Atrial natriuretic factor (ANF) after laparoscopy and morphine application for pain therapy

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Summary

Objective: ANF is a potent diuretic, natriuretic and vasorelaxant hormone. The objective of the present study was to examine the effect of opioid receptor stimulation by morphine on endogenous ANF production and diuresis after surgery.

Methods: Prospectively, nine women undergoing surgery for either uterine leiomyomas, chronic pelvic discomfort or desire for definitive contraception by laparoscopy were evaluated. Venous samples were collected at fixed times. Concentrations of ANF were measured by commercially available radioimmunassay test kits. Statistical analysis was performed by the Friedman Two-way ANOVA, Kruskal-Wallis 1-way ANOVA and Mann-Whitney U-Wilcoxon Rank Sum W Test. The level of significance was set at a probability below 0.05.

Results: There were no statistically significant changes in serum levels of ANF ($p=0.98$), in diastolic blood pressure ($p=0.14$) or pain score ($p=0.86$) after surgery. Systolic blood pressure ($p=0.0032$), pulse rate ($p=0.019$) and urinary flow rate ($p<0.0001$) showed significant changes during observation.

Conclusion: Our results show that i.v. administered morphine induces a potent diuretic effect via activation of opioid receptors but it can not be suggested that this effect is due to an enhanced release of ANF.

Key words: Morphine; Laparoscopy; Pain Therapy; ANF; Stress.

Introduction

Great interest has been focused on the relationships between endogenous opioids and the cardiovascular and renal systems. The ability of morphine to alter urine flow rate has been observed in several species and its antidiuretic effect – particularly in high doses – is well documented. Vasopressin release, altered adrenal cortical function, the involvement of the sympathetic and parasympathetic nervous systems and several other mechanisms have been proposed to explain the antidiuretic effect. Morphine has also been shown to produce significant diuresis. So far, no mechanism has been proposed to explain the diuretic effect except the fact that morphine is one of the most potent stimuli of ANF release [1]. ANF is a potent diuretic, natriuretic and vasorelaxant hormone [2]. The objective of this present study was to examine the effect of opioid receptor stimulation by morphine on endogenous ANF production and diuresis after surgery.

Patients and Methods

Prospectively, nine women undergoing surgery for either uterine leiomyomas, chronic pelvic discomfort or desire for definitive laparoscopy were evaluated. All patients were healthy, free of intercurrent disease, without endocrine disorders; none of them received drugs before this study. All patients received premedication with either dikaliumclorazepat (20 - 30 mg) or flunitrazepam (1 - 1.5 mg) at 7 a.m. before surgery was started. The operations were started approximately at the same time between 8:00 and 8:30 a.m., to avoid influence of the circadian rhythm. The anesthetic procedure was similar in the two groups. Anesthesia was maintained as total intravenous anesthesia (TIVA) with nitrogene oxide (N_2O) and oxygene (O_2) 2:1 minimal alveolar concentration (MAC); further N_2O/O_2 administration was tailored to the surgical stimulation on the basis of the patient's response in terms of heart rate and blood pressure. Laparoscopy was performed by using a transumbilical 10-mm laparoscope and two 5-mm canulas that were introduced suprapubically as accessory instruments (Karl Storz GmbH, Tuttlingen, Germany). Laparoscopic surgery was performed according to accepted techniques. Postoperative analgesia with morphine 0.15 mg/kg intravenously was administered to all women directly after surgery. No additional analgesia was performed during the study. Pain scores were measured by using the visual analogue scale (VAS; 0=no pain, 10=most pain) as described previously [3]. Venous samples were collected at fixed times as demonstrated in Table 1. Concentrations of ANF were measured by commercially available radioimmunassay test kits. Statistical analysis was performed by the Friedman Two-way ANOVA, Kruskal-Wallis 1-way ANOVA and Mann-Whitney U-Wilcoxon Rank Sum W Test. The level of significance was set at a probability below 0.05.

Results

There were no statistically significant changes in serum levels of ANF ($p=0.98$), in diastolic blood pressure ($p=0.14$) or pain score ($p=0.86$) after surgery. Systolic blood pressure ($p=0.0032$), pulse rate ($p=0.019$) and urinary flow rate ($p<0.0001$) showed significant changes during observation (see Tables 2-4).

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Table 1. — *Design of the study.*

Time of collecting samples	Sample	Clinical parameter
T0: end of the operation	ANF	RRD, RRS, P, PSC, U
AM: application of morphine		
T1: 5 minutes after application	ANF	RRD, RRS, P, PSC, U
T2: 10 minutes after application	ANF	RRD, RRS, P, PSC, U
T3: 20 minutes after application	ANF	RRD, RRS, P, PSC, U
T4: 30 minutes after application	ANF	RRD, RRS, P, PSC, U
T5: 45 minutes after application	ANF	RRD, RRS, P, PSC, U
T6: 60 minutes after application	ANF	RRD, RRS, P, PSC, U
T7: 90 minutes after application	ANF	RRD, RRS, P, PSC, U
T8: 120 minutes after application	ANF	RRD, RRS, P, PSC, U

ANF: atrial natriuretic factor, RRD: diastolic blood pressure, RRS: systolic blood pressure, P: pulse rate, PSC: pain score, U: urinary flow rate.

Table 2. — *Patient characteristics.*

	Laparoscopy
Mean (± SD) age (years):	37.2 (28 - 62)
Mean (± SD) body weight (kg):	65.4 (51 - 90)
Mean (± SD) operating time (min.):	23.6 (16 - 31)

Table 3. — *Plasma values (pg/ml) of ANF.*

	Laparoscopy
T0	167.86 (SD: ± 68.36)
T1	172.29 (SD: ± 62.68)
T2	179.00 (SD: ± 78.94)
T3	173.43 (SD: ± 64.62)
T4	170.43 (SD: ± 37.93)
T5	172.50 (SD: ± 63.19)
T6	173.67 (SD: ± 58.26)
T7	137.00 (SD: ± 54.11)
T8	175.14 (SD: ± 82.91)

p=0.9831
(Kruskal-Wallis 1-way ANOVA)

Discussion

The results of the present study show that a significant diuresis is caused after the application of morphine i.v.. This increase in urine volume is not preceded by increased levels of circulating ANF, a known potent diuretic and natriuretic substance, while only slight changes in systolic blood pressure are observed, indicating that circulating ANF does not seem to be involved in changes of urinary flow after application of morphine.

Great interest has been focused on the relationships between opioids and the cardiovascular and renal systems. The ability of morphine to alter urine flow rate has been described previously in several studies [4]. The antidiuretic effect of morphine is well documented [5] and is particularly manifested when morphine is administered in high doses or in volume expanded humans [6, 7], vasopressin release [8], altered adrenal cortical function [9], and the involvement of the sympathetic and parasympathetic nervous systems [10].

Systemically administered morphine has also been shown to produce significant diuresis [11, 12], however the mechanisms through which this effect is mediated are unclear. Previous studies have shown that less than 1% of a parenterally administered dose crosses the blood barrier [13, 14]. Furthermore, stimulation of opioid receptors within the central nervous system by drugs such as clonidine or morphine produce a marked release of ANF [1, 15-19]. Therefore it has been hypothesized that this diuretic effect of morphine is due to the enhanced release of ANF, a potent diuretic, natriuretic and vasorelaxant hormone [2]. Because morphine crosses the blood-brain barrier [13, 14] it is conceivable that the actions of systemically administered morphine could be mediated through central nervous system opioid receptors.

The consensus exists that the most important stimulus for ANF release is the activation of stretch receptors within the atria of the heart. The results of the present study however demonstrate that stimulated opioid receptors may induce ANF release without hemodynamic changes. This observation together with the findings of previous studies that showed that opioids fail to reduce ANF release directly from the atria [20] suggest that regulation of ANF release is complex. Thus for example, morphine could increase sympatho-adrenomedullary and elevate plasma catecholamines, which subsequently could stimulate ANF release. Although the effect of selective ß-agonists on ANF release is a matter of controversy, the majority of evidence indicate that ß-receptors are involved in the release of ANF from the atria [21-23]. Another hypothetical mechanism is the activation of the reninangiotensin system by morphine with a consequent increase of plasma ANF-values caused by angiotensin II [24, 25].

In summary, our results show that i.v. administered morphine induces a potent diuretic effect via activation of opioid receptors but it can not be suggested that this effect is due to an enhanced release of ANF.

Table 4. — *Clinical data.*

	RRS (mmHg)	RRD (mmHg)	PSC	P (beats/min.)	U (ml/dT)
T0:	118.33 (SD: ± 11.07)	68.22 (SD: ± 7.31)	1.78 (SD: ± 3.23)	68.11 (SD: ± 9.52)	0.0
T1:	103.33 (SD: ± 7.16)	62.56 (SD: ± 9.67)	0.89 (SD: ± 1.96)	67.33 (SD: ± 10.52)	6.67 (SD: ± 8.31)
T2:	108.89 (SD: ± 13.31)	63.89 (SD: ± 9.66)	0.44 (SD: ± 1.01)	64.89 (SD: ± 13.09)	10.67 (SD: ± 8.87)
T3:	108.44 (SD: ± 12.50)	65.11 (SD: ± 9.36)	0.44 (SD: ± 0.73)	67.67 (SD: ± 12.02)	21.67 (SD: ± 27.47)
T4:	107.22 (SD: ± 7.63)	68.56 (SD: ± 8.11)	0.67 (SD: ± 0.87)	64.22 (SD: ± 8.04)	46.33 (SD: ± 62.65)
T5:	111.56 (SD: ± 10.30)	70.22 (SD: ± 8.83)	0.67 (SD: ± 0.87)	66.33 (SD: ± 11.96)	59.56 (SD: ± 80.09)
T6:	109.22 (SD: ± 11.54)	67.00 (SD: ± 7.98)	0.44 (SD: ± 0.73)	63.67 (SD: ± 11.07)	80.11 (SD: ± 102.69)
T7:	114.56 (SD: ± 12.77)	67.22 (SD: ± 6.94)	0.44 (SD: ± 0.73)	66.89 (SD: ± 10.83)	109.67 (SD: ± 111.63)
T8:	112.00 (SD: ± 9.60)	67.67 (SD: ± 7.65)	0.56 (SD: ± 0.73)	72.00 (SD: ± 14.79)	157.44 (SD: ± 125.64)
	p=0.0032*	p=0.1388*	p=0.8591*	p=0.019*	p<0.0001

References

[1] Ogütman C., Özben T., Sadan G. *et al.*: "Morphine increases plasma immunoreactive atrial natriuretic peptide levels in humans". *Ann. Cli. Biochem.*, 1990, *27*, 21.

[2] Genest J., Cantin M.: "The atrial natriuretic factor: its physiology and biochemistry". *Rev. Physiol. Biochem. Pharmacol.*, 1988, *110*, 1.

[3] Huskinson E. C.: "Visual analogue scales". In Melzack R. ed.: "Pain measurement and assessment". New York, Raven, 1983.

[4] Huidobro F., Diez C., Croxatto R. *et al.*: "Morphine antidiuresis in the rat: biphasic effect of the opiate on the excretion on urine electrolytes". *J. Pharm. Pharmacol.*, 1981, *33*, 815.

[5] Huidobro F., Huidobro-Toro J. P.: "Antidiuretic effect of morphine and vasopressin in morphine tolerant and non tolerant rats differential effect of urine composition". *Eur. J. Pharmacol.*, 1979, *59*, 55.

[6] Stanley T. H., Gray N. H., Biwai A. R. *et al.*: "The effects of high dose morphine and morphine plus nitrous oxid on urinary output in man". *Can. Anaesth. Soc. J.*, 1974, *21*, 379.

[7] Grell S., Christensen J. D., Fjalland B.: "Morphine antidiuresis in conscious rats: contribution of vasopressin and blood pressure". *Acta Pharmacol. Toxicol.*, 1985, *56*, 38.

[8] De Bodo R. D.: "The antidiuretic effect of morphine and its mechanism". *J. Pharmacol. Exp. Ther.*, 1944, *82*, 74.

[9] De Souza E. B., Van Loon G. R.: "D-Ala-Met-enkephalinamide, a potent opioid peptide alters pituitary-adrenocortical secretion in rats". *Endocrinology*, 1982, *111*, 1483.

[10] Ledda F., Mantelli L., Corti V. *et al.*: "Inhibition of the cardiac response to sympathetic nerve stimulation by opioid petides and its potentiation by morphine and methadone". *Eur. J. Pharmacol.*, 1984, *102*, 443.

[11] Inturrisi C. E., May D. G., Fujimoto J. M.: "The diuretic effect of morphine in the chicken". *Eur. J. Pharmacol.*, 1968, *5*, 79.

[12] Marchand C.: "The diuretic and antidiuretic effect of morphine sulfat in rats". *Proc. Soc. Exp. Biol. Med.*, 1970, *133*, 1303.

[13] Miller J. W., Elliot H. W.: "Rat tissue levels of carbon-14-labelled analgetics as related to pharmacological activity". *J. Pharmacol. Exp. Ther.*, 1995, *11*, 283.

[14] Johannesson T., Woods L. A.: "Analgesic action and brain and plasma levels of morphine and codeine in morphine tolerant, codeine tolerant and non-tolerant rats". *Acta Pharmacol. Toxicol.*, 1964, *21*, 381.

[15] Pan L., Gutkowska J.: "Is clonidine-induced diuresis mediated by atrial natriuretic factor?". *Endocrinology*, 1988, *123*, 1259.

[16] Gutkowska J., Racz K., Garcia R. *et al.*: "The morphine effect on plasma ANF". *Eur. J. Pharmacol.*, 1986, *131*, 91.

[17] Vollmar A. M., Arendt R. M., Schulz R.: "The effect of opioids on rat plasma atrial natriuretic peptide". *Eur. J. Pharmacol.*, 1987, *143*, 315.

[18] Crum R. I., Brown R. M.: "Effects of morphine and opioid peptides on plasma levels of atrial natriuretic peptide". *Life Sci.*, 1988, *43*, 851.

[19] Chen M., Lee J., Huang B. S. *et al.*: "Clonidine and morphine increase atrial natriuretic peptide secretion in anesthetized rats". *Proc. Soc. Exp. Biol. Med.*, 1989, *191*, 299.

[20] Ferrari R., Agnoletti G.: "Atrial natriuretic peptide: its mechanism of release from the atrium". *Int. J. Cardiol.*, 1989, *24*, 137.

[21] Garcia R., Lachance D., Thibault G. *et al.*: "Mechanisms of release of atrial natriuretic factor. Effect of chronic administration of alpha and beta adrenergic and cholinergic agonists on plasma and atrial ANF in the rat". *Biochem. Biophys. Res. Commun.*, 1986, *136*, 510.

[22] Gibbs D.: "Beta-adrenergic control of atrial natriuretic factor secretion from dispersed rat atrial myocytes". *Reg. Pept.*, 1987, *19*, 73.

[23] Rankin A. J., Wilson N., Ledsome J. R.: "Influence of isoproterenol on plasma immunoreactive atrial natriuretic peptides and plasma vasopress in the anesthetized rabbit". *Pflüg. Arch.*, 1987, *208*, 124.

[24] Lal J., Atkinson J.: "Involvement of the renin angiotensin system in the dipsogenic effect of morphine". *Arch. Int. Pharmacodyn. Ther.*, 1985, *278*, 273.

[25] Volpe M., Pepino P., Lembo G. *et al.*: "Modulatory role of angiotensin II in the secretion of atrial natriuretic factor in rabbits". *Endocrinology*, 1991, *128*, 2427.

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