Evaluation of the secretion of the atrial natriuretic factor (ANF) after laparotomy

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Summary

Background: 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 after surgery on endogenous ANF production and diuresis.

Methods: Prospectively, 11 women undergoing surgery for either uterine leiomyomas, chronic pelvic discomfort or desire for definitive contraception by laparotomy 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 probability below 0.05.

Results: There were statistically significant changes in the serum levels of ANF ($p=0.0028$), in pain score ($p<0.0001$) and urinary flow rate ($p<0.0001$) after operation, while the diastolic ($p=0.0671$) and systolic ($p=0.0543$) blood pressure showed slightly significant changes.

Conclusion: Our results show that i.v. administered morphine induces a potent diuretic effect via activation of opioid receptors and suggest that this effect is due to the enhanced release of ANF. However the mechanism by which morphine induces the ANF release remains to be evaluated.

Key-words: Morphine; ANF; Laparotomy; Stress.

Introduction

Since the discovery of endogenous opioids, great interest has been focused on the relationship between opioids and the cardiovascular and renal systems in both homeostatic and pathophysiological conditions. 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. Several mechanisms have been proposed to explain the antidiuretic effect including vasopressin release, altered adrenal cortical function and the involvement of the sympathetic and parasympathetic nervous systems. Nevertheless, morphine has also been shown to produce significant diuresis. 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 in animals and in humans [1]. ANF is a potent diuretic, natriuretic and vasorelaxant hormone [2]. The objective of the present study was to examine the effect of opioid receptor stimulation by morphine after surgery on endogenous ANF production and diuresis.

Patients and Methods

Prospectively, 11 women undergoing surgery for either uterine leiomyomas or chronic pelvic discomfort or desire for definitive contraception by laparotomy 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. Anesthesia was maintained as total intravenous anesthesia (TIVA) with nitrogen oxide (N_2O) and oxygen (O_2) 2:1 minimal alveolar concentration (MAC); further $N_20/0_2$ administration was tailored to the surgical stimulation on the basis of the patient's response in terms of heart rate and blood pressure. Postoperative analgesia with morphine 0.15 mg/kg intravenously was administered to all women directly after surgery. No additional analgesia was given 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 probability below 0.05.

Results

There were statistically significant changes in the serum levels of ANF ($p=0.0028$), in pain score ($p<0.0001$) and urinary flow rate ($p<0.0001$) after surgery, while the diastolic ($p=0.0671$) and systolic ($p=0.0543$) blood pressure showed slightly significant changes (see Tables 2-4).

Revised manuscript accepted for publication

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 arte.

Table 2. — *Patient characteristics.*

	Laparotomy
Mean (+/–SD) age (years):	53.4 (35 - 60)
Mean (+/–SD) body weight (kg):	67.7 (52 - 76)
Mean (+/–SD) operating time (mins):	77.0 (49 - 116)

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

	Laparotomy
T0:	184.80 (SD:+/–89.56)
T1:	214.20 (SD:+/–78.34)
T2:	206.50 (SD:+/–71.35)
T3:	238.78 (SD:+/–71.47)
T4:	214.50 (SD:+/–86.76)
T5:	131.75 (SD:+/–57.65)
T6:	133.78 (SD:+/–51.07)
T7:	123.56 (SD:+/–49.59)
T8:	130.89 (SD:+/–68.89)
	p=0.0028

(Kruskal-Wallis 1-way ANOVA)

Discussion

Great interest has been focused on the relationship 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 have been shown [10].

Systemically administered morphine has also been shown to produce significant diuresis [11, 12], however the mechanisms through which this effect is mediated have been 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 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 preceded by increased levels of circulating ANF, a known potent diuretic and natriuretic substance, while only slight changes in blood pressure are observed, indicating that circulating ANF is perhaps involved but not exclusively responsible for changes of urinary flow after application of morphine.

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 stimulation of 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 the sympatho-adrenomedulla and elevate plasma catecholamine, which subsequently could stimulate ANF release. However, effect of selective ß-agonists on ANF-release is a matter of controversy. The majority of evidence indicates that ß-receptors are involved in the release of ANF from the atria [21-23]. Another hypothetical mechanism is the activation of the renin-angiotensin system by morphine with a consequent increase of plasma ANF-values caused by angiotensin II [24, 25].

Table 4. — *Clinical data.*

	RRS (mmHg)	RRD (mmHg)	PSC	P (beats/min)	U (ml/dt)
T0	140.45 (SD:+/–22.06)	82.64 (SD:+/–15.03)	4.00 (SD:+/–2.14)	67.18 (SD:+/–11.19)	0.0
T1	137.27 (SD:+/–24.89)	77.09 (SD:+/–10.32)	3.00 (SD:+/–1.67)	67.36 (SD:+/–10.29)	8.09 (SD:+/–13.00)
T2	132.55 (SD:+/–22.41)	77.00 (SD:+/–8.90)	3.09 (SD:+/–1.51)	67.64 (SD:+/–9.33)	18.09 (SD:+/–19.96)
T3	134.45 (SD:+/–19.70)	77.91 (SD:+/–11.23)	3.27 (SD:+/–1.35)	68.27 (SD:+/–9.00)	35.18 (SD:+/–51.55)
T4	135.82 (SD:+/–20.15)	78.27 (SD:+/–10.66)	3.45 (SD:+/–1.63)	68.27 (SD:+/–10.11)	51.55 (SD:+/–43.05)
T5	132.18 (SD:+/–18.64)	77.09 (SD:+/–9.06)	4.18 (SD:+/–1.94)	68.73 (SD:+/–7.62)	83.18 (SD:+/–73.98)
T6	135.36 (SD:+/–22.34)	78.18 (SD:+/–10.51)	4.73 (SD:+/–2.10)	70.91 (SD:+/–69.64)	118.27 (SD:+/–113.97)
T7	131.00 (SD:+/–16.27)	74.73 (SD:+/–11.17)	5.45 (SD:+/–2.21)	69.64 (SD:+/–8.41)	158.91 (SD:+/–122.18)
T8	128.27 (SD:+/–18.33)	73.00 (SD:+/–11.25)	6.82 (SD:+/–2.09)	73.55 (SD:+/–10.04)	206.27 (SD:+/–156.59)
	p=0.0543*	p=0.0671*	p<0.0001*	p=0.3438*	p<0.0001*

* Friedman Two-way ANOVA

Conclusion

Our results show that i.v. administered morphine induces a potent diuretic effect via activation of opioid receptors and suggest that this effect is due to the enhanced release of ANF. However the mechanism by which morphine induces the ANF release remains to be evaluated.

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