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Endocrine Consequences of Long-Term Intrathecal Administration of Opioids

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ABSTRACT

Intrathecal administration of opioids is a very efficient tool in the long-term control of intractable nonmalignant pain. However, despite the well known role of opioids in endocrine regulation, few data are available about possible effects on hypothalamic-pituitary function during this treatment.

Seventy-three patients (29 men and 44 women; mean age, 49.2 ± 11.7 yr) receiving opioids intrathecally for nonmalignant pain were enrolled for extensive endocrine investigation. At the time of hormonal determination, the mean duration of opioid treatment was 26.6 ± 16.3 months; the mean daily dose of morphine was 4.8 ± 3.2 mg. The control group consisted of 20 patients (11 men and 9 women; mean age, 54.2 ± 14.0 yr) with a comparable pain syndrome but not treated with opioids.

Decreased libido or impotency was present in 23 of 24 men receiving opioids. The serum testosterone level was below 9 nmol/L in 25 of 29 men and was significantly lower than that in the control group ($P < 0.001$). The free androgen index was below normal in 18 of 29 men and was significantly lower than that in the control group ($P < 0.001$). The serum LH level was less than 2 U/L in 20 of 29 men and was significantly lower than that in the control group ($P < 0.001$). Serum FSH was comparable in both groups. Decreased libido was present in 22 of 32 women receiving opioids. All 21 premenopausal females developed either amenorrhea or an irregular menstrual cycle, with ovulation in only 1. Serum LH, estradiol, and progesterone levels were lower in the opioid group. In all 18 postmenopausal females significantly decreased serum LH ($P < 0.001$) and FSH ($P = 0.012$) levels were found. The 24-h urinary free cortisol excretion was below 20 μg/day in 14 of 71 opioid patients and was significantly lower than that in the control group ($P = 0.003$). The peak cortisol response to insulin-induced hypoglycemia was below 180 μg/L in 9 of 61 opioid patients and was significantly lower than that in the nonopioid group ($P = 0.002$). The insulin-like growth factor I SD score was below −2 SD in 12 of 73 opioid patients and was significantly lower than that in the control group ($P = 0.002$). The peak GH response to hypoglycemia was below 3 μg/L in 9 of 62 subjects and was significantly lower than that in the control group ($P = 0.010$). Thyroid function tests and PRL levels were considered normal. No metabolic disturbances were recorded, apart from significantly decreased high density lipoprotein cholesterol levels ($P = 0.041$) and elevated total/high density lipoprotein cholesterol ratio ($P = 0.008$) in the opioid group compared to the control group. Supplementation with gonadal steroids improved sexual function in most patients.

In conclusion, of all patients receiving intrathecal opioids, the large majority of men and all women developed hypogonadotropic hypogonadism, about 15% developed central hypocorticism, and about 15% developed GH deficiency. These findings suggest that further investigations are required to determine the need for systematic endocrine work-up in these patients and the necessity for substitutive therapy. (*J Clin Endocrinol Metab* **85:** 2215–2222, 2000)

CHRONIC NONMALIGNANT pain, persisting more than 6 months, affects 15–30% of the population. The majority of chronic pain patients respond to a combination of physical modalities and nonopioid analgesics. However, approximately 20% of these patients do not derive sufficient pain relief from traditional measures and may benefit from therapy with opioids. The use of opioids, however, has been impeded by concerns about addiction, tolerance, systemic side-effects, high cost, and fear of regulatory action. Fortunately, clinical experience has showed that this apprehension was exaggerated and that opioids can effectively be used over prolonged periods of time without causing addiction or tolerance and without inducing unacceptable side-effects (1, 2). Recently, the intrathecal route has become a popular alternative way of administrating opioids to overcome some disadvantages of the oral form (3, 4). If morphine is given intrathecally, a 30 times lower dose is sufficient to obtain a comparable pain relief to systemic administration. This procedure reduces expenses, as morphine in high doses is rather expensive, even if all costs of the drug delivery system are taken into account (5). There are some indications that patients can obtain more effective pain control from intrathecal treatment, as morphine is supplied directly at the level of the spinal cord (6). Other medications, such as clonidine, nonsteroidal antiinflammatory drugs, neostigmine, ketamine, octreotide, and aspirin, can be added intrathecally to enhance the analgesic effects of morphine (7). By contrast, the hope that the intrathecal administration of opioids would substantially reduce the number of side-effects associated with oral morphine has not been fulfilled (8). Sedation is less pronounced, but pruritus and urinary retention are more frequently seen. Other common side-effects include nausea and vomiting, constipation, and complications due to the

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technicalities of the procedure, such as dislodging, bleeding, leakage, and infection (9).

Despite the fact that opioids are known to control or influence several endocrine pathways (10), no studies have looked systematically for possible hormonal changes induced by long term intrathecal opioid administration. Only one article mentioned a decrease in serum testosterone in six male patients (11). The occurrence of endocrine side-effects, however, may become an important issue if patients with pain of nonmalignant cause, including many young people, are treated for prolonged periods of time. Therefore, we thoroughly studied the endocrine and metabolic status of a large group of patients receiving long-term intrathecal opioids and compared these results to the data obtained from a control group of patients with chronic pain taking nonopioid analgesics.

Subjects and Methods

Patients

A total of 73 patients with a mean age of 49.2 ± 11.7 yr (range, 23–81 yr) were enrolled in this retrospective study. They consisted of 29 males, with a mean age of 48.4 ± 11.0 yr (range, 23–66 yr), and 44 females, with a mean age of 49.8 ± 12.3 yr (range, 27–81 yr). They all suffered intractable pain of nonmalignant origin, which could not be controlled by nonopioid analgesics or oral opioids. They were referred to the different pain clinics for intrathecal opioid therapy. All patients underwent a socioeconomic, psychological, and psychiatric screening before implantation of intrathecal device. Opioid administration was always preceded by a 4-week period of placebo infusion. No patient had been given corticosteroids in any form for a period of less than 1 week during the previous 6 months, and no patient had received corticosteroids for longer than 1 week during the previous year.

The main cause of the pain syndrome was failed back surgery (n = 47). Other causes were chronic pancreatitis, complex region pain syndrome I and II, polyneuritis, neurinoma, spinal stenosis, phantom limb pain, scoliosis, and neck pain. All patients received a disability pension because of the pain syndrome. The type of opioid administered was morphine (n = 68) or hydromorphone (n = 5). Taking into account that hydromorphone is 5 times as potent as morphine (12), the mean daily opioid dose was 4.8 ± 3.2 mg (range, 0.6–15.0). The mean duration of opioid treatment at the time of the analysis was 26.6 ± 16.3 months (range, 3–61). Adverse events related to opioid administration were actively sought, in particular the sexual history. Perception of health was assessed by use of the Nottingham Health Profile (NHP) (13). The items related to pain perception in the NHP were examined separately.

Control population

In all patients, except for two cases, no hormonal data were available before starting intrathecal opioid administration. This was due to the fact that intrathecal opioid therapy had been initiated before possible hormonal side-effects became recognized. To determine whether long-standing severe pain can influence hormonal status, a group of 20 controls (mean age, 55.0 ± 13.0 yr; range, 32–81 yr) with a comparable pain syndrome but not receiving opioid treatment was selected. The group consisted of 11 males with a mean age of 54.2 ± 14.0 yr (range, 37–81 yr) and 9 females with a mean age of 56.0 ± 12.4 yr (range, 32–70 yr). Compared with patients taking opioids, no differences were noted regarding concurrent medical problems, psychological diagnoses, or medication. Pain control by nonopioid analgesics was poor in this group, and patients were considered possible candidates for opioid therapy. The main reason for pain was failed back surgery (n = 18). Other causes were pancreatitis and neck pain. The control group was assessed in an identical way as the opioid group.

Methods

For all patients and controls the following variables were recorded: gender, age, body mass index, waist/hip ratio, and blood pressure. Body composition was measured by bioelectrical impedance analysis, and percentages of fat-free mass, fat mass, and total body water were determined. Bone mineral density (BMD) was measured by dual photon absorptiometry at the level of the fourth and fifth lumbar vertebra and at the femoral neck. Hematological and selected biochemical measurements were determined, inclusive total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides. Low density lipoprotein (LDL) cholesterol was calculated according to the formula: LDL = total cholesterol − HDL − triglycerides/5.

The gonadal axis was evaluated by determining serum estradiol and progesterone in females and by determining serum testosterone and sex hormone-binding globulin (SHBG) and calculating the free androgen index (FAI = testosterone/SHBG) in males. LH and FSH were measured twice with a 15-min interval between measurements, and the lowest value was chosen to avoid a peak due to pulsatile secretion.

Adrenal function was assessed by measuring the 24-h urinary excretion of free cortisol and aldosterone. The pituitary reserve of ACTH and the subsequent adrenal secretion of cortisol were determined during insulin-induced hypoglycemia (0.10–0.15 U/kg BW, iv) by sampling at −15, 0, 15, 30, 45, 60, and 90 min. Cortisol-binding globulin, dehydroepiandrosterone sulfate (DHAS), and PRA were also measured.

Somatotroph function was measured by determining serum insulin-like growth factor I (IGF-I). IGF-I was adapted to age according to the formula: IGF-I SD = (log IGF-I − [5.95 − (0.0197 × age in years])/0.282. The GH reserve was studied during the same insulin tolerance test (ITT) and during an arginine infusion (30 g, iv, over 30 min) and clonidine administration (0.3 mg, orally) by sampling at −15, 0, 15, 30, 45, 60, and 90 min.

Thyroid function was measured by determining serum free T_4, free T_3, and TSH. The pituitary TSH reserve was assessed by the TRH test, consisting of an injection of 200 μg TRH, iv, and measurement of TSH at −15, 0, 15, 30, and 60 min. The PRL response was also measured during the same TRH stimulatory test.

All parameters were measured by commercial RIAs or immunoradiometric assays. Normal values are given in the different tables. An adequate response of cortisol to hypoglycemia was considered when the peak value reached 180 μg/L (14). A normal peak GH response to hypoglycemia was accepted with a value above 10 μg/L, and severe GH deficiency was diagnosed with a value below 3 μg/L (15).

A replacement therapy with hydrocortisone and androgens or estrogens was started depending on the hormonal deficiency. The clinical response to this administration was also assessed.

Informed consent was obtained from each patient before the study, and the study was approved by the ethics committees.

Assays

All determinations were performed using commercial RIA and immunoradiometric assay kits.

The sensitivity of the GH assay (hGHRIA, Pharmacia & Upjohn NV Diagnostics, Brussels, Belgium) was 0.1 μg/L; the interassay coefficient of variation was 5.1% at 0.6 μg/L and 2.9% at 2.1 μg/L; theintraassay coefficient of variation was 5.6% at 0.6 μg/L and 4.3% at 2.1 μg/L.

The sensitivity of the IGF-I assay (SMC, Biosource Technologies, Inc. Europe SA, Fleurus, Belgium) was 9 μg/L; the intraassay coefficient of variation was 6.1% at 54 μg/L and 4.7% at 491 μg/L; the intraassay coefficient of variation was 9.9% at 121 μg/L and 9.3% at 494 μg/L.

The sensitivity of the ACTH assay (ACTH Immunoassay, Nichols Institute Diagnostics, Paris, France) was 0.4 pmol/L; intraassay coefficient of variation was 3.0% at 15 pmol/L and 3.2% at 161 pmol/L; the interassay coefficient of variation was 7.8% at 16 pmol/L and 6.8% at 158 pmol/L. The normal value for plasma ACTH is 4–22 pmol/L.

The sensitivity of the cortisol assay (GammaCoat Cortisol, DiaSorin, Inc. SA, Antony, France) was 6 nmol/L; the intraassay coefficient of variation ranged from 6.6% at 80 nmol/L to 6.8% at 1300 nmol/L; the interassay coefficient of variation was 9% at 102 nmol/L and 8.8% at 1018 nmol/L. The normal value for serum cortisol is 190–660 nmol/L at 0800 h and less than 140 nmol/L at 2400.

The sensitivity of PRL assay (AutoDelfia, Wallac, Inc., Oy, Turku, Finland) was 0.1 μg/L; the intraassay coefficient of variation was 1.2% at 3.2 μg/L and 3.1% at 110 μg/L; the interassay coefficient of variation was 1.9% at 3.2 μg/L and 3.1% at 110 μg/L. The normal value for serum PRL is less than 20 μg/L.

The sensitivity of the TSH assay (AutoDelfia, Wallac, Inc., Oy) was 0.005 mU/L; the intraassay coefficient of variation was 11.6% at 0.05 mU/L and 2.8% at 17.7 mU/L; the interassay coefficient of variation was 5.8% at 0.05 mU/L and 2.4% at 17.8 mU/L. The normal value for serum TSH is 0.15–3.5 mU/L.

Statistics

As summary statistics for the serial measurements, the area under the curve (AUC; expressed by units variable × time unit), baseline and peak values were examined. Differences between groups were tested for significance using Student's *t* test for independent samples or the Mann-Whitney test when appropriate. For paired observations, the Wilcoxon signed rank test was used. Normality was tested by the Shapiro-Wilk test. The proportions among groups were compared by the χ^2 test or Fisher's exact test; paired proportions were compared with the McNemar test. $P < 0.05$ (two-sided) was considered statistically significant.

Results

Clinical characteristics (Table 1)

No differences were found between the opioid group and the control group for following parameters: gender, age, NHP total score, NHP pain score, body mass index, waist/hip ratio, systolic and diastolic blood pressure, fat-free mass, fat mass, and total body water. No differences were apparent when males and females were analyzed separately. Measurement of BMD in 49 opioid-treated patients revealed a z-score of −0.19 ± 1.54 SD (range, −4.17 to 2.40) at the lumbar spine and −0.53 ± 1.46 SD (range, −5.91 to 2.87) at the femoral neck. BMD was not measured in the control group.

Gonadal axis in males (Table 2)

Twenty-five of 26 males from the opioid group retrospectively considered libido as normal before opioid therapy, whereas 9 of 10 control patients had no sexual complaints. Twenty-three of 24 males (95.8%) recorded a rather sudden decrease and even disappearance of libido and potency shortly after initiating opioid administration.

Serum testosterone ($P < 0.001$) and FAI ($P < 0.001$) were significantly lower in the opioid group compared to the control group. Twenty-five of the 29 male opioid patients (86.2%) and 1 control patient showed a serum testosterone level less than 9.0 nmol/L. Eighteen of the 29 male opioid patients (62.1%) and 1 control patient showed a FAI less than 20. There was no difference in serum SHBG between the groups.

The serum LH concentration was significantly lower in the opioid group ($P < 0.001$). Twenty of the 29 male opioid patients (69.0%) and 2 control patients had a LH level less than 2.0 U/L. There was no difference in serum FSH between the groups. Two of the 29 male opioid patients (6.9%) and no control patient had a FSH level less than 2.0 U/L.

Serum LH and testosterone concentrations in the two patients with preopioid determinations were suppressed below normal values within 2 months of the start of intrathecal opioid administration.

TABLE 1. Clinical characteristics of patients receiving opioids long term intrathecally

	Opioid group	Control group	*P*
No.	73	20	
Gender	29M/44F	11M/9F	NS
Age (yr)	49.2 ± 11.7 (23–81)	55.0 ± 13.0 (32–81)	NS
NHP total score	280.8 ± 131.4 (0–555)	305.8 ± 129.8 (73–579)	NS
NHP pain score	62.9 ± 30.9 (0–100)	79.1 ± 22.3 (33–100)	NS
Body mass index (kg/m^2)	27.5 ± 5.7 (17.0–41.3)	27.2 ± 6.8 (16.3–41.2)	NS
Waist/hip ratio	0.89 ± 0.10 (0.70–1.15)	0.88 ± 0.08 (0.75–1.02)	NS
Systolic blood pressure (mm Hg)	126.1 ± 14.1 (100–180)	132.0 ± 14.5 (100–155)	NS
Diastolic blood pressure (mm Hg)	79.8 ± 6.5 (60–100)	80.0 ± 8.9 (60–90)	NS
Fat free mass (kg)	67.6 ± 7.7 (52.3–87.6)	70.0 ± 9.4 (52.6 –84.1)	NS
Fat mass (kg)	29.4 ± 7.7 (12.4–47.7)	30.0 ± 9.4 (15.9–47.4)	NS
Total body water (L)	49.2 ± 6.1 (38.8–70.5)	50.1 ± 8.3 (35.2–61.3)	NS

Values are the mean ± SD.

Gonadal axis in females (Table 2)

Thirty-two of 36 women receiving opioids considered libido as normal before the start of treatment. Libido decreased or disappeared shortly after initiating opioid therapy in 22 of 32 women (68.8%). Four of 5 controls had no sexual complaints.

Of the 21 premenopausal women receiving opioids, 14 became amenorrheic and 7 developed an irregular menstrual cycle, with ovulation in only 1. The 3 premenopausal control women had regular menstrual cycles. Serum LH, FSH, estradiol, and progesterone concentrations were clearly lower in the opioid group than in the control group. However, probably due to the small number of control patients, no significance could be drawn from statistical analysis. Nine of the 21 premenopausal opioid patients (42.9%) and no control patient showed a LH level less than 2 U/L. Five of the 21 premenopausal opioid patients (23.8%) and no control patient showed a FSH level less than 2 U/L.

In the 18 postmenopausal women, serum LH ($P < 0.001$) and FSH ($P = 0.012$) concentrations were significantly lower than those in the 6 postmenopausal control women. All 18 postmenopausal opioid patients (100.0%) and no control patients showed a LH level less than 13 U/L. Sixteen of the 18 postmenopausal opioid patients (88.9%) and 2 control patients showed a FSH level less than 38 U/L.

Adrenal axis (Table 3 and Fig. 1)

A significant lower urinary excretion of free cortisol was found in the opioid group ($P = 0.003$). Moreover, 14 of 71 opioid patients (19.7%) showed a free cortisol excretion less than 20 μg/L, whereas no patient from the control group had decreased cortisoluria.

The basal plasma ACTH concentration, peak ACTH value, and ACTH AUC after ITT were similar in both groups. Nineteen of the 72 opioid patients (26.4%) and 5 of 20 control patients (25.0%) showed a basal ACTH level below 10 ng/L.

TABLE 2. Pituitary-gonadal axis in patients receiving opioids long term intrathecally

	Normal Values	Opioid group	Control group	*P*
Males		n = 29	n = 11	
Testosterone (nmol/L)	9–26	6.9 ± 5.2 (1.4–25.0)	15.4 ± 4.4 (8.3–20.0)	<0.001
Free androgen index	20–80	23.1 ± 20.7 (5–108)	53.3 ± 19.8 (19–83)	<0.001
SHBG (nmol/L)	10–70	36.1 ± 20.9 (12–85)	31.2 ± 8.6 (24–49)	NS
LH (U/L)	2–9	1.7 ± 1.4 (0.1–7.2)	4.3 ± 2.1 (1.3–7.0)	<0.001
FSH (U/L)	2–7	4.7 ± 2.6 (0.3–10.6)	5.7 ± 4.4 (2.4–18.0)	NS
Females		n = 44	n = 9	
Premenopausal females		n = 21	n = 3	
LH (U/L)	2–8	2.7 ± 2.6 (0.1–9.0)	12.4 ± 14.2 (3.8–28.8)	NS
FSH (U/L)	2–8	6.4 ± 5.6 (0.1–26.0)	9.4 ± 9.2 (3.9–20.1)	NS
Estradiol (pmol/L)	110–800	127.0 ± 124.0 (18–437)	383.3 ± 404.6 (84–844)	NS
Progesterone (nmol/L)	3–60	1.6 ± 2.6 (0.3–11.8)	8.6 ± 13.7 (0.3–24.4)	NS
Postmenopausal females		n = 18	n = 6	
LH (U/L)	>13	3.3 ± 3.3 (0.1–9.4)	27.7 ± 14.1 (13.5–46.2)	<0.001
FSH (U/L)	>38	14.6 ± 17.6 (0.5–66.9)	39.8 ± 22.7 (15.9–66.7)	0.012
Estradiol (pmol/L)	<110	100.2 ± 122.6 (18–125)	55.8 ± 33.6 (29–113)	NS
Progesterone (nmol/L)	<3	1.0 ± 0.6 (0.3–1.2)	1.0 ± 0.6 (03–1.9)	NS

Values are the mean ± SD; the range is in *parentheses*.

TABLE 3. Pituitary-adrenal axis in patients receiving opioids long term intrathecally

	Normal values	Opioid group		Control group		*P*
		Mean ± SD	n	Mean ± SD	n	
24-h urinary free cortisol (μg/day)	20–90	36.0 ± 21.0 (7.0–112.0)	71	50.7 ± 18.4 (20.0–89.0)	20	0.003
24-h urinary aldosterone (μg/day)	3–20	8.3 ± 7.7 (0.2–20.6)	72	7.3 ± 5.3 (0.6–17.6)	19	NS
Basal ACTH (ng/L)	10–52	20.1 ± 14.3 (4–83)	72	16.9 ± 8.9 (4–37)	20	NS
Peak ACTH after ITT		193.8 ± 157.3 (18–854)	62	202.1 ± 105.0 (18–401)	18	NS
ACTH AUC after ITT		365.9 ± 316.4 (61–2008.5)	62	357.6 ± 186.7 (54.5–738.5)	18	NS
Basal cortisol (μg/L)	50–250	135.3 ± 53.8 (20–286)	71	160.1 ± 43.9 (81–250)	20	NS
Peak cortisol after ITT		245.4 ± 62.1 (102–417)	61	300.8 ± 73.6 (200–451)	18	0.002
Cortisol AUC after ITT		1146.8 ± 323.3 (425.5–2042.5)	61	1357.4 ± 309.9 (800–1953.5)	18	0.02
CBG (μg/L)	32–50	45.2 ± 14.0 (27–111)	72	47.9 ± 11.4 (28–76)	19	NS
DHAS (μg/L)	<3000	764.2 ± 615.1 (31–2980)	72	562.9 ± 357.7 (103–1470)	19	NS
PRA (ng/L·s)	0.3–1.1	2.1 ± 2.8 (0.0–5.9)	70	1.6 ± 1.5 (0.3–5.8)	19	NS

The basal serum cortisol concentration was statistically not different between the groups. Seven of the 72 opioid patients (9.2%) and no control patients showed a basal cortisol level below 50 μg/L. There was a significant difference in cortisol peak ($P = 0.002$) and cortisol AUC ($P = 0.02$) after ITT. A peak cortisol value below 180 μg/L was not achieved in 9 of 61 opioid patients (14.8%), but this inadequate response was never observed in the control group.

In the opioid group, no correlation was found between a basal ACTH level less than 10 ng/L or a basal cortisol level less than 50 μg/L and a peak cortisol value less than 180 μg/L after ITT. No correlation existed between a basal ACTH

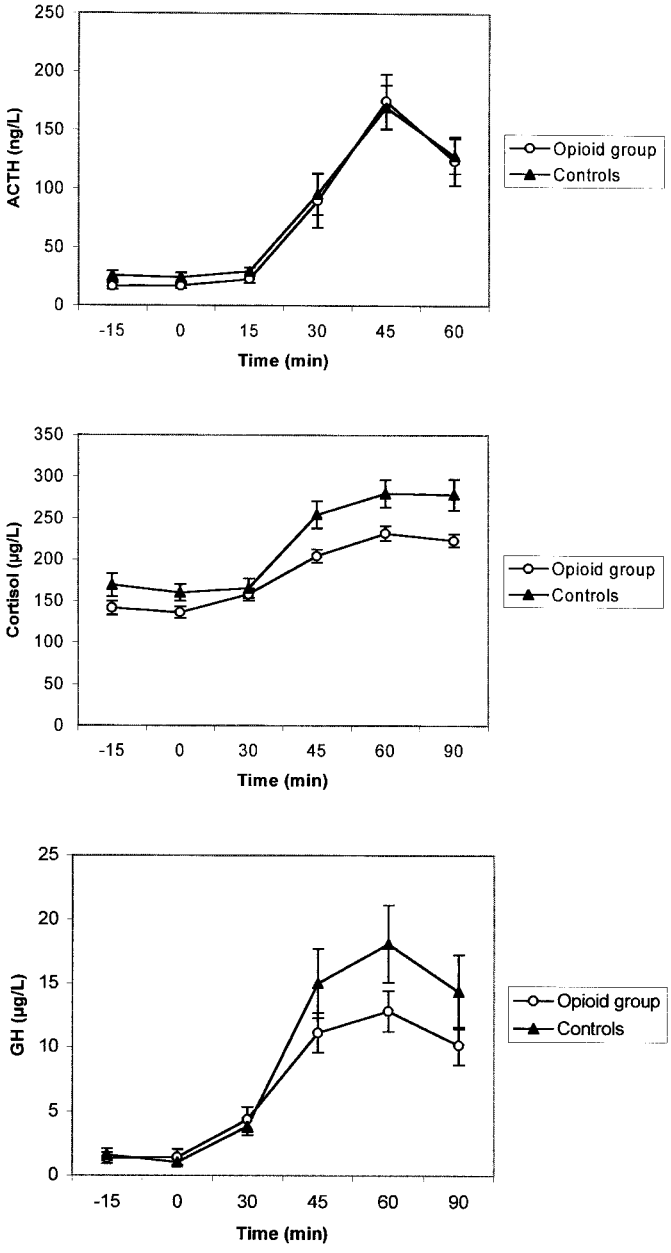

FIG. 1. Evolution of plasma ACTH (*top*), serum cortisol (*middle*), and GH (*bottom*) during an ITT in patients taking intrathecal opioids and in controls.

level less than 10 ng/L and free cortisoluria below 20 μg/day, but the correlation was highly significant between a basal cortisol level less than 50 μg/L and free cortisoluria below 20 μg/day ($P = 0.001$).

No significant difference in serum cortisol-binding globulin and dehydroepiandrosterone sulfate was present between the opioid patients and the controls. Also, no difference in PRA and 24-h urinary excretion of aldosterone was found between the groups.

One patient developed symptomatology of an Addisonian crisis during an episode of important fever due to pneumonia. He recovered uneventfully after supplementation with corticosteroids.

GH-IGF-I axis (Table 4 and Fig. 1)

The basal serum IGF-I concentration ($P = 0.045$) and IGF-I SD score ($P = 0.002$) were significantly lower in the opioid group (n = 72) compared to the control group (n = 20). Twelve opioid patients (16.7%) showed an IGF-I SD score below −2, whereas none of the control group did.

The GH peak ($P = 0.010$) and GH AUC ($P = 0.048$) were significantly lower during ITT in the opioid group (n = 62) compared to the control group (n = 18). Nine opioid patients (14.5%) and no control patient showed a peak GH level below 3 μg/L after ITT. Another 14 opioid patients (22.6%) had a peak GH level less than 10 μg/L, as did 2 control patients (11.1%).

The GH peak and GH AUC during arginine (n = 10) and clonidine (n = 28) administration in the opioid group are given in Table 4.

Other hormonal and biochemical characteristics (Table 5)

The occurrence of any endocrine dysfunction had no relationship with the dose of opioids or the duration of administration.

The combination of hypogonadism (defined as a FAI <20 in men, an irregular menstrual cycle in premenopausal women, a LH level <13 U/L in postmenopausal women), hypocorticism (defined as a free cortisol excretion <20 μg/day or a peak serum cortisol <180 μg/L during ITT) and a GH deficiency (defined as a IGF-I SD score below −2 or a peak serum GH <9 μg/L during ITT) occurred in seven patients (9.6%). Ten patients showed the combination of hypocorticism and GH deficiency.

Serum free T_4, basal TSH, and TRH-stimulated TSH concentrations were not different from those in the control group. Serum free T_3 level was slightly but significantly higher in the opioid group ($P = 0.001$). Basal PRL and TRH-stimulated PRL concentrations were similar in opioid and control groups.

No difference in plasma glucose, serum creatinine, sodium, potassium, and triglycerides were found between the groups. The total cholesterol concentrations were comparable in the 2 groups. Similarly, 42 opioid patients (57.5%) and 9 control patients (50.0%) showed a total cholesterol level above 5.2 mmol/L. High density lipoprotein (HDL) cholesterol was significantly lower in the opioid group ($P = 0.041$). Moreover, 24 opioid patients (32.9%), but only 2 control patients (11.1%), showed a HDL cholesterol level below 0.9 mmol/L. The total/HDL cholesterol ratio was significantly higher in the opioid group ($P = 0.008$). Likewise, 34 opioid patients (46.6%) and 4 control patients (22.2%) showed a ratio above 5. The calculated LDL cholesterol was not different in both groups, whereas 21 opioid patients (29.2%) and 2 control patients (11.1%) had a level above 4.1 mmol/L.

Effect of hormonal replacement therapy

Supplementation with androgens was started in 14 hypogonadotropic males and resulted in a significant amelioration of libido in 10 cases. Estrogens and progestagens were supplemented in 12 premenopausal females, and this improved libido in 7 of them. Replacement therapy with hy-

TABLE 4. GH-IGF-I axis in patients receiving opioids long term intrathecally

	Opioid group		Control group		*P*
	Mean ± SD (range)	n	Mean ± SD (range)	n	
IGF-I (μg/L)	138.5 ± 64.1 (33–321)	72	162.0 ± 55.3 (70–270)	20	0.045
IGF-I SD score	−0.53 ± 1.45 (−5.28–2.39)	72	0.57 ± 1.00 (−1.49–2.66)	20	0.002
GH peak (μg/L) after ITT	14.5 ± 12.7 (0.1–58.3)	62	20.9 ± 11.5 (3.3–46.7)	18	0.010
GH AUC (μg/L) after ITT	47.0 ± 49.1 (0.8–266.0)	62	63.3 ± 42.0 (10.7–169.4)	18	0.048
GH peak (μg/L) after arginine	6.4 ± 5.1 (0.5–14.7)	10			
GH AUC (μg/L) after arginine	16.9 ± 12.5 (1.4–39.9)	10			
GH peak (μg/L) after clonidine	2.6 ± 3.1 (0.1–13.7)	28			
GH AUC (μg/L) after clonidine	7.7 ± 11.6 (0.8–59.4)	28			

TABLE 5. Pituitary-thyroid axis, PRL, and selected biochemical measures in patients receiving opioids long term intraspinally

	Normal values	Opioid group		Control group		*P*
		Mean ± SD (range)	n	Mean ± SD (range)	n	
fT_4 (pmol/L)	11.0–24.0	15.4 ± 2.6 (9.7–21.4)	72	15.9 ± 3.1 (11.3–24.5)	20	NS
fT_3 (pmol/L)	3.4–7.2	5.2 ± 0.7 (3.8–7.4)	70	4.6 ± 0.7 (3.8–6.3)	20	0.001
TSH (mU/L)	0.4–3.2	1.5 ± 0.9 (0.1–4.6)	72	1.2 ± 0.5 (0.4–2.6)	20	NS
TSH peak after TRH (mU/L)		8.5 ± 5.1 (0.4–36.0)	70	8.0 ± 4.2 (2.4–17.7)	20	NS
PRL (μg/L)	<20	6.8 ± 7.0 (1.0–52.6)	73	4.9 ± 2.6 (1.9–12.1)	20	NS
PRL peak after TRH (μg/L)		30.7 ± 22.0 (8.8–125.4)	71	31.0 ± 18.7 (10.1–79.4)	20	NS
Glucose (mmol/L)	3.9–6.1	5.2 ± 2.1 (3.1–15.5)		4.8 ± 1.0 (3.9–8.3)		NS
Creatinine (μmol/L)	50–110	70.2 ± 17.7 (26.5–132.6)	73	80.0 ± 26.5 (53.0–159.1)	19	NS
Sodium (mmol/L)	135–147	139.8 ± 2.4 (135–146)		140.6 ± 3.0 (133–146)		NS
Potassium (mmol/L)	3.5–5.0	4.1 ± 0.4 (3.1–5.5)		4.2 ± 0.4 (3.1–4.9)		NS
Total cholesterol (mmol/L)	<5.2	5.8 ± 1.2 (3.1–8.1)	73	5.1 ± 1.8 (3.4–7.0)	18	NS
HDL cholesterol (mmol/L)	>0.9	1.1 ± 0.4 (0.6–2.3)	73	1.4 ± 0.5 (0.7–2.8)	18	0.041
Total/HDL ratio	<5	5.5 ± 2.2 (2.5–12.1)	73	4.0 ± 1.1 (2.1–6.1)	18	0.008
LDL cholesterol (mmol/L)	<4.1	3.5 ± 1.1 (0.7–5.9)	72	3.0 ± 0.8 (1.8–4.4)	18	NS
Triglycerides (mmol/L)	<1.8	2.1 ± 1.7 (0.5–12.6)	72	1.6 ± 1.0 (0.4–3.7)	18	NS

drocortisone did not affect perceived general well-being, but was nevertheless judged necessary.

Discussion

In this study involving a large cohort of patients suffering from nonmalignant pain, we were able to clearly demonstrate that long-term intrathecal opioid therapy may have profound effects on neuroendocrine function.

Opioid peptides are found throughout the central nervous system. Both acute and chronic neuroendocrine effects of opiates and different opioid peptides have been studied extensively in animals and humans. In humans, the acute administration of opioids increases PRL, GH, TSH, and ACTH secretion while inhibiting LH release (10, 16, 17). The restraint on LH release is predominantly mediated through central inhibition of hypothalamic GnRH secretion (18). Taking into account the receptor subtypes, PRL is preferentially activated by ϵ-receptors, TSH by μ-receptors, and ACTH probably by δ- or κ-receptors, whereas the inhibitory control of LH involves ϵ-receptors (19, 20). The receptors involved in GH stimulation remain unclear. During chronic administration of opioids, the stimulatory effect on PRL, GH, and TSH

secretion is abolished, whereas ACTH will be inhibited and LH remains suppressed (10). The inhibition of ACTH release can be explained by the concomitant release of β-endorphin with ACTH under all physiological conditions, a system that is sensitive to feedback suppression by exogenous opiates (21). Endogenous opiates thus play a major role in the regulation of gonadotropins, especially LH, through a tonic inhibitory control and probably a minor acute neuromodulatory role in the stimulatory regulation of PRL, GH, and TSH. This is in contradistinction with the rat in which endogenous opiates appear to have a much more significant effect on PRL, GH, and TSH (10).

The clinical experience of long-term administration of opiates was predominantly established in narcotic addicts or patients taking methadone (22). The increasing and prolonged use of opioids in patients with cancer and pain of nonmalignant origin has added a new group of patients with possible neuroendocrine dysfunction. In a first review regarding adverse events with the use of intrathecal opioids, endocrine side-effects, such a loss of libido, were virtually absent (23). Later reports mentioned disturbance of libido in 4.9% (24), amenorrhea in 2.4%, and loss of potency in 26.8% of patients (8). Although sexual dysfunction as an adverse event of intrathecal opioids was gradually recognized in the literature, the reported figures were considered an underestimation. The selection of patients was difficult, as most of them had a long medical history, with repeated surgery and additional illnesses, and were taking various drugs that may confound the results of neuroendocrine tests. The ideal situation would have been to use the patients as their own controls by testing them both before and after intrathecal opioids and free of other medications. The rather small number of patients eligible for the study and the fact that some of them were already taking oral opioids was considered to possibly weaken the results, as oral opioids would alter basal neuroendocrine function. A control group of patients with chronic nonmalignant pain not taking opioids seemed the better option. The perception of pain in both groups was deemed to be the same because the questions related to pain were rated in an identical manner in the NHP questionnaire.

The present results showed a clear and significant suppression of LH and testosterone in virtually all males and a similar decrease in LH secretion with a disrupted menstrual cycle in females. Despite the significant difference in LH, estradiol, and progesterone levels in premenopausal women, significance was not reached because of the low number of women in the control group. Nevertheless, the data confirm and extend the initial observation of decreased sexual function in six males receiving intraspinal opioids (11). The data also parallel the previously known negative influence on sexual function in heroin addicts (21). The effect, however, seems to be more pronounced in patients taking intrathecal opioids than in patients taking oral opiates, as some heroin addicts only show a diminished quality of semen with maintenance of testosterone levels (25) or have slightly subnormal testosterone values (26). A difference in absorption of oral *vs.* intrathecal administration would explain why some patients did not have an affected sexual function while taking oral opioids before starting intrathecal therapy. A higher dose, a more continuous exposure, and the direct intrathecal supply of opioids by pain pumps may be responsible. Although a poor general condition may also reduce sex steroid hormone levels, no such phenomenon was found in our control group. Moreover, in the two patients tested before and after intrathecal therapy, a clear drop in testosterone levels was found within 2 months of initiation. The suppression of sex steroids is of clinical importance in all men and in premenopausal women not taking contraceptives. Substitution therapy by sex steroids restored libido in most men and women, although this effect was not uniformly or completely obtained.

An abnormally low urinary free cortisol excretion and an inappropriate cortisol response during insulin-induced hypoglycemia were found in, respectively, 20% and 15% of the patients. Primary adrenal insufficiency was carefully excluded, as well as all interference by oral or systemic corticosteroids or an inadequate response due to insufficient hypoglycemia. Mild suppression of cortisol levels has been described both in patients maintained on opiates (27–29) and in patients with epidural morphine infusion postoperatively (30). One of our patients developed an Addisonian crisis, and we consider this an argument to check adrenal function at regular time points.

About 15% of patients fulfilled the criterion of adult GH deficiency syndrome, having an inadequate increase in GH during hypoglycemia. The clinical picture has been well characterized in recent years and is especially recognized in patients with pituitary pathology. It is known to induce significant deleterious effects on body composition, muscle strength, and metabolic parameters and results in reduced quality of life and life expectancy (31, 32). Chronic disorders might be associated with reduced GH secretion, but this was not found in our control group. For the moment, as most patients suffer from chronic pain and often have additional illnesses, it is difficult to judge to what extent GH deficiency might negatively influence their quality of life or to predict whether GH replacement therapy would reverse some of their complaints. Further studies should be undertaken to determine whether these opioid patients would benefit from GH replacement therapy.

No effect was seen on PRL secretion. Although a rise of PRL is seen after a single injection, tolerance usually develops during long-term administration (10). Thyroid hormones were unaffected, except for a small, but significant, rise in free T_3 levels. Although intrathecal opioid therapy is known to induce edema, possibly by stimulation of vasopressin release, no difference in body water content was found between the opioid and the control group. The effect on vasopressin seems to be reduced when patients are treated for longer periods of time. Few differences between opioid-treated and nontreated patients were found regarding body composition and metabolic parameters, except for a tendency toward more body fat and slightly higher low density lipoprotein cholesterol and lower HDL cholesterol in opioid group. This might be explained by longer immobility or partly by GH deficiency in some patients. The tendency toward decreased BMD might be induced by an underlying bone disorder and the lack of physical activity, but gonadal and GH deficiency may aggravate the condition.

We can conclude that long-term intrathecal opioid therapy induces hypogonadotropic hypogonadism in a high percent-

age of patients. This is clinically important in the majority of men and in premenopausal women. Substitutive therapy with sex steroids should therefore be considered in this group of patients. A lower, but substantial, percentage of patients may develop hypocorticism. This condition should be properly diagnosed and treated to avoid Addisonian crises. GH deficiency may affect an equivalent number of patients. The need for GH replacement therapy is still not defined. Also, an unfavorable lipid profile is apparent. We argue that these findings should be taken into account in all patients considered for intrathecal opioid administration and that regular endocrine check-ups are necessary.

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