Persistence of fertility despite semen alterations in a pinealectomised patient treated with melatonin

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Abstract

OBJECTIVES: Little is known about the effect of chronic melatonin treatment on human reproductive function. We report here on the effect of 10 months treatment with a controlled-release melatonin preparation (Circadin®, 2 mg) on spermatogenesis and gonadotropic hormone status in a pinealectomised patient whose melatonin secretion was abolished.

METHODS: Semen analysis, hormone (Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), inhibin B, prolactin, testosterone and estradiol) and Sex Hormone-Binding Globulin (SHB G) concentrations were determined before and at the end of 4 and 10 months of, treatment.

RESULTS: At the end of treatment, testosterone, sex hormone-binding globulin, prolactin and inhibin B levels did not display significant variation with time, whereas FSH and LH levels showed a tendency to a decrease, but remained in the normal range. Sperm concentration and total spermatozoa count dropped below the lower limit of the reference range during melatonin treatment, whereas motility and normal form percentages remained in the normal range. Fertility was preserved, since the patient's wife became pregnant during month 10 of melatonin treatment and gave birth to a healthy female baby.

CONCLUSIONS: this isolated clinical observation shows that more investigations in large patient series are needed to document possible side-effects of melatonin administration on male reproductive function. One should therefore be cautious about melatonin prescription for circadian rhythm sleep disorders in young males.

CASE REPORT

INTRODUCTION

The pineal gland, acting via the hormone melatonin, acts as an endogenous synchronizer able to synchronize circadian rhythms, amplify some of them and maintain their phase relationship (Claustrat *et al.* 2005). Patients suffering from tumours of the pineal area display decreased or abolished melatonin secretion due to the destruction of normal parenchyma by the tumour or following surgery and/or radiotherapy. These patients display symptoms including daytime

fatigue and sleepiness (Chazot *et al.* 1991; Petterborg *et al.* 1991), alteration of the sleep-wake cycle (Kocher *et al.* 2006) and psychiatric disorders that can be alleviated by melatonin administration (Quera-Salva *et al.* 2011). However, side-effects following chronic melatonin treatment, especially on reproductive function, are not completely known in humans (Sack *et al.* 2007; Srivanasan *et al.* 2009).

In animals, effects of melatonin on seasonal reproduction have well been described in a variety of species. Melatonin displays a suppressive effect in long-day breeding animals, such as the hamster, and a stimulatory effect on short-day breeders, such as the sheep (Pévet 2003). In both cases, the time of year at which a given species can successfully mate is determined by the duration of the gestational period when environmental temperatures are becoming warmer and food availability is increasing (i.e., the spring and early summer). In humans, the role of melatonin in the regulation of reproductive function is a matter of debate (Sack *et al.* 2007). Human seminal fluid and follicular fluid contain melatonin (Bornman *et al.* 1989) and spermatozoa possess membrane melatonin receptors (Van Vuuren *et al.* 1992). Conflicting results on the *in vitro* effects of melatonin on sperm motility have been reported. Irez *et al.* (1992) reported an inhibitory effect on sperm motility, whereas Du Plessis *et al.* (2010) reported the opposite. Also, short-term *in vitro* exposure to melatonin, at least at millimolar concentration improves aspects of sperm mobility and high endogenous melatonin concentrations enhance sperm quality (Ortiz *et al.* 2011). Finally there is only one report showing that in young men chronic melatonin administration (3 mg/day for 6 months) induces a decrease in sperm concentration and motility (Luboshitzky *et al.* 2002).

We here report on the effects of long-term administration of a controlled-release melatonin preparation on spermatogenesis in a pinealectomised patient with no melatonin secretion.

MATERIALS AND METHODS

For the last 15 years, we have followed up a man who presented with daytime hypersomnia which appeared after surgery and radiotherapy for a germinoma of the pineal gland, diagnosed when he was 21-years-old (Kocher *et al.* 2006). Melatonin secretion was completely abolished. In order to improve symptoms related to hormone deficiency, melatonin treatment was undertaken after explaining to the patient the possible side-effects, especially on reproductive function. The administration of fast-release melatonin capsules results in plasma profiles that do not mimic endogenous secretion. Since a controlled-release melatonin preparation (Circadin®, 2 mg melatonin) had become available, we suggested its use to the patient, since it has been showed to be effective in pinealectomised patients (Quera-Salva *et al.* 2008). During month 10 of treatment, his wife became pregnant and gave birth to a healthy female baby after a 40-week pregnancy. This baby was the sister of a healthy boy born two and a half years earlier. Before treatment and at the end of month 4 and 10 of Circadin® administration, hormone and semen analysis was performed. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and sex hormone-binding globulin (SHBG) were measured by immunoradiometric assays (CIS Bio-international, Gif-sur-Yvette, France) and serum levels of inhibin B were measured by ELISA (Argene Biosoft, Varilhes, France). Testosterone and 17-β-estradiol (E2) were measured by radioimmunoassay as described previously (Szulc *et al.* 2004).

Semen analysis

Semen samples were collected by masturbation following 3 days of sexual abstinence and analysed sequentially in the same laboratory by a trained technician. After 30 minutes of liquefaction, standard semen parameters (volume, total motility, concentration and morphology) were immediately evaluated according to the World Health Organization guidelines (2010); motility was also evaluated 4 hours after ejaculation. Total motility is defined as the sum of rapid and slow progressive motility and non-progressive motility; to be in the normal range, at least 40% of the spermatozoa should show motility. The spermatozoon concentration was determined using a Thoma Hemocytometer® counting chamber; to be in the normal range, the concentration should be $>20\times10^6$ spermatozoa per ml and the normal total spermatozoon count $>40\times10^6$ spermatozoa per ejaculate. Morphology was evaluated by counting spermatozoa with a normal form based on the classification of David *et al.* (1975); to be in the normal range, at least 30% of spermatozoa should have a normal morphology.

RESULTS

Serum hormone levels before and during treatment are presented in Table 1. Testosterone, E2, SHBG, prolactin and inhibin B levels did not display significant variation with time and either remained in the normal range (testosterone, prolactin and inhibin B) or close to the normal lower limit (E2 and SHBG). A tendency to a decrease in both serum LH and FSH levels was observed. FSH levels were slightly increased before and at the end of month 4 of treatment, but in the normal range at the end of month 10. The testosterone/E2 ratio was stable after 4 months of treatment; data were not available for month 10. Semen analysis results are shown in Table 2. Sperm concentration and total spermatozoon count showed a significant decrease below the lower limit of the reference range during the melatonin treatment period, whereas the percentages of spermatozoa with normal motility and a normal form remained in the normal range.

DISCUSSION AND CONCLUSIONS

In this study, we examined the effects of exogenous melatonin on sperm production and hormone concentrations in a patient who lacked melatonin secretion following pinealectomy. Before treatment, hormone levels were normal compared to healthy controls, except for a slight increase in FSH levels, which might be related to pinealectomy, since the influence of pineal secretions, especially melatonin, on the gonadotropic axis in humans is not known. Ten months treatment with Circadin® resulted in a moderate decrease in sperm concentration and count. However, motility and morphology remained in the normal range, in agreement with maintenance of fertility. Regulation of FSH secretion in the male involves a complex interplay between the stimulatory effect of hypothalamic gonadotropin releasing hormone, autocrine/paracrine modulation by activin and follistatin and negative feedback induced by gonadal secretion of inhibin B and sex steroids, especially of E2 on FSH levels and of testosterone on LH levels (Boepple *et al.* 2008). Melatonin treatment did not modify prolactin, testosterone or E2 levels or the testosterone/E2 ratio at least up to the end of month 4 of treatment. In addition there was no change in inhibin B levels, a decrease in which is a marker of male factor infertility, irrespective of aetiology (Kumanov *et al.* 2006). As the result of the observed decrease in sperm concentration and spermatozoa count, we expected to observe a decrease in inhibin B levels and an increase in FSH levels, since these hormones are negatively correlated (Rendtorff *et al.* 2011). In fact, inhibin B levels were normal, possibly as a result of maintained sperm quality, while, although serum FSH and LH levels remained in the normal range, they displayed a progressive decrease, a possible effect of exogenous melatonin on the gonadotropic axis. Recently, hypothalamic gonadotropin-inhibitory hormone (GnIH) has been shown to inhibit gonadotropin secretion in mammals (Gingerich *et al.* 2009). Melatonin stimulates GnIH release via receptors expressed by GnIH neurons (Tsutsui 2009). FSH secretion at the end of month 10 of treatment was sufficient to maintain normal spermatogenesis. In contrast, quantitative semen parameters were altered, which could be related to a direct effect of melatonin on spermatogenesis, as a result of the high dose given over a long time. Indeed, although it mimics endogenous secretion, a 2 mg controlled-release melatonin preparation leads to nocturnal blood hormone levels that are about ten times higher than physiological and persist for several hours. This result is in agreement with the results of Luboshitzky *et al.* (2002), who showed a decrease in sperm concentration and motility in 2 out of 8 young men after daily treatment with 3 mg of melatonin for 6 months. In these 2 subjects, unlike in our patient, the testosterone/E2 ratio increased, suggesting inhibition of testicular and epididymal aromatase, and six months after cessation of melatonin treatment, sperm concentration and motility remained abnormal, as did the testosterone/E2 ratio. Since serum gonadotrophin levels did not change in either of their two subjects, the decrease in testosterone to E2 conversion did not influence FSH regulation. Finally, in a study comparing serum and seminal fluid parameters in fertile and infertile males, the infertile males were found to have lower serum and seminal melatonin levels than the fertile males, especially in patients displaying reduced motility (Awad *et al.* 2006). These data suggest that physiological local melatonin production is beneficial for spermatogenesis, whereas exogenous supraphysiological administration could be detrimental.

Tab. 1. Plasma hormone concentrations before and during Circadin® treatment: Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), E2, Testosterone, Prolactin, Sex Hormone Binding Globulin (SHB G), Inhibin B.

Hormone concentration	Before Circadin®	After 4 months of treatment	After 10 months of treatment
FSH (mUI/ml) Normal range: 1.3–11.5 UI/L	13.4	13.0	8.6
LH (mUI/ml) Normal range: 0.5–10.0 UI/L	4.4	2.3	1.6
E2 (pmol/L) Normal range: 66–139 pmol/L	65	57	–
Testosterone (nmol/L) Normal range: 10.4–26 nmol/L	24.1	17.4	20.8
Prolactin (µg/L) Normal range: < 25 µg/L	5.7	2.3	9.5
SHBG (nmol/L) Normal range: 17–45 nmol/L	51	–	42
Inhibin B (ng/L) Normal range: 55–309 ng/L	67	49	71

Tab. 2. Semen parameters (sperm concentration, total sperm count, total motility and normal form percentages) before and during Circadin® treatment.

Semen parameters	Before Circadin®	After 4 months of treatment	After 10 month of treatment
Sperm concentration: Spermatozoa ($\times 10^6$)/ml (lower normal limit: 20)	27.2	12.9	14.6
Total sperm count: Spermatozoa ($\times 10^6$)/ejaculation (lower normal limit: 40)	22.4	38.6	30.7
Total motility percentage : After 30' After 4 h	 30% 35%	 45% 40%	 35% 40%
Normal form percentage (lower normal limit >30%)	47%	30%	40%

In conclusion, this isolated clinical observation shows that more investigations in large patient series are needed to document possible side-effects of chronic melatonin administration on male reproductive function. One should therefore be cautious about melatonin prescription for circadian rhythm sleep disorders in young males. This concern is never raised in the scientific literature evaluating melatonin treatment of circadian rhythm sleep disorders (Sack *et al.* 2007). We suggest restricting melatonin administration in young males to a few weeks, i.e. only the time necessary to obtain a corrective phase advance of the circadian system, then maintaining the result by respecting sleep hygiene.

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Conflict of interest
None

Complementary data
At the end of 2012, the patient's wife is 5 months pregnant with their third child whereas her husband has been treated for 4 years with Circadin®.

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