Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia

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Background High rates of osteoporosis in schizophrenia may result from the prolactin-raising effects of some antipsychotic medication.

Aims To examine bone mineral density in relation to relevant endocrine variables in patients with schizophrenia taking prolactin-raising antipsychotics.

Method Fifty-five patients who had been receiving prolactin-raising antipsychotic medication for >10 years underwent dual-energy X-ray absorptiometry of their lumbar and hip bones. Among the endocrine variables assessed were plasma prolactin and sex hormones.

Results Age-related reduced bone mineral density measures were found in 17 (57%) of the male and 8 (32%) of the female patients. Higher doses of medication were associated with increased rates of both hyperprolactinaemia and bone mineral density loss. Bone loss for the whole group was correlated with medication dose, and for men was inversely correlated with testosterone values.

Conclusions These results suggest that patients with schizophrenia on long-term prolactin-raising antipsychotic medication are at high risk of developing reduced bone mineral density as a consequence of hyperprolactinaemia-induced hypogonadism.

A previous study from this group has demonstrated that most individuals on typical antipsychotic medications have pathologically elevated prolactin levels and, if female, are hypogonadal (Smith *et al*, 2002). Hyperprolactinaemia is associated with reduced bone mineral density, which is probably mediated by the inhibition exerted by prolactin on the hypothalamic–pituitary–gonadal axis and the resulting hypogonadism (Schlecter *et al*, 1983). It is known that osteoporosis is associated with schizophrenia (Halbreich *et al*, 1995; Bilici *et al*, 2002) and several recent review papers have pointed to the potential importance of an association between antipsychotic-induced hyperprolactinaemia and osteoporosis (Naidoo *et al*, 2003; Wieck & Haddad, 2003). The aim of this study was to examine the relationship between bone mineral density, prolactin levels and hypothalamic–pituitary–gonadal axis function using a cross-sectional design in individuals with schizophrenia.

METHOD

Study participants

Male and post-menopausal female patients with a diagnosis of schizophrenia on long-term prolactin-raising antipsychotic medication (>10 years) were eligible for inclusion in the study. Post-menopausal status was defined as absence of menstruation for at least 2 years and being >52 years of age. Participants were recruited from out-patient clinics attached to three psychiatric hospitals: St Ita's and St John of God's Hospital, Dublin and the Maudsley Hospital, London. Exclusion criteria included any medications known to be associated with the development or treatment of osteoporosis or the presence of medical disorders known to be risk factors for osteoporosis. Patients with a history of eating disorders were also excluded. Ethical approval was sought from and granted by each hospital involved in the study and written informed consent to participate in the study was obtained from each participant.

Clinical assessment

Clinical assessment included a semi-structured clinical interview with resultant DSM–IV diagnoses (American Psychiatric Association, 1994). Illness severity was measured using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and the Schedule for Assessment of Negative Symptoms (SANS; Andreason, 1983). A medical history was obtained detailing relevant information, such as a history of fractures or polydipsia. Each participant had a full physical examination, including body mass index evaluation.

A detailed drug history was recorded. In order to have a comparable value for each patient, medication was converted to chlorpromazine equivalents (Taylor *et al*, 2001). The atypical antipsychotics olanzapine and risperidone were converted according to the best pharmacological match for dopamine 2 receptor blockade to typicals: clozapine and haloperidol, respectively (Seeman, 1992). A modified version of an osteoporosis questionnaire was completed for each participant. This questionnaire examines information relevant to bone mineral density, such as family history, parity, dietary and weight-bearing exercise habits.

Endocrine assessment

A blood sample was drawn from each patient to measure oestradiol, progesterone, testosterone, follicle-stimulating hormone, luteinising hormone and sex hormone binding globulin (a marker of gonadal hormone concentrations). Plasma prolactin, cortisol, thyroid-stimulating hormone, thyroxine and triiodothyronine were also measured in each patient. Samples were collected at random times during the day (09.00–18.00 h), spun within 1 hour and the frozen serum/plasma was batch analysed. Blood sampling was not related to the timing of meals.

Prolactin, oestradiol, luteinising hormone, follicle-stimulating hormone, thyroid-stimulating hormone and thyroxine levels were measured using time-resolved fluoroimmunoassays methods with commercial kits (AutoDELFIA, PerkinElmer, Inc.: human hormone references supplied by Wallac Oy, Turku, Finland). Progesterone, testosterone and sex-hormone-binding

Table I Demographic and clinical details of male and female participants

	Male group (n=30) Mean (s.d.)	Female group (n=25) Mean (s.d.)
Age (years)	43.5 (11.4)*	59 (5.5)
Treatment duration (years)	16 (7.7)*	21 (7.8)
Treatment dose[1]	547 (528)	444 (405)
BPRS score	12.2 (12.7)	12.4 (17.4)
SANS score	18.6 (23)	14.8 (23)
Cigarettes (per day)	19.6 (16.8)*	11 (14)
Body mass index	28.0 (4.4)	30.3 (4.6)
Alcohol (units/week)	9.6 (12)	3.8 (14)
Exercise (min/day)	40.3 (34.4)***	19.2 (15.7)

BPRS, Brief Psychiatric Rating Scale; SANS, Schedule for Assessment of Negative Symptoms.
1. Dose in milligram chlorpromazine equivalents per day.
*$P < 0.05$; ***$P < 0.001$.

globulin were measured using radioimmunoassay kits (17x-Hydroxyprogesterone ^{125}I RIA Kit, Testosterone ^{125}I RIA and Sex Binding Globulin [125]I Immunoradiometric Assay Kit supplied by ICN Pharmaceuticals).

Bone mineral density assessment

Osteoporosis is defined by the World Health Organization as a bone mineral density of more than 2.5 standard deviations below the mean value for peak bone mass in young adults when measured by dual-energy X-ray absorptiometry (DEXA) (World Health Organization Study Group, 1994). The bone mineral density was determined in lumbar vertebrae L1–L4 and in the femoral neck, trochanteric and intertrochanteric regions of the left hip using a DEXA scan, which is currently the most precise and widely used method of assessing bone mineral density. Bone density is measured in relation to two sets of values generated by the DEXA scanner: t scores compare the patients' results with standardised peak bone mass of females/males 20–30 years old; and Z scores compare the bone mineral density with the average for her/his age group. Only Z scores are reported in this paper.

Statistical analysis

The SPSS for Windows (1999 version) was used to analyse the data. Results were analysed both for the whole group and separately for each gender. Independent t-tests (two-tailed) were used to identify differences between groups, and cross-tabulations were performed using χ^2 analyses when appropriate. Multiple regression analyses were performed to examine associations between the multiple variables hypothesised to be correlated with bone mineral density. Results are expressed as means and standard deviations.

RESULTS

Demographic data

Demographic data are shown in Table 1. Twenty-five post-menopausal women and 30 men were recruited into the study. The subjects were either of Caucasian ($n=46$) or African–Caribbean ($n=9$) ethnicity. There was a significant difference between male and female groups in terms of age ($P < 0.01$), number of cigarettes smoked per day ($P < 0.05$) and daily exercise taken ($P < 0.001$). Females had been exposed to medication for significantly longer periods than males ($P = 0.04$).

Clinical data

No associations were found between bone mineral density values and clinical measures of psychiatric illness (BPRS or SANS), or the presence of polydipsia. Among the lifestyle variables, only cigarette smoking was significantly correlated with reduced Z scores in L4 for the combined group ($r = -0.27$, $P = 0.04$).

Endocrine data (see Table 2)

Both gender groups had a mean prolactin level of approximately three times the upper limit of normal, with no gender or ethnicity differences in mean values between groups. Hyperprolactinaemia was present in 62% of the overall group (18 (60%) of males and 16 (64%) of females) and the mean dose of medication was higher in those who were hyperprolactinaemic (602 (s.d.=477) mg/day) compared with those who were normoprolactinaemic (267 (s.d.=336) mg/day): $t = 2.8$, d.f.=53, $P < 0.01$).

Medication (see Table 3)

Within the total group, 17 (31%) were receiving more than one antipsychotic agent. All patients taking the prolactin-sparing antipsychotic olanzapine were also on a conventional depot antipsychotic drug.

Table 2 Endocrine data of male and female participants

Hormone (normal range)[1]	Male group (n=30) Mean (s.d.)	Female group (n=25) Mean (s.d.)
Prolactin (50–300 mIU/l)	908 (1282)[2]	1053.5 (1130)[2]
Thyroid-stimulating hormone (0.5–4.2 mIU/l)	1.9 (2.6)	3.1 (5.4)
Thyroxine (8–21 pmol/l)	13.7 (2.5)	12.9 (2.3)
Testosterone (0.7–2.8 (f); 10–50 (m) nmol/l)	15.7 (6.7)	1.1 (0.48)
Free testosterone index (0.8–12 (f); 20–350 (m) nmol/l)	50.59 (21.45)	2.6 (1.4)
Oestradiol (<100 (f); <130 (m) pmol/l)	74.4 (33.1)	54.6 (29.5)
Sex-hormone-binding globulin (20–120 (f); 11–71 (m) nmol/l)	36.3 (18.2)	45.1 (17.01)
Follicle-stimulating hormone (30–120 (f); 1–7 (m) mIU/ml)	5.0 (3.8)	57.0 (27.8)
Luteinising hormone (20–150 (f); 2–14 (m) mIU/ml)	5.4 (3.6)	27.0 (15.2)
Progesterone (0.3–7.6 nmol/l)	2.0 (2.1)	2.9 (6.1)
Cortisol (110–700 nmol/l)	287.5 (180)	264.7 (130)

f, female; m, male.
1. Reference ranges for normative data in parentheses.
2. Mean values falling outside the normal range.

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Table 3 Frequency of antipsychotic use in the study population

	Males (n=30)		Females (n=25)	
	n	%	n	%
Flupentixol	7	23	9	36
Fluphenazine	7	23	4	16
Chlorpromazine	0	0	1	4
Olanzapine	3	10	3	12
Zuclopenthixol decanoate	5	16	1	4
Haloperidol decanoate	3	10	3	12
Risperidone	8	27	4	16
Haloperidol	3	10	2	8
Sulpiride	1	0	4	0
Thioridazine	1	3	3	12

Participants were divided into two groups: those receiving more than the upper limit of the *British National Formulary* range for 'usual maintenance dose' of chlorpromazine (300 mg/day) and those receiving less than this. There were no significant differences between these groups in terms of age, gender, treatment duration, lifestyle variables or scores on clinical rating scales.

Significantly more patients had hyperprolactinaemia and bone loss in the high- compared with the low-dose group: 20 (81%) *v.* 11 (45%) for hyperprolactinaemia (χ^2=7.505, d.f.=1, $P<0.01$) and 15 (62%) *v.* 7 (27%) for bone loss (χ^2=6.42, d.f.=1, $P=0.01$), respectively. Similarly, patients in the high- compared with the low-dose group had significantly more severely reduced bone mineral density scores (<2 s.d. below normative data): 9 (35%) and 3 (11.5%), respectively (χ^2=4.73, $P=0.03$).

Bone mass density measures

Overall, 17 (57%) of the men and 8 (32%) of the women had reduced bone mineral density values on at least one bone measure.

Correlational measures

Hormone levels and bone mineral density

The free testosterone index (testosterone/sex-hormone-binding globulin) was correlated with the bone mineral density Z summary lumbar score (see Fig. 1). The summary lumbar score is a DEXA-generated calculation of bone mineral density scores from L1 to L4 for each individual, and thus reflects the total bone density in the lumbar spine. This correlation was not found in the hip region. There

Table 4 Correlations between age-matched bone mineral density values and chlorpromazine equivalence scores in the male group

Z femoral neck	
Pearson's correlation	−0.309*
P (two-tailed)	0.022
n	55
Z L1	
Pearson's correlation	−0.319*
P (two-tailed)	0.018
n	55
Z L2	
Pearson's correlation	−0.407**
P (two-tailed)	0.002
n	55
Z L3	
Pearson's correlation	−0.352**
P (two-tailed)	0.008
n	55
Z L4	
Pearson's correlation	−0.391**
P (two-tailed)	0.003
n	55

*$P<0.05$; **$P<0.01$.

was no statistical relationship between prolactin, follicle-stimulating hormone, luteinising hormone, oestradiol, progesterone or thyroid hormones and bone mineral density values.

Chlorpromazine equivalents and bone mineral density (see Table 4 and Fig. 2)

There was a significant correlation between chlorpromazine equivalence scores and both lumbar-weighted scores ($r=0.4$, $P=0.002$) and combined lumbar- and hip-weighted scores ($r=0.35$, $P=0.009$).

Multivariate regression analysis

In a multivariate regression analysis for both genders combined examining clinical, endocrine and lifestyle variables, only the chlorpromazine equivalence scores were statistically predictive of reduced bone mineral density scores at L1–L4 ($P<0.0001$). When genders were analysed separately, no further factors were predictive of bone mineral density loss in females. In the male group the free testosterone index was also predictive of low bone mineral density in L1–L4 ($P=0.03$); and sex-hormone-binding globulin almost reached significance as a predictive value ($P=0.06$).
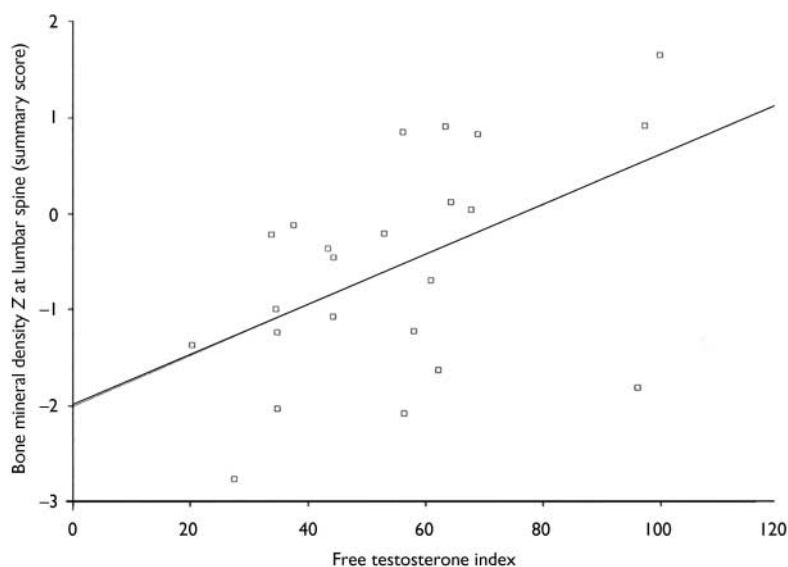

Fig. 1 Scatterplot of summary lumbar bone mineral density Z scores and free testosterone index levels in males. There is a significant correlation between free testerosterone indices in males and the summary lumbar Z scores ($r=0.5$, $P=0.01$). Free testosterone index: normal reference range 20–350 nmol/l.
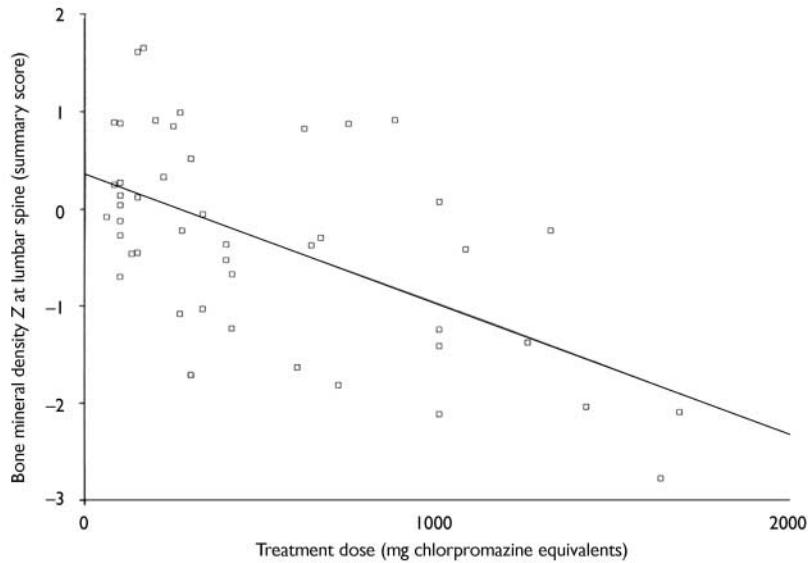
Fig. 2 Scatterplot of summary lumbar bone mineral density Z scores and the dose of antipsychotic in chlorpromazine equivalents. There is a significant correlation between summary lumbar Z scores and the dose of antipsychotic prescribed ($r=0.5$, $P=0.01$).

DISCUSSION

Main findings

This study was designed to evaluate the long-term effects of prolactin-raising antipsychotic medication on bone metabolism in patients with a diagnosis of schizophrenia. Both male and female groups had high rates of hyperprolactinaemia (62%) and had a range of osteopenic and osteoporotic measures that fell outside the normal age-related values. Age-consistent osteopenia or osteoporosis was found in 57% and 32% of the male and female groups, respectively. High levels of medication were associated with high prolactin levels and reduced bone mineral density scores. In a multivariate analysis for both genders combined, only treatment dose remained associated with bone loss but low free testosterone index values were additionally correlated with bone loss in the male group.

The findings of associations between chlorpromazine equivalents scores and both prolactin levels and low bone mineral density values is novel. Antipsychotic medication blocks the type 2 dopamine (D_2) receptors on the lactotrophs of the anterior pituitary, thus releasing these cells from dopamine inhibition and consequently suppression of prolactin secretion (Dickson *et al*, 2000). One positron emission tomography study has demonstrated that hyperprolactinaemia is likely to occur when central D_2 receptor occupancy exceeds 72% (Kapur *et al*, 2000). This physiological process may underlie the strong statistical relationship between chlorpromazine equivalence scores and prolactin levels. Any potent D_2-blocking antipsychotic, whether 'typical' or 'atypical', is likely to cause prolactin secretion and thus all patients in this study taking the antipsychotic risperidone had hyperprolactinaemia, in keeping with the established prolactin-raising profile of this drug (Kinon *et al*, 2003).

Bone strength is largely determined by calcium content and rate of bone loss, which in turn is determined by genetic factors, weight, ethnicity, diet, exercise, hormone status and gender (Hobson & Ealston, 2001). Although the physiological processes mediating bone loss are complicated, the most common cause of bone loss is sex hormone deficiency (Schlecter *et al*, 1983; Davies *et al*, 1995). The bone loss associated with hyperprolactinaemic states, whether prolactin is elevated pathologically or physiologically, is probably mediated by secondary hypogonadism, although other mechanisms have been proposed (see Wieck & Haddad, 2003). Prolactin interferes with the pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus and may also have a peripheral effect at the level of the gonads, inhibiting some luteinising hormone- and follicle-stimulating hormone-mediated effects.

The association of low free testosterone index with osteoporosis in this study supports hyperprolactinaemic-induced hypogonadism as being the relevant pathological process in the male patients because the association was present in males only in the gender-specific multivariate regression analysis. Free testosterone index values represent the biologically active, or unbound, part of the circulating testosterone. Bone loss was associated with the free testosterone index in the lumbar spine region only, and not the hip joint. The absence of bone loss in the hip joint in this relatively young male sample is in keeping with the fact that bone loss typically first occurs in the spine region (in 92% of individuals).

The female group was post-menopausal and thus uniformly hypogonadal, preventing an *a priori* hypothesis of an association between gonadal status and bone measures to be tested. A previous study by our group found that 75% ($n=15$) of a group of premenopausal females with a diagnosis of schizophrenia on prolactin-raising antipsychotics were hyperprolactinaemic and high prolactin levels were negatively correlated with both oestradiol and progesterone levels (Smith *et al*, 2002). A recently published study has also reported associations between high prolactin levels and low key reproductive hormone levels in males and females on antipsychotic medication (Kinon *et al*, 2003).

Osteoporosis and schizophrenia

Decreased bone mineral density in psychiatric patients has been recognised for some time but only recently investigated. Cases of osteoporosis have been reported in women and men with anorexia nervosa, chronic alcoholism, depression and schizophrenia (Delva *et al*, 1989; Abraham *et al*, 1995; Halbreich *et al*, 1995). Halbreich *et al* (1995) reported that patients, particularly males with major depressive disorder, schizophrenia, schizoaffective disorders, mania and adjustment disorders, had significantly decreased bone mineral density. Original reports of osteoporosis in people with schizophrenia suggested an association with polydipsia (Delva *et al*, 1989) but we found no correlation between polydipsia and reduced bone mineral density. Bilici *et al* (2002) reported increased rates of reduced lumbar spine

bone mineral density scores in a group of patients with schizophrenia taking 'classical' antipsychotic medication compared with a group on atypical antipsychotics and a healthy control group. That study did not examine relative prolactin levels in the groups but all the patients in the 'classical' antipsychotic group were on prolactin-raising agents, whereas 38% in the atypical group (n=15) were on prolactin-sparing agents. Previous studies have not specifically addressed a possible association between osteoporosis and antipsychotic-induced hyperprolactinaemia, but more recent reviews have focused on the possibility of such a relationship (Naidoo *et al*, 2003; Wieck & Haddad, 2003).

Other established risk factors, such as high alcohol intake and cigarette smoking, could possibly account for the high rates of osteopenia/osteoporosis found in this sample with schizophrenia. We did find a correlation between bone mineral density scores in the lumbar spine and smoking, but this significance was lost in the multivariate analysis, suggesting that the medication-related risk factors were more significant. There was no association between alcohol intake and any of the bone measures. Immobility is an unlikely cause of reduced bone mineral density even in individuals with negative symptoms of schizophrenia because activity levels involved in routine daily living are sufficient to retard bone mineral density loss in weight-bearing bones. It is unknown to what degree decreased exposure to sunshine and dietary deficiency contribute to reduced bone mineral density in patients with chronic mental illnesses, but all participants in our study indicated on the osteoporosis questionnaire that they had adequate intake of calcium in their diet. Low body mass index is another established risk factor for bone mineral loss, but all participants in this study were overweight with a mean body mass index bordering on obese.

It is conceivable that bone loss found in these people may be related to a metabolic disorder that is part of the syndrome of schizophrenia rather than the endocrine consequences of antipsychotic medication. This is unlikely, given the findings of significant associations between bone loss measures and medication and endocrine variables, and the absence of associations between clinical symptom scores and bone mineral density measures.

CLINICAL IMPLICATIONS

■ Patients with schizophrenia on long-term typical antipsychotic medication have high rates of hyperprolactinaemia and BMD loss.

■ Higher doses and dopamine 2 blocking potency of antipsychotic medication predict both hyperprolactinaemia and BMD loss.

■ Patients on long-term prolactin-raising antipsychotics are at high risk of developing osteoporosis, suggesting that these drugs are an unidentified risk factor for this disease.

LIMITATIONS

■ The study did not have a comparison group: either individuals with schizophrenia who had been exposed to prolactin-sparing antipsychotic medication, or a healthy group without psychiatric illness.

■ The high rates of bone loss in this group could have been contributed to by other risk factors prevalent in this population, such as smoking, poor diet and inactivity, or could be related to a metabolic disorder that is part of the syndrome of schizophrenia rather than the endocrine consequences of antipsychotic medication.

■ The female group were post-menopausal, preventing any associations between gonadal status and other variables from being assessed.

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Osteoporosis: morbidity and mortality

According to the World Health Organization, osteoporosis affects 30% of women over the age of 50 years, with the risk of hip fracture increasing 2.6-fold for each standard deviation decrease in hip bone mineral density. Hip fracture complications include a mortality of 20% in one year, with only 25% of patients recovering full function and 25% requiring long-term institutional care (Hobson & Ealston, 2001).

The absence of evidence associating prolactin-raising antipsychotic drug use with bone loss may explain why drugs such as glucocorticoids, lithium, anticonvulsants, thyroxine and gonadotrophin-releasing hormone antagonists are listed by the World Health Organization and the Royal College of Physicians as being associated with the development of osteoporosis but antipsychotic drugs are not (World Health Organization Study Group, 1994).

Limitations of this study

The study is limited by the absence of a control group of patients with schizophrenia who were receiving prolactin-sparing antipsychotics. We were unable to recruit the latter group because prolactin-sparing antipsychotics have not been widely in use for the time duration required for this study.

A potential limitation of the study was the collection of blood samples at random times during working hours, given that

the secretion of prolactin is subject to a diurnal rhythm. This is not important, however, in the context of either low- or high-grade hyperprolactinaemia because the diurnal rhythm is largely obliterated in both states (Veldman *et al*, 2001). In states of normal prolactin secretion, the nocturnal surge accounts for the diurnal variation and levels between 09.00 h and 24.00 h are generally stable.

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