Effect of Pethidine on the Contractility of Myometrial Strips from Human Term Gravid Uterus in Vitro

Manee Rattanachaiyanont MD,
Supatra Lohsiriwat MD,
Winyarat Tansiri MD.

Department of Physiology,
Faculty of Medicine Siriraj Hospital,
Mahidol University, Bangkok 10700, Thailand

Abstract: *The effect of pethidine on the contractility of myometrial strips was studied in vitro. Myometrial strips were taken from the lower segment of 32 term parturients, undergoing low transverse caesarean section at Siriraj Hospital. Nine parturients were excluded from the study because their myometrial strips showed no spontaneous contraction in vitro. Of the 23 parturients with active strips, 10 were in latent phase and 13 were in active phase. The myometrial specimen from each parturient was divided into 2-6 small strips of equal size which were then randomly used as either control or experimental strips. The pattern of isotonic contraction was studied. In comparison with the time-matched control, pethidine in therapeutic concentrations (0.25, 1, and 4 μg/ml) did not exert any effect on the amplitude and period of myometrial contraction. However, at the extra-high concentration of 40 μg/ml, which was 160 times greater than the therapeutic serum level, pethidine lowered the amplitude or strength of myometrial contraction in the active phase group, while the period of contraction was shortened in both the active and latent phase groups. Further study is suggested to confirm these effects in vivo. (Thai J Obstet Gynaecol 1992; 4: 1-6.)*

Key words: pethidine, myometrial contraction, in vitro

Pethidine, a morphine derivative, has long been used as an obstetric analgesic. Its effect on the uterine contractility became a point of interest in 1943 when Gilbert and Dixon[1] observed that pethidine shortened the course of labour. Despite the fact that many investigators have reported the effect of pethidine on the uterine or the myometrial contractility, the results still remain inconclusive. The results may be enhancement, inhibition or no effect at all[2-11]. The controversy based on several different factors, such as study design, dosage of pethidine, route of drug administration, contamination with other agents, condition of the subjects, data and parameters analysis, etc.[12-13].

The objective of this study is

to investigate the direct effect of pethidine on the myometrial strips from the lower segment of human term gravid uterus, *in vitro.*

Materials and Methods

Informed consents were obtained from 32 term gravidas (37-42 weeks of gestation). Unfortunately 9 parturients were excluded afterwards because their myometrial stips showed no spontaneous contraction *in vitro.* Among the 23 parturients who fulfilled our experimental criteria, 10 were in latent phase and thirteen in active phase of labour. None had previously scarred uterus. None received any drugs potentially effecting uterine contractility within 24 hours before operation. These women underwent caesarean section under epidural anaesthesia in the Department of Obstetrics and Gynaecology at the Faculty of Medicine Siriraj Hospital, Mahidol University, from January to December 1989.

A small segment of uterus was excised from the upper margin of the uterine incision during low transverse caesarean delivery. The tissue was rapidly immersed in Kreb's solution[14], then delivered to the laboratory to be immediately tested or stored at 4° C over night and tested the next day.

In general, each uterine specimen was divided into 2-6 small strips, approximately 10x5x2 mm in size. These myometrial strips were dissected in such a way that the long axis of collagen fiber oriented parallel to the long axis of the strips. One end of each strip was anchored to a L-shaped glass rod in a 25 ml smooth muscle chamber containing Kreb's solution at 37° C, pH 7.35-7.45, continuously gassed with 95% O_2 and 5% CO_2, the other end was suspended to a displacement transducer (Myograph type A:NARCO Bio-system, part No. 705-0001) which transformed mechanical events to electrical impulses then transferred the impulses to a physiograph (NARCO Bio-system : amplifier type 7070, part No. 7160038). The experimental sets were left not more than 3 hours for the regular pattern of isotonic contraction to be detected. Any strips without spontaneous contraction within 3 hours were discarded. The active strips were randomly taken as either a control or experimental strip. In this study the control strip was called "time-matched control" because it was compared simultaneously with the experimental strip.

The baseline contractions were observed for 30 minutes then the interventions were performed. One hundred microliters of distilled water was added to the control chamber. At the same moment, 100 microliters of diluted pethidine was added to the experimental chamber. The contractions were observed for another 30 minutes then the tracing of myogram was obtained for analysis.

The tracings were sent to an assistant for data measurement to prevent observational bias. The parameters of contraction analysed in this

study were the amplitude and the period. A period of contraction was defined as the time - interval between the beginning of a contraction of interest and the beginning of a previous contraction[14]. A period of contraction represents a reverse assessment of frequency within a brief period of time. The contractility changes were presented in ratio between the value of parameters which averaged 30 minutes after the intervention (AF) to those before the intervention (BE), or AF/BE. The difference between AF/BE of the experimental strips and that of the control strips was assessed by Wilcoxon signed rank test. The *p value* of less than 0.05 was considered to represent a significant difference.

Results

The characters of the 23 parturients including age, length of gestation, gravidity, parity, number of abortion and indications for caesarean section are presented in Table 1. The pattern of contraction before the intervention was represented by the period averaged for 30 minutes before intervention as shown in Table 2. In the latent group, the average period of control strips was 10.70 ± 6.08 minutes and that of the experimental strips was 12.00 ± 7.78 minutes. In the active group, they were 11.92 ± 7.72 minutes and 11.75 ± 6.02 minutes respectively. The data, as tested by Wilcoxon signed rank test, demonstrated that the pattern of contraction before any intervention was the same in the control and in the experimental groups.

Table 1 Characters of the 23 parturients

Characters	Mean	SD
Age (yr)	24.30	3.98
GA (wk)	39.65	1.68
Gravida	1.52	0.93
Para	0.22	0.51
Abortion	0.35	0.36
Indications for C/S		n
Breech		18
Fetal distress		3
Placenta previa		2

Table 2 Patterns of the contraction before intervention

Groups	Period (minutes)			p
	n	Mean	SD	
Latent				0.1827
Control	24	10.70	6.08	
Experiment	24	12.00	7.78	
Active				0.3934
Control	35	11.92	7.27	
Experiment	35	11.57	6.02	

The effects of pethidine on the contractility of myometrial strips are shown in Table 3. In comparison with the time-matched control, therapeutic dose of pethidine, e.g. the concentration of 0.25, 1 and 4 μg/ml (22, 23), did not exert any effect on amplitude and period in the latent group. Similar results were obtained in the active group except at the dosage of 4 μg/ml

where the period was slightly decreased. However, at the extra-high concentration of 40 μg/ml, which was 160 times greater than the therapuetic serum level, pethidine lowered the amplitude or strength of myometrial contraction in the active phase group, while the period of contraction was shortened in both the active and latent phases groups.

Discussion

From this *in vitro* study, it was illustrated that pethidine in a therapuetic dosage did not exert any marked direct effect on both the period and amplitude of contraction of the myometrial strips from the lower uterine segment. The effects on the strips from latent and active phase parturients were similar. This finding contrasted to those of many recent studies, both *in vivo* and *in vitro*, which reported the enhancement effect trend[2-8].

It is difficult to interpret those

Table 3 Ratio of the parameters after intervention (AF) to the parameters before intervention (BE)

Group	Pethidine		AF/BE						
Active	dose		Control		Experiment		Difference		p
	(μg/ml)	n	Mean	SD	Mean	SD	Mean	SD	
Amplitude	0.25	11	1.01	0.15	1.01	0.20	0.00	0.26	0.4646
	1.00	9	1.00	0.17	1.11	0.29	0.11	0.35	0.1871
	4.00	7	0.93	0.13	0.92	0.27	-0.01	0.34	0.4329
	40.00	8	0.91	0.09	0.72	0.06	-0.20	0.14	0.0086
Period	0.25	11	1.08	0.41	1.23	0.40	0.15	0.66	0.1870
	1.00	9	1.00	0.13	1.17	0.46	0.17	0.45	0.3392
	4.00	7	1.06	0.10	0.94	0.12	-0.13	0.18	0.1455
	40.00	8	1.00	0.11	0.74	0.24	-0.27	0.31	0.0178
Group	**Pethidine**		**AF/BE**						
Latent	**dose**		**Control**		**Experiment**		**Difference**		**P**
	(μg/ml)	**n**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Amplitude	0.25	6	0.94	0.26	1.02	0.15	0.08	0.24	0.2315
	1.00	8	0.97	0.32	1.01	0.32	0.04	0.58	0.4443
	4.00	6	0.96	0.12	1.04	0.18	0.08	0.10	0.1727
	40.00	4	0.87	0.20	0.68	0.17	-0.19	0.24	0.0721
Period	0.25	6	1.12	0.45	1.08	0.26	-0.04	0.28	0.3766
	1.00	8	1.03	0.40	0.13	0.36	0.11	0.35	0.1313
	4.00	6	1.19	0.34	1.15	0.50	-0.04	0.46	0.3766
	40.00	4	1.08	0.36	0.61	0.08	-0.48	0.32	0.0339

in vivo studies because many conditions effecting uterine contractility may act as confounding factors. Example of these factors are gestational length, point of labour, status of membranes, drug dosage, and route of administration. Besides, research protocols such as condition of control and methods of result measurement and analyses have to be considered[12-13].

Among *in vitro* studies[9-10], this research possessed two major differences from others. They were the subjects (human vs. animal) and the concentrations of pethidine (therapuetic vs. very high level). The concentrations used in this study were more reasonable because these levels could be found in the serum of parturients receiving a therapuetic dose of pethidine[15].

Although considerable factors and environment can be controlled *in vitro*[16] and the accuracy of the results may be improved, these results can not be extrapolated to *in vivo*. Pethidine, *in vivo*, may indirectly effect the uterine contractility by its action on the neuro-endocrine system[3-5]. Thus, further *in vivo* studies are still necessary to confirm this *in vitro* finding. The appropriate study design, e.g. double-blind randomized control trial, is preferred to those of previous reports but the ethic is also a matter of concern.

From this *in vitro* study, pethidine in the therapuetic dosage did not exert any marked direct effect on either amplitude or period of contraction of myometrial strips from lower uterine segment. In extra-high concentration, pethidine reduced the strength of meometrial contraction but increased its frequency.

Acknowledgement

The authors would like to thank Assoc. Prof. Dr. Pachara Visutkul, Head of the Department of Physiology and Prof. Dr. Suporn Koetsawang, Head of the Department of Obstetrics and Gynaecology for their kindness in supplying the necessary materials used in this study, and to Prof. Dr. Sommai Toongsuwan for his valuable comments.

References

1. Gilbert G, Dixon AB. Observations on demerol as an obstetric analgesia. Am J Obstet Gynecol 1943;45:320-9.
2. Sica-Blanco Y, Rozana H, Remedis MR. Effects of meperidine on uterine contractility. Am J Obstet Gynecol 1967;97:1096-100.
3. Filler WW, Hall WC, Filler NW. Analgesia in obstetrics: The effect of analgesia on uterine contractility and fetal heart rate. Am J Obstet Gynecol 1967;98:832-46.
4. DeVoe SJ, DeVoe K Jr, Rigsby WC, McDaniels BA. Effect of meperidine on uterine contractility. Am J Obstet Gynecol 1969;105:1004-7.
5. Riffel HD, Nochimson DJ, Paul RH, Hon EHG. Effect of meperidine and promethazine during labor. Obstet Gynecol 1973;42: 738-50.
6. Ballas S, Toaff ME, Toaff R. Effect of intravenous meperidine and meperidine with promethazine on uterine activity and fetal heart rate during labor. Isr J Med Sci 1976;12:1141-7.
7. Bergman A, Eckstein N, Yedwab G,

David MP. Fetal distress due to intravenous administration of pethidine (meperidine) with promethazine during labor. Aust NZ J Obstet Gynaecol 1982;22:215-7.

8. Fazackerley J, Pleuvry BJ. Stimulant action of pethidine on the pregnant rat uterus in vitro. J Pharm Pharmacol 1987;39:491-2.
9. Petrie RH, Wu R, Miller FC, et al. The effect of drugs on uterine activity. Obstet Gynecol 1976;48:431-41.
10. Talbert LM, McGauhey HS Jr, Corey EL, Thornton WN Jr. Effects of anesthetic and sedative agents commonly employed in obstetric practice on isolated human uterine muscle. Am J Obstet Gynecol 1958;75:16-22.
11. Eskes TKAB. Effects of meperidine upon uterine contractility in late pregnancy. Am J Obstet Gynecol 1962;84:281-9.
12. Mitchell MD, Flint APE, Ribby J, et al. Rapid increases in plasma prostaglandin concentrations after vaginal examination and amniotomy. Br Med J 1977;2:1183-5.
13. Spielmen FJ. Systemic analgesics during labour. Clin Obstet Gynecol 1987;30:495-504.
14. Bird LM, Anderson NC Jr. Chandler ML, Young RC. The effects of aminophylline and nifedipine on contractility of isolated pregnant human myometrium. Am J Obstet Gynecol 1987;157:171-7.
15. Kuhnert BR, Kuhnert PR, Tu AS, et al. Meperidine and normeperidine levels following meperidine administration during labor:I mother. Am J Obstet Gynecol 1979;133:904-8.
16. Di-Tommaso M, D' Alessandro A, Farruggia A, Branconi F. In vitro study on isolated tissues : application to perinatology. Biol Res Pregnancy Perinator 1986;7:111-2.