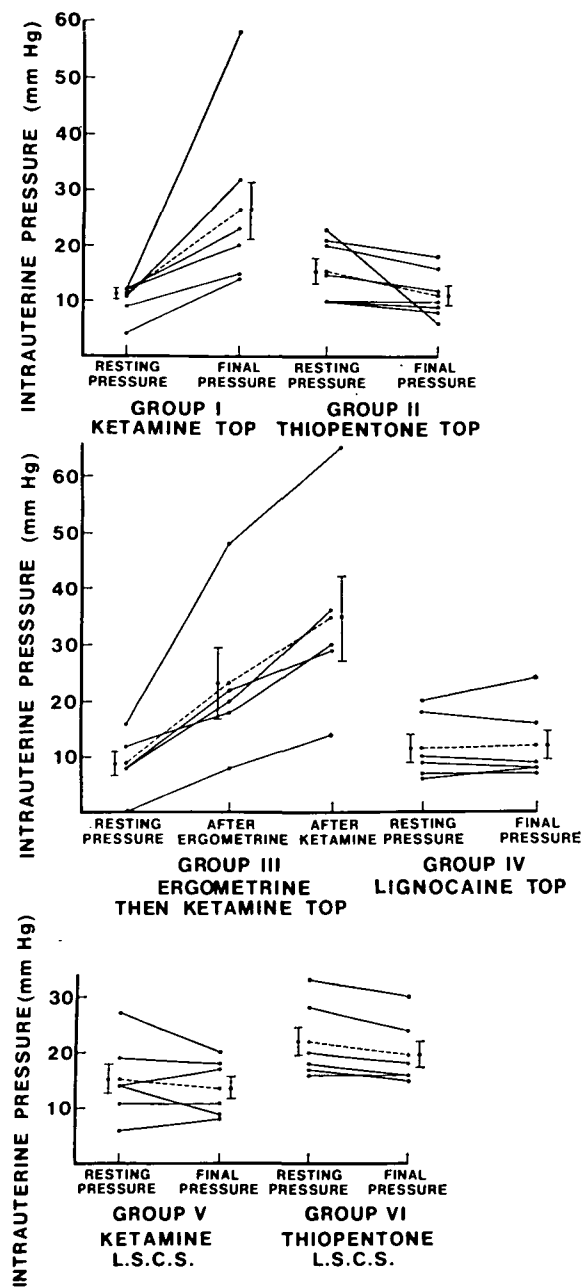


FIG. 1. Changes in intra-uterine pressure following drug administration. — = individual patients; - - - - = mean change; I = SEM; TOP = termination of pregnancy; L.s.c.s. = lower segment Caesarean section.

The response of the human myometrium to oxytocin changes markedly during pregnancy. It is

resistant to its action except in very great concentrations until the onset of labour when there is a rapid increase in sensitivity (Theobald, Robards and Suter, 1969). The reaction of uterine muscle to ketamine is quite different, suggesting that this action is not mediated by oxytocin.

Unlike ketamine, prostaglandins  $E_2$  and  $F_{2\alpha}$  have a relatively uniform effect on uterine muscle throughout pregnancy. This would indicate that ketamine does not act directly through the release of prostaglandin or, if it does, its action is modified considerably by other hormonal changes.

Ketamine has been shown by Unni and Bovill (1972) to release both noradrenaline and adrenaline. Human myometrium contains  $\alpha$ - and  $\beta$ -adrenergic receptors, the former being stimulatory and the latter inhibitory to uterine contraction. The fact that adrenergic nerve terminals decrease in number in late pregnancy (Klopper and Gardner 1973) could explain, at least in part, the decreased sensitivity of uterine muscle to ketamine in late pregnancy.

The contraction of the uterine muscle produced by ketamine in the first and probably second trimester (Galloon, 1973) is ideal from an operative point of view, as it enables safe curettage and decreases blood loss. The lack of response at term means that uterine blood flow and thus fetoplacental exchange is not diminished.

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## EFFETS DE LA KETAMINE SUR L'UTERUS GRAVIDE

### RESUME

La pression intra-utérine a été enregistrée en plaçant un cathéter de Foley dans l'espace extra-amniotique, avant la fin de la grossesse de 25 personnes et avant de procéder à une opération césarienne sur 12 autres. Les effets de l'administration par voie i.v. de kétamine à raison de 2 mg par kg du poids du corps, de thiopentone de sodium à raison de 4 mg kg<sup>-1</sup> et d'ergométrine sur la base de 0,5 mg, et de xylocaïne 20 ml à 0,5% par voie intra-cervicale ont été mesurés au cours du premier trimestre de la grossesse. Les effets de la kétamine et du thiopentone de sodium administrés par voie i.v. ont été évalués vers la fin de la grossesse. On a trouvé que la kétamine produisait des contractions utérines au début de la grossesse (augmentation moyenne de 16,1 mm Hg) égales à celles produites par l'ergométrine (augmentation moyenne 14,8 mm Hg), mais n'avait aucun effet vers la fin de la grossesse (diminution moyenne -1,33 mm Hg). La xylocaïne administrée comme blocage paracervical en début de grossesse n'avait aucun effet significatif sur la pression intra-utérine (augmentation moyenne 0,33 mm Hg). Le thiopentone de sodium administré en fin de grossesse n'a eu aucun effet significatif sur la pression intra-utérine (diminution moyenne -4,28 mm Hg lors du premier trimestre de grossesse et -2,22 mm Hg à terme).

## WIRKUNGEN VON KETAMIN AUF DEN SCHWANGEREN UTERUS

### ZUSAMMENFASSUNG

Intrauteriner Druck wurde durch Einführung eines Foley-Katheters in den äusseren Amnionraum von 25 Patientinnen unmittelbar vor der Schwangerschaftsunterbrechung eingeführt, und bei 12 Patientinnen mit Kaiserschnitt. Die Wirkungen von 2 mg kg<sup>-1</sup> Körpergewicht Ketamin intravenös, von 0,5 mg Ergometrin und von 0,5% Xylocain 20 ml, intrazervikal wurden im ersten Trimester der

Schwangerschaft gemessen, die von intravenösem ketamin und sodium thiopenton bei späteren Schwangerschaftsstadien. Ketamin bewirkte Uteruskontraktion (mittlerer Anstieg 16,1 mm Hg) gleich wie ergometrin (mittlerer Anstieg 14,8 mm Hg) in der frühen Schwangerschaft, hatte aber keine Wirkung (mittlerer Abstieg 1,33 mm Hg) in der späteren Schwangerschaft. Als parazervikale Blockierung bei früher Schwangerschaft verabreichtes Xylocain hatte keine Auswirkung auf den intrauterinen Druck (mittlerer Anstieg 0,33 mm Hg). Sodium thiopenton (mittlerer Abstieg -4,28 mm Hg erstes Trimester und -2,22 mm Hg später) hatte in der späteren Schwangerschaft ebenfalls keinen wesentlichen Einfluss auf den intrauterinen Druck.

## EFFECTOS DE LA QUETAMINA SOBRE EL UTERO EMBARAZADO

### SUMARIO

Se registró la presión intra-uterina en 25 pacientes antes del término del embarazo y en 12 pacientes antes de la operación cesárea, al colocarles una sonda de Foley en el espacio extra-amniótico. Los efectos de la administración i.v. de 2 mg kg<sup>-1</sup> peso corporal de quetamina, de 4 mg kg<sup>-1</sup> peso corporal de tiopentona sódica y de 0,5 mg de ergometrina, así como de xilocaina al 0,5% 20 ml intra-cervical fueron medidos en el primer trimestre del embarazo, y los de la quetamina y tiopentona sódica i.v. en la última parte del mismo. Se estableció que la quetamina ocasionaba contracciones uterinas (aumento medio 16,1 mm Hg) iguales a las de la ergometrina (aumento medio 14,8 mm Hg) en la primera parte del embarazo, pero no tenía ningún efecto (aumento medio -1,33 mm Hg) en la última parte del mismo. La xilocaina administrada como bloque paracervical en la primera parte del embarazo no tenía efectos significativos algunos en la presión intra-uterina (aumento medio 0,33 mm Hg). La tiopentona sódica (aumento medio -4,28 mm Hg en el primer trimestre y -2,22 mm Hg al término) no tenía ningún efecto significativo en la presión intra-uterina en la última parte del embarazo.