Effects of testosterone treatment on bone mineral density in hypogonadal men receiving intrathecal opioids

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ABSTRACT

Opioid induced depression of sex hormones is a common finding in chronic pain patients receiving long-term opioids by oral, parenteral and even intrathecal routes of administration. The hypothalamic suppression by opioids leads to a hypogonadal state with low testosterone levels in males and subsequent low bone mineral density (BMD). We have studied the effects of intrathecally-administered opioids on BMD in a group of male chronic pain patients. In addition, we have studied the effects of supplementary testosterone on bone metabolism to see if the adverse effects of intrathecal opioids can be reversed. Eleven of the 27 patients were on supplementary testosterone having previously been diagnosed as hypogonadal with low serum testosterone. Duration of testosterone supplementation was greater than 2 years in all 11 patients. Both serum total and free testosterone levels were higher in patients on supplementary testosterone than in patients who did not receive this treatment. Of the 16 patients not on testosterone supplement, 14 (87%) had low serum testosterone levels (<10 nmol/L) and 11 (69%) had low or osteoporotic T scores. Within this group, low free testosterone was associated with low BMD scores, and this persisted after correcting for age. Eight of the patients on testosterone supplement had normal BMDT scores and three (27%) had low or osteoporotic T scores. T and age-corrected BMDZ-scores were significantly greater in the 11 patients on testosterone supplements than BMD scores in the other 16 patients. Testosterone supplementation was found to largely correct the effects of intrathecal opioids on testosterone levels and BMD.

KEY WORDS: Intrathecal opioids, testosterone, hypogonadism, bone mineral density

INTRODUCTION

There are widespread neuroendocrine consequences of opioid therapy including hypogonadism and osteoporosis.[1-6] It can even be said that testosterone serves to maintain health in every system of the body![7] Opioid induced androgen deficiency can occur after opioids are administered by oral, transdermal, parenteral and intrathecal routes.[8-11] Opioids reduce androgen production, mainly by suppression of the hypothalamic secretion of gonadotrophin releasing hormone (GRH). Suppression of GRH in turn suppresses the release of luteinising hormone from the pituitary gland, with subsequent effect on the Leydig cells of the testes.[12] There is also a possible direct effect on the testes.[13] This cascade of suppression leads to low levels of testosterone and dihydrotestosterone with subsequent reduction of bone mineral density (BMD) in male patients receiving opioids.[10, 14]

We have previously studied patients receiving intrathecal opioids for chronic benign pain both retrospectively[15] and prospectively.[16] We found that they developed hypogonadotrophic hypogonadism. Metabolic sequelae of hypogonadism, such as osteoporosis, were considered at the time but no metabolic bone studies were conducted. Consequently, we have studied male patients who were continuing to receive intrathecal opioids for chronic benign pain for signs of low BMD and altered bone metabolism. In addition, we have studied the effects of supplementary administered testosterone on those

patients receiving intrathecal opioids and who were previously diagnosed with opioid induced hypogonadism.

METHODS

After obtaining institutional ethics approval from Murdoch University and Sir Charles Gairdner Hospital, Perth, Western Australia and informed consent from participating patients, 27 males with chronic benign pain between the ages of 36 to 83 years attending a chronic pain clinic and who had implanted intrathecal pumps (Medtronic Syncromed 11) delivering either morphine sulphate (range 1-20 mg/day, mean 7.2 mg/day) or hydromorphone (range 1-8.5 mg/day, mean 4.15 mg/day) were studied. Other secondary causes of low bone density including thyroid disease, hyperparathyroidism, malabsorption and administered corticosteroids were grounds for patient exclusion from this study. Blood and urine were taken for an early morning fasting metabolic bone study as an index of bone metabolism. Serum total testosterone (Roche, competitive electro-chemiluminescence immune testosterone assay), sex hormone binding globulin (SHBG), free testosterone calculated with the Vermeulen equation, serum alkaline phosphatase (AP) as a measure of osteoblastic activity, serum parathyroid hormone, 25-OH vitamin D and urine N-telopeptide/creatinine (NTx) as a measure of osteoclastic function were measured. Hypogonadism was considered present with a serum testosterone level of <10 nmol/L. Bone densitometry by dual emission X-ray absorptiometry (DEXA) was conducted in the femoral neck, the total hip and the radius or lumbar spine to determine the BMD, expressed in g/cm^2. From this, T and Z scores were derived and the lowest T and Z scores determined. The T score was defined as the number of standard

deviations (SD) below the mean for peak bone density at age 30 years. The Z score was calculated as the number of standard deviations below the age matched mean. Using World Health Organisation (WHO) diagnostic criteria, osteoporosis was considered present if the T score was at or below -2.5. Low bone density (osteopenia) was considered present at T score values between <-1.0 and >-2.5. Values obtained in the lumbar spine were excluded if the patient had previously undergone spinal surgery or had increased density due to degenerative changes.

RESULTS

Diagnostic categories for patients not receiving testosterone included 13 with spinal pain, 2 with Complex Regional Pain Syndrome I and one with a painful ankle fusion. Eleven of the 27 patients were on supplementary testosterone having previously been diagnosed as hypogonadal with low serum testosterone levels. Diagnostic categories included 10 with spinal pain and one with abdominal pain. The mode of supplementation included 9 patients receiving depot testosterone undecanoate 1000mg every three months, one receiving depot testosterone enanthate 250 mg/3 weekly and one applying transdermal testosterone gel 50mg daily. Duration of testosterone supplementation was greater than 2 years in all 11 patients. (Range 2.5-17 years, m=8.68, std. error 1.42) There was no association between duration of testosterone supplementation and BMD. At the time of this study, both serum total and free testosterone levels were higher in patients on supplementary testosterone than in patients who did not receive this treatment (Table)

Of the 16 patients not on testosterone supplement, 14 (87%) had low serum testosterone levels (<10 nmol/L) and 11 (69%) had osteopenic (8 patients) or osteoporotic (3 patients) T scores. Within this group, low free testosterone was associated with low BMD scores (Pearson's correlation coefficient = 0.88, p = 0.004), and this persisted after correcting for age (partial correlation coefficient = 0.86, p = 0.014).

Eight of the patients on testosterone supplement had normal BMDT scores and three (27%) had osteopenic T scores. T and age-corrected BMDZ-scores were significantly greater in the 11 patients on testosterone supplements than BMD scores in the other 16 patients (Table). As well, urinary NTx (an index of bone resorption) was significantly smaller in the testosterone supplement group than in the other patients (Table). Other measures of bone health (serum alkaline phosphatase, parathyroid hormone and vitamin D levels) were, however, similar in both groups.

DISCUSSION

The results of this small study show that an opioid induced sex hormone endocrinopathy becomes almost universal in patients receiving intrathecal opioids. This finding is in line with previous studies, including our earlier work, which included prospective data.[15-17]

Opioids administered by any route can induce secondary hypogonadism, and their effects on fertility have been noted in nineteenth and mid twentieth century literature.[18-21] Although intrathecal opioids provide undisputed benefits for some patients with intractable pain states, they are associated with a number of unwelcome side effects, many of which can be related to hypogonadotrophic

hypogonadism. Such side effects include lethargy, depression, loss of libido and sexual function.[10, 22-24] Metabolic side effects have also been described including the onset of osteoporosis in patients receiving opioids by oral and parenteral routes.[23]

Low androgen levels are associated with abnormal bone metabolism, especially in younger males.[10, 23, 25, 26] Androgen deficiency is thought to be an important factor in males suffering hip and vertebral fractures.[27-29] Gonadal androgens are most probably the principal bone-active steroid hormones in males.[26] Opioids can also have a direct effect on bone metabolism[9, 10] but our patients receiving opioids by the intrathecal route have low serum levels of these drugs. Androgen suppression by opioids via the hypothalamic-pituitary-gonadal axis provides a more logical explanation.

In this study, low free testosterone was associated with low bone density, an effect that persisted after correction for age. These findings replicate our earlier pilot study[30] and a recent study by Duarte et al. of 20 patients receiving intrathecal opioids for chronic benign pain.[31] We have extended this finding to study the effects of supplementary testosterone treatment on BMD. Our data suggest that testosterone supplementation can correct the adverse effects of intrathecal opioids on testosterone levels and BMD. Eight of eleven patients (73%) on testosterone supplement had normal bone density in comparison with low or osteoporotic T scores in eleven of sixteen patients (69%)not on supplement. The beneficial effects of testosterone treatment on BMD in men with testosterone deficiency syndrome have been observed previously and significant effects have been noted at 12 and 24 months.[32] It is reasonable to assume that an improvement in BMD by testosterone treatment can be expected in men

rendered hypogonadal by intrathecal opioids. This study provides evidence in support of this assumption. Early monitoring of testosterone and BMD levels in patients recently commenced on intrathecal opioids might even circumvent some of the adverse features of intrathecal opioid therapy. It is unknown how long testosterone supplementation is required for an improvement in BMD to occur as all patients in this study had undergone treatment for more than 2 years and there was no association between duration of treatment and BMD.

A weakness of the study is the low numbers available for the estimation of bone metabolism and androgen levels. We chose to study only male subjects to simplify the hormonal changes expected with aging. Our female patients receiving intrathecal opioids are pre, peri and post-menopausal; however, it is expected this group will also demonstrate significant effects on gonadal hormone secretion and bone density. A profound inhibition of ovarian sex hormone and adrenal androgen can be demonstrated in women chronically consuming sustained action opioids.[33] A further weakness of this study is the lack of BMD data from prior to the commencement of testosterone supplementation. The improvement in BMD levels seen in patients on testosterone supplementation is therefore highly suggestive of cause and effect, but not proven.

In this study, SHBG was higher in untreated patients as a whole than in the group that received testosterone supplements. SHBG is a glycoprotein produced in the liver that is regulated by numerous factors and binds with high affinity to sex hormones, in particular testosterone and oestradiol, regulating their bioavailability. Both of these hormones inhibit osteoporosis in men.[34] Elevated SHBG levels have been associated with osteoporotic fractures in older men and correlate with greater bone loss.[35] SHBG rises with age and cirrhosis of the liver

and is reduced with obesity and hypothyroidism. A higher level of SHBG reduces the availability of free testosterone and oestradiol, and is therefore estimated when calculating free testosterone.[36] The estimation of total testosterone may not be as reliable as free testosterone for determining hypogonadism.[37] In a recent study of twenty patients receiving intrathecal opioid, however, no significant differences were observed between the diagnosis of hypogonadism based on total or free testosterone estimation.[38]

Testosterone levels can fluctuate widely in normal individuals but are usually higher in the early mornings. The levels can be affected by smoking cigarettes and alcohol consumption, raised Body Mass Index (BMI) and some centrally acting drugs such as anticonvulsants.[23] Surprisingly, benzodiazepines and antidepressants, which are also centrally acting, are not associated with reduced bone density.[39-41] Many factors other than androgen levels also affect bone metabolism including nutrition and weight bearing exercise.[42]

Hypogonadism in its various forms can be countered by androgen supplementation[1, 22, 43, 44] and it is interesting in this study that a large proportion of patients who were receiving testosterone supplement had a normal bone density. It would therefore be reasonable to recommend assessment of testosterone levels and BMD at <6 months from the commencement of intrathecal opioid therapy. Testosterone-depleted patients can present with higher pain scores[45] and administered androgen may even have analgesic effects[46], providing a further reason for treating the hypogonadism that develops in chronic pain patients receiving intrathecal opioids. Reduction or elimination of opioid treatment is, however, the only reliable method for reducing the metabolic effects of opioid endocrinopathy. Scant attention has

been paid to these long-term adverse effects of opioids, particularly on bone density in an aging population. It is perhaps time that this changed.

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Table: Clinical characteristics

	Mean ± S.E.			
	Testosterone Supplements (N = 11)	No Testosterone Supplements (N = 16)	t-test	p
Age (years)	57.7 ± 3.5	61.4 ± 2.5	.88	.39
Number receiving morphine sulphate	7 (63%)	4 (25%)		
Number receiving hydromorphone	4 (27%)	12 (75%)		
Opioid dosage: morphine sulphate (mg)	5.8 ± 1.3	9.5 ± 4.7	.95	.37
Opioid dosage: hydromorphone (mg)	5.0 ± 1.6	3.9 ± .5	.91	.38
Number with low serum testosterone (< 10 nmol/L)	2 (18%)	14 (87%)		.001
Number with low bone density (T score < -1.0)	3 (27%)	11 (69%)		.034
Serum testosterone (nmol/L)	20.8 ± 4.5	6.5 ± 1.1	3.64	.001
SHBG (nmol/L)[a]	27.5 ± 4.4	52.0 ± 7.1	2.70	.019
Free testosterone (pmol/L)[a]	576 ± 149	114 ± 32	3.49	.005
Bone density (T score)	-.73 ± .13	-1.61 ± .23	2.97	.006
Age-corrected bone density (Z score)	-.15 ± .16	-.94 ± .24	2.49	.02
Serum alkaline phosphatase (nmol/L)	74.5 ± 7.5	81.8 ± 5.8	.78	.44
Urine NTx (BCE/mmol)	30.3 ± 4.2	46.0 ± 4.3	2.56	.017
Parathyroid hormone (pmol/L)	5.3 ± .9	6.3 ± .8	.91	.37
Vitamin D (nmol/L)	65.9 ± 8.5	75.2 ± 14.4	.51	.62

[a] Measured in 6 patients who received testosterone supplements and 8 patients without testosterone supplements.

Legend: Bone density values (T /Z scores) and serum testosterone values for patients treated with intrathecal opioids receiving testosterone supplements (n=11) and those not receiving testosterone supplements (n=16). Biochemical indices of bone formation and resorption are included. The T score is calculated as the number of standard deviations (SD) below the mean for peak bone density at age 30 years. The Z score is the number of standard deviations below the age matched mean. Using WHO criteria, osteoporosis is defined as a T score at or below -2.5. Low bone density (osteopenia) is defined at T score values between <-1.0 and >-2.5. Serum alkaline phosphatase can be considered as an indicator of

osteoblastic activity and urine NTx as an index of bone resorption or osteoclastic activity.