Differences in the effect of second-generation antipsychotics on prolactinaemia: Six weeks open-label trial in female in-patients

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Abstract

OBJECTIVES: The main objective was to evaluate the effect of five second-generation antipsychotics (amisulpride, quetiapine, olanzapine, risperidone, and zotepine) on prolactinaemia during 6 week therapy in 433 female in-patients with mainly schizophrenic disorders. Secondary objectives included identification of dynamics of change in serum prolactin levels and correlations of changes of prolactinaemia with some demographic and clinical parameters.

METHODS: The trial was a prospective, open-label, single-center one with a flexible dosing of SGAs. The therapeutic effect of SGAs was assessed by a change of scores of CGI-S and CGI-I scales from a baseline to the endpoint. Blood samples were taken in the morning under fasting condition.

RESULTS: Amisulpride and risperidone increased prolactinaemia significantly in 100% of patients, as early as after week 1 of the therapy. Quetiapine and zotepine relatively reduced prolactinaemia significantly, as early as from week 1 of the quetiapine treatment. Olanzapine led to a transient mild prolactin elevation. The much lower prevalence of hyperprolactinaemia over 2 000 mIU/l differentiates olanzapine from amisulpride and risperidone. Prolactin elevation did not correlate with age, menopausal condition, therapeutic efficacy, antipsychotic daily dose, serum levels of lipids and glucose. There was significant correlation with first vs. subsequent psychotic episodes, weight, EPS and serum levels of thyroid hormones.

CONCLUSION: Amisulpride and risperidone had marked and early prolactin elevating effects, requiring, therefore, more frequent monitoring of prolactinaemia and associated undesirable effects and risks than olanzapine, quetiapine and zotepine.

ORIGINAL ARTICLE

INTRODUCTION

The primary mechanism of action of all available antipsychotics is a blockade of dopamine D2 receptors in the central nervous system (CNS). Blocking dopamine D2 receptors in the tuberoinfundibular region leads to the suppression of the inhibitory effect of dopamine on lactotrophic cells of the anterior pituitary gland and, thus, to increased prolactin release (Clemens *et al*., 1974; for a review see Haddad and Wieck, 2004). Hyperprolactinaemia associated with use of phenothiazines was first described by Beaumont *et al*. (1974). No hyperprolactinaemia was found in schizophrenic antipsychotic naïve patients (Goodnick *et al*., 2002; Meaney *et al*., 2002). Prospective open-label and double-blind studies showed that prolactinaemia increases up to 10 times after 3 to 9 weeks of antipsychotic medication (for reviews see Haddad and Wieck, 2004; Volavka *et al*., 2004; Wieck and Haddad, 2003). Hyperprolactinaemia is more prominent in women than men and in pre-menopausal than in post-menopausal women (Zhong *et al*., 2006; Kinon *et al*., 2003; Smith *et al*., 2002; David *et al*., 2000; Kuruvilla *et al*., 1992; Wode-Lelgodt *et al*., 1977; Haddad and Wieck, 2004). Hyperprolactinaemia occurs as early as several hours to a few days after the administration of an antipsychotic (Wieck and Haddad, 2003; Turrone *et al*., 2002; Gruen *et al*., 1978; Meltzer and Fang, 1976). Even relatively prolactin-sparing second-generation antipsychotics (quetiapine, clozapine, olanzapine, ziprasidone) are associated with a transient increase of prolactinaemia; this hyperprolactinaemia falls back to normal within several hours after an administration of an antipsychotic and does not persist until the next dose is administered (Turrone *et al*., 2002; Crawford *et al*., 1997). The increase in prolactinaemia occurs especially in the early phase of this antipsychotic therapy.

The original assumption was that higher doses of an antipsychotic medication should lead to higher hyperprolactinaemia (Montgomery *et al*., 2004; Kleinberg *et al*., 1999). Other authors observed the elevation of prolactinaemia after low doses of antipsychotics too (Kopecek *et al*., 2004; Nishikawa *et al*., 1985; Meltzer *et al*., 1976). David *et al*. (2000) claim there is no relation between daily doses of antipsychotics and a level of prolactinaemia, similarly Daniels *et al*. (2001), Kearns *et al*. (2000), and Tran *et al*. (1997). It seems, that a relation between a daily dosage of antipsychotics and prolactinaemia depends on the kind of antipsychotic medication used. It is not present for instance in the case of quetiapine or clozapine, but it is proven for risperidone (Zhong *et al*., 2006; Kopecek *et al*., 2006).

Some authors believe there is a significant correlation between an elevation of prolactinaemia and the therapeutic effect of antipsychotics (Goodnick *et al*., 2000; Chou *et al*., 1998).

Second-generation antipsychotics (SGA) include preparations elevating prolactinaemia (amisulpride, risperidone) as well as drugs which are neutral with respect to prolactinaemia or which reduce it (clozapine, quetiapine). Olanzapine affects prolactinaemia to a minimum extent; nevertheless, prolactinaemia may occur in association with higher doses (Tollefson *et al*., 1999; Crawford *et al*., 1997).

A reported prevalence of hyperprolactinaemia, associated with SGAs used in our study, differ in available literature. Prevalence of hyperprolactinaemia during risperidone therapy is 80–94% (Bushe *et al*., 2007; Melkersson, 2005; Montgomery *et al*., 2004; Kleinberg *et al*., 1999; Tran *et al*., 1997), but lower is also reported: 59% (Markianos *et al*., 1999) or even 30% (David *et al*., 2000). There is a general consensus that amisulpride increases prolactinaemia, but its prevalence is rarely reported; Bushe *et al*. (2007) reported it in 100% of patients. Most psychiatrists agree that quetiapine ranks among those antipsychotics which only rarely induce prolactinaemia (in 22% of patients, Montgomery *et al*., 2004; Hamner *et al*., 1996) or even decrease it (Zhong *et al*., 2006). Olanzapine ranks among those antipsychotics which induce only mild hyperprolactinaemia; most authors report an prevalence of 7–24% (Bushe *et al*., 2007; Melkersson, 2005; Crawford *et al*., 1997). Occasionally, a higher prevalence of 40% (Montgomery *et al*., 2004) or 51% (Tran *et al*., 1997) is reported. The effect of zotepine on prolactinaemia is little known and has not been studied systematically. In small groups of patients and healthy volunteers zotepine-associated hyperprolactinaemia was observed (Kondo *et al*., 1994; Otani *et al*., 1994; von Bardeleben *et al*., 1987).

Hyperprolactinaemia has its clinical effects. Hyperprolactinaemia and subsequent hypoestrogenism in women (Melkersson *et al*., 1999) are associated with menstruation abnormalities, galactorrhea, gynaecomasty, infertility, sexual dysfunctions, osteopenia/osteoporosis, (for a review see Haddad and Wieck, 2004), an increase in pituitary volume (Macmaster *et al*., 2007), and a potential increased risk of thromboembolism (Walaschofski *et al*., 2001; Urban *et al*., 2005) and possible risk of breast and endometrial cancer (Tworoger *et al*., 2007; Yamazawa *et al*., 2003).

TRIAL OBJECTIVE

The main objective of our trial was to evaluate an effect of five second-generation antipsychotics on prolactinaemia in female in-patients during 6 weeks of therapy. An evaluation included an identification of the dynamics of serum prolactin changes.

Secondary objectives included the identification of correlations between the prolactinaemia changing effect of a SGA and some demographic parameters: age, menopause, number of previous psychotic episodes. The correlations with other parameters were also evaluated: clinical (therapeutic efficacy, extrapyramidal side effects, obesity, comorbid hypothyreosis), pharmacological (SGA type and daily dose), and biochemical (TSH, T4, fasting glycaemia, lipids). All values of prolactinaemia over the

period of 6 weeks and the specific daily dose of SGA at the time of a corresponding blood sample were used for the calculation of the correlation.

METHODOLOGY

This is a prospective, 6-week, open-label, single-center trial with a flexible dosing of SGAs.

The therapeutic effect of SGAs was assessed by a change in score of CGI-S (Clinical Global Impression – Severity) and CGI-I (Clinical Global Impression – Improvement) scales from the baseline to the endpoint after 6 weeks of therapy with a SGA: amisulpride, olanzapine, quetiapine, risperidone, and zotepine. The following parameteres were evaluated at baseline and after 6 weeks of therapy: serum prolactin, TSH, T4, cholesterol, triglycerides, and blood glucose. Prolactinaemia was measured weekly. Blood samples were taken in the morning under fasting conditions. Prolactin evaluation was made using the sandwich chemiluminiscence immunoanalysis on the Architect analyser. The analytical sensitivity of the method was 12.6 mIU/l (ng/ml x 21.4 = mIU/l). Blood pressure, pulse rate and weight were measured at baseline and then weekly.

Statistical methods

The statistical analyses of the comparison between the baseline and the endpoint prolactinaemia and between specific SGAs were done by using the non-parametric Wilcoxon test. Relations between serum levels of prolactin and other parameters (age, weight, lipids, T4, TSH and glycaemia) were explored using simple and multidimensional linear regression and multidimensional correlation analysis; this included its partial form employed to filter out mediated influence.

Prolactinaemia was compared in women:

- with and without a menstrual cycle,
- with BMI (Body Mass Index) ≥30 and BMI <30,
- with a presence of EPS (extrapyramidal symptoms) and without EPS,
- with and without concomitant anticholinergic medication,
- with the first vs. repeated episode,
- with CGI-S and I values in two disjunct intervals (1+2 vs. ≥3points)

Both the parametric t-test and the Fisher Snedecore test were used, but the Wilcoxon test served as the basic statistical method.

The basic test for the comparison of the dynamics of serum prolactin levels for specific SGAs was the matched-pair t-test. The analysis of the correlation between daily dosages and prolactin levels was based on linear regression.

Patient sample

433 hospitalized female patients were included in the trial.

Characteristics of the sample:

- Mean age was 40.58 ± 14 years (ranging between 17 and 81),
- History of psychotic disorder had lasted for 7.64±9 years,
- 303 (70%) patients had diagnosis of schizophrenia,
- 84 (19.4%) schizoaffective disorder,
- 31 (7.1%) psychotic depression,
- 15 (3.5%) bipolar affective disorder, manic or mixed episodes (all diagnosis according to ICD-10),
- The patients experienced on average 3.49±3.2 psychotic episodes,
- The mean duration of the index episode was 77.34±99 days,
- The index episode was the first episode in 139 (32%) patients,
- 165 (38.10%) patients were married,
- 183 (42.1%) were single,
- 67 (15.5%) were divorced,
- 19 (4.4%) were widows,
- 185 (42.8%) women had a job or were students,
- 174 (40.2%) were drawing disability or retirement pension,
- 74 (17%) were unemployed,
- 324 (74.8%) patients were premenopausal and 109 (25.2%) postmenopausal,
- 160 (37%) women had also a diagnosis of a somatic disease.

The most frequent somatic illnesses were hypothyreosis (n=56; 12.9%), hypertension (n=38; 8.8%), diabetes mellitus (n=17; 3.9%), ischaemic heart disease (n=11; 2.5%), bronchial asthma (n=10; 2.3%), cystic mastopathy (n=7; 1.6%), duodenal ulcers (n=6; 1.4%) and glaucoma (n=6; 1.4%). 66 (15%) patients were obese (BMI ≥30) and 106 (24.5%) patients were overweight (BMI 25–29). 96 (22%) patients were smokers and 52 (12%) patients had been diagnosed with alcohol abuse or alcohol dependency.

Treatment

The in-patients were treated with one of 5 SGAs in monotherapy for 6 weeks. 93 patients were treated with amisulpride (daily dose 100–1 200 mg; median 800 mg), 125 with olanzapine (daily dose 10–30 mg; median 20 mg), 84 patients with quetiapine (daily dose 200–1 200mg; median 700 mg), 93 patients with risperidone (daily dose 3–16 mg; median 5 mg), and 38 with zotepine (daily dose 50–500 mg; median 150 mg). The dosing was flexible and based on the patient's condition.

104 (24%) patients were antipsychotic naïve at baseline, 145 (33.6%) were treated with typical antipsychotics at baseline, 165 (38%) with a SGA and 19 (4.4%) with antidepressants only.

The permitted concomitant medication was: anticholinergics, anxiolytics, hypnotics, and promethazine. Other psychotropics such as antidepressants and mood-stabilizers were not permitted as a new treatment, but it

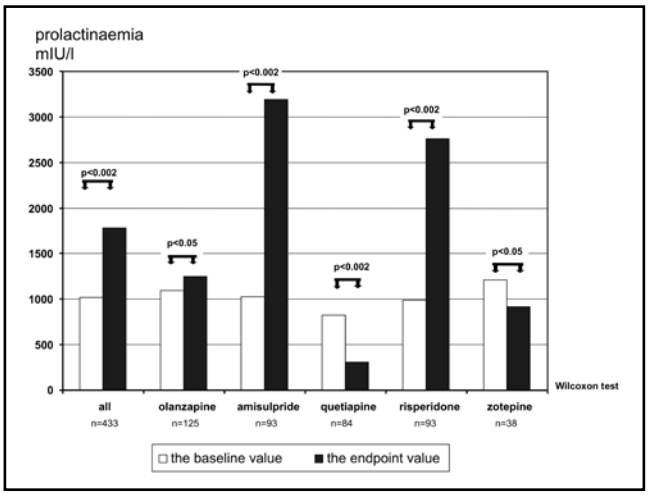

Figure 1. Within group comparison of baseline and endpoint means of serum prolactin levels.

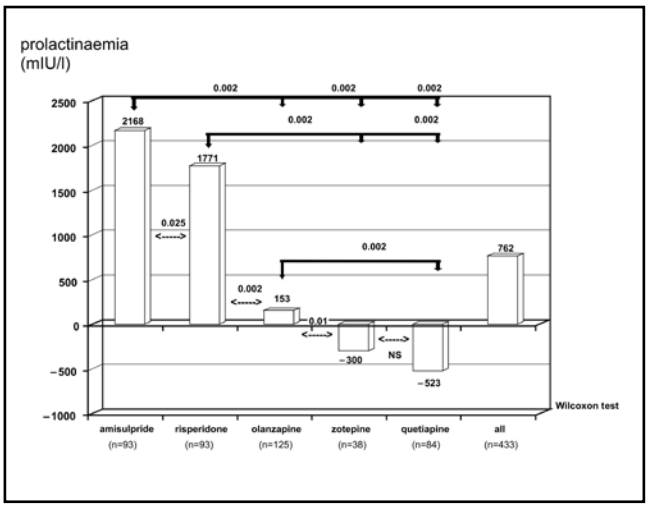

Figure 2. Pair-wise comparison of mean serum prolactin changes from the baseline to the endpoint (6 weeks of treatment).

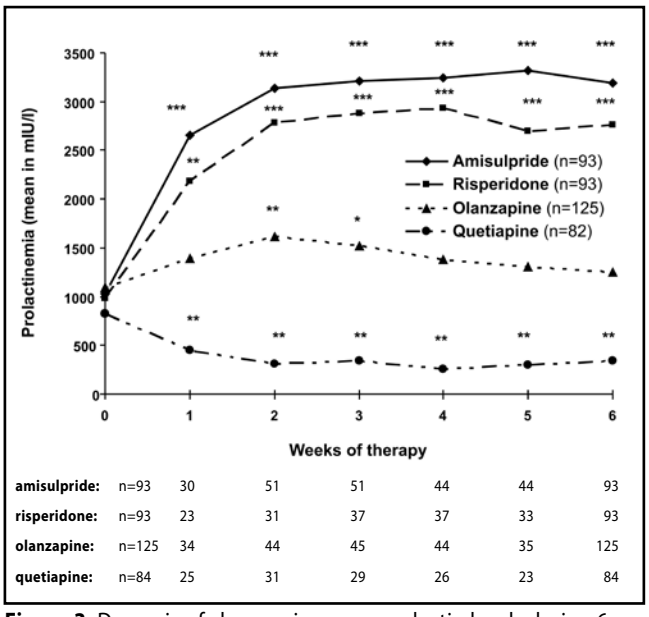

Figure 3. Dynamic of changes in serum prolactin levels during 6-weeks treatment by SGAs in monotherapy.
*p<0. 05, **p<0.01, ***p<0.001 vs. the baseline (Wilcoxon test).

was possible to use them from previous time. The same applied to drugs with significant effect on prolactinaemia such as dopamine agonists, levodopa, amantadine, reserpine, alpha-methyldopa, opiates, phenytoin, cyproheptadine, verapamil, histamine H2 antagonists (cimetidine, ranitidine) and ketotiphene.

During the trial, the patients were taking benzodiazepines (41%), promethazine (38%), anticholinergics (29%), and zolpidem (11%). Mood-stabilizers were continued to 4.8% and antidepressants to 2.5% of the patients.

RESULTS

The 6 weeks of SGA therapy led to a significant increase in prolactinaemia in the whole group: the baseline mean 1 015 and the endpoint mean 1 777 mIU/l, p<0.002) (Figure 1). The used SGAs could be divided in relatively prolactin-sparing and prolactin-increasing groups based on our findings. SGAs with a minimal effect on serum prolactin or which even decrease it include quetiapine (the baseline mean 828 vs. the endpoint mean prolactinaemia 304 mIU/l; p<0.002) and zotepine (the baseline mean 1 213 vs. the endpoint mean prolactinaemia 913 mIU/l; p<0.05). Prolactinaemia was elevated to a smaller or greater extent by the other SGAs: mildly by olanzapine (1 095 vs. 1 247 mIU/l; p<0.05) and markedly by risperidone (986 vs. 7 758 mIU/l; p<0.002) and especially by amisulpride (1 025 vs. 3 193 mIU/l; p<0.002).

The comparison of differences in the prolactin-elevating effect of the specific SGA is shown in Figure 2. Amisulpride and risperidone increased prolactinaemia significantly more than olanzapine, zotepine, and quetiapine. Amisulpride increased prolactinaemia significantly more than quetiapine and olanzapine more than quetiapine.

The results of the subsequent analysis of levels of prolactinaemia after the 6-week therapy are shown in Table 1. The highest prevalence of pathological levels of prolactinaemia was associated with amisulpride and risperidone. None of the patients treated with amisulpride or risperidone for six weeks had prolactinaemia lower than 620 mIU/l. The opposite pole was represented by quetiapine; 91% of patients treated with quetiapine had the endpoint mean prolactinaemia up to 620 mIU/l. Olanzapine and zotepine were associated with largely medium-pathological prolactinaeamia levels in 60% and 54% of patients, respectively.

Dynamics of changes in serum prolactin levels

Prolactinaemia was measured weekly in all patients during the 6 weeks trial with the exception of the patients in the zotepine group with irregular prolactinaemia measurements. Therefore this subgroup was excluded from this analysis. The analysis consisted in comparing levels of prolactinaemia after 1, 2, 3, 4, 5 and 6 weeks of therapy with the baseline data. The results are shown in Figure 3.

The group of prolactinaemia-elevating SGAs included amisulpride and risperidone. Both antipsychotics were

Table 1. Proportions of patients treated by SGAs in monotherapy according serum prolactin levels.

Antipsychotic	% of patients with mean prolactinaemia at the endpoint (mIU/l)				
	<620	620–1 199	1 200–1 999	2 000–2 999	>3 000
amisulpride	0	3.13	10.42	35.42	51.65
olanzapine	24.63	35.07	25.37	9.70	2.99
quetiapine	91.01	6.74	1.12	0	1.12
risperidone	0	2.06	25.77	38.96	35.05
zotepine	39.47	35.90	17.95	7.69	0

associated with a significant increase in prolactinaemia as aerly as the end of week 1 ($p<0.001$) and this significant increase lasted for 6 weeks. With either drug, the only significant difference between values pair-wise was recorded between week 1 and 2.

Therapy with quetiapine reduced prolactinaemia significantly as early as the end of week 1 ($p<0.01$) and this significant decrease persisted for 6 weeks of the therapy.

During therapy with olanzapine, prolactinaemia was elevated only after weeks 2 and 3 compared with the baseline ($p<0.01$ and $p<0.05$, respectively). The subsequent decrease in prolactinaemia in week 5 was considerably more than the decrease in week 4 ($p<0.05$). The endpoint prolactinaeamia in week 6 compared to the baseline was borderline only when the t-test was used ($p<0.05$) and insignificant when Wilcoxon test was used.

In summary, changes in serum prolactin levels were statistically significant as early as the end of week 1 with amisulpride, risperidone and quetiapine, and in week 2 with olanzapine. The changes of prolactinaemia persisted throughout the observation period in the amisulpride, risperidone and quetiapine group. Olanzapine was an exception, causing a significant increase in mean prolactinaemia only at the end of weeks 2 and 3. Changes versus the baseline were not statistically significant in the following weeks, excepting the borderline difference in week 6.

Correlation of levels of prolactinaemia and clinical and biochemical parameters:

The changes in prolactinaemia during the treatment by SGAs were subjected to correlation analysis with respect to the demographic, clinical and biochemical parameters of the patients. The unmatched t-test was used to compare two groups of prolactin values of differing size. Multidimensional linear regression was used to study how prolactin levels are influenced by the simultaneous effect of several variables. The independent variables in multidimensional linear analysis included patients' age and weight and – in the category of biochemical parameters – thyroid hormone serum levels (TSH, T4), total cholesterol, triglycerides and fasting blood glucose.

Table 2. Multidimensional regression analysis of the relation between prolactinaemia and other parameters – partial correlations.

Variable	prolactin	age	weight	cholesterol	triglycerides	T4	TSH	glycaemia
prolactin	–1.00000 (400)	0.03956 (400)	–0.16295 (400)	–0.00388 (400)	–0.22289 (400)	0,22280 (400)	0.11359 (400)	–0.01407 (400)
age	0.03956 (400)	–1.00000 (400)	0.12233 (400)	0.29430 (400)	0.04635 (400)	0.11466 (400)	–0.05583 (400)	0.05377 (400)
weight	–0.16295 (400)	0.12233 (400)	–1.00000 (400)	–0.01053 (400)	0.08599 (400)	–0.08599 (400)	0.03237 (400)	0.02938 (400)
cholesterol	–0.00388 (400)	0.29430 (400)	–0.01053 (400)	1.00000 (400)	0.45921 (400)	–0.10835 (400)	0.13187 (400)	–0.02683 (400)
triglycerides	–0.09354 (400)	0.04635 (400)	0.08599 (400)	0.45921 (400)	–1.00000 (400)	–0.08231 (400)	0.00299 (400)	0.03889 (400)
T4	0.22280 (400)	0.11466 (400)	–0.05511 (400)	–0.10835 (400)	–0.08231 (400)	–1.00000 (400)	–0.18642 (400)	–0.03984 (400)
TSH	0.11359 (400)	–0.05583 (400)	–0.03237 (400)	0.13187 (400)	0.00299 (400)	–0.18642 (400)	–1.00000 (400)	–0.01422 (400)
glycaemia	–0.01407 (400)	0.05377 (400)	0.02938 (400)	–0.02683 (400)	0.03984 (400)	–0.03984 (400)	–0.01422 (400)	–1.00000 (400)

Correlation (sample size) significance level.

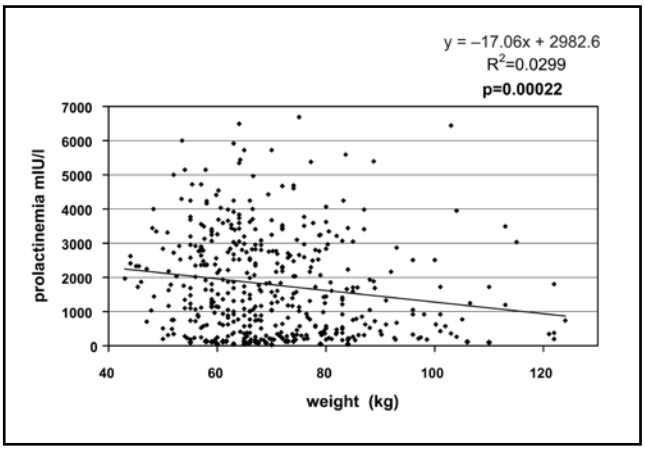

Figure 4. The linear regression curve of the dependence of post-therapy prolactinaemia on weight.

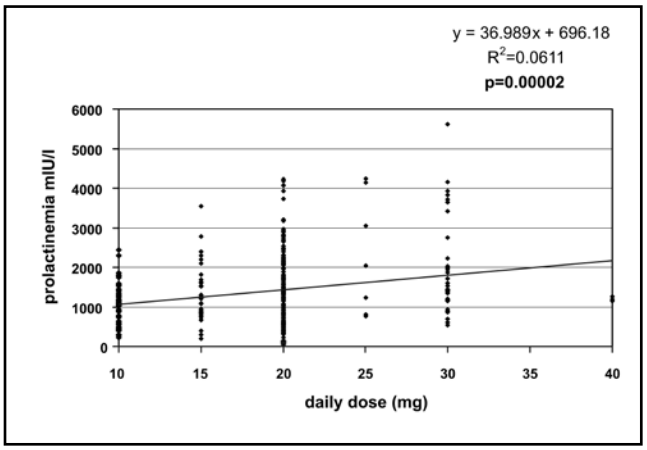

Figure 5. The linear regression curve of the dependence of the end-point prolactinaemia on the daily dose of olanzapine.

The results of the multidimensional regression analysis are shown in Table 2.

The multidimensional regression linear analysis revealed no correlation between the endpoint prolactinaemia and patients' age (t=0.7839, p=0.4336).

Prolactinaemia and weight

The analysis of the relation between the endpoint patients' weight and prolactinaemia showed a negative correlation (t=–3.2700; p=0.00022). The higher was the prolactinaemia, the lower was the patients´ weight. This correlation was confirmed by comparing obese patients and non-obese patients. Obese patients with BMI ≥30 had significantly lower levels of prolactinaemia than patients with with BMI <29 (n=76, mean prolactinaemia 130 mIU/l; n=356, mean prolactinaemia 1 864 mIU/l, respectively; t=2.846, p<0.005).

Prolactinaemia and menopause

No significant difference in prolactinaemia between premenopausal and postmenopausal women was found (n=315, mean prolactinaemia 1 811 mIU/l; n=112, mean prolactinaemia 1 673 mIU/l, respectively; t=0.886, p>0.05).

Prolactinaemia and SGA therapeutic efficacy

After 6 week of SGA therapy, at the endpoint, 63.4% of the patients were evaluated as "very much improved" or "much improved" on the CGI-I scale (with a score of 1 and 2, respectively). The severity of a underlying disease was evaluated on the CGI-S scale. 46.2% of the patients were evaluated as "normal, not at all ill" and "borderline mentally ill" on this scale – with a score of 1 and 2, respectively.

No statistically significant difference was found in mean prolactinaemia between responders (CGI-I 1 or 2) and non-responders (CGI-I ≥3), (n=265, mean prolactinaemia 1 715 mIU/l; n=153, mean prolactinaemia 1 910 mIU/l, respectively; t=0.912, p>0.05).

There was no statistically significant difference in mean prolactinaemia according to the severity of underlying condition; patients with CGI-S score 1 or 2 vs. patients with CGI-S score ≥3 (n=154, mean prolactinaemia 1 583 mIU/l; n=179, mean prolactinaemia 1 744 mIU/l, respectively; t=0.582, p>0.05).

Prolactinaemia and first psychotic episode

Our comparison of patients with their first episode and patients with more psychotic episodes revealed that patients with their first episode had higher prolactinaemia than patients who had more psychotic episodes(n=149, mean prolactinaemia 2 218 mIU/l; n=303, mean prolactinaemia 1 562 mIU/l, respectively; t=46.55, p<0.0005).

Prolactinaemia and EPS

The group of patients with extrapyramidal symptoms (EPS) showed markedly higher prolactinaemia than the group of patients without EPS (n=152, mean prolactinaemia 2 487 mIU/l; n=274, mean prolactinaemia 1 381 mIU/l, respectively; t=8 783, p<0.005). This significant difference was confirmed by using the parameter of number of patients with/without anticholinergic concomitant medication (n=130, mean prolactinaemia 2 566 mIU/l; n=303, mean prolactinaemia 1 439 mIU/l, respectively; t=7 866, p<0.0005).

Prolactinaemia and thyroid gland functions

Thyroid gland functions were evaluated by assessing TSH and T4 serum concentrations. The prolactinaemia at the endpoint was positively correlated with both T4 (t=4.5250, p=0.0000) and TSH serum levels (t=2.2636, p=0.0241). Because of this correlation a comparison of an endpoint prolactinaemia in patients with and without hypothyreosis was performed. No relation of the endpoint prolactinaemia and the diagnose of hypothyreosis was found (n=57, mean prolactinaemia 1 712 mIU/l; n=376, mean prolactinaemia 1 787 mIU/l, t=0.653, p>0.05).

Prolactinaemia and lipids

Total cholesterol and triglycerides serum concentrations were analyzed. The endpoint prolactinaemia was

correlated with neither total cholesterol levels (t=–0.0768, p=0.9388) nor triglycerides levels (t=–1.8602, p=0.0636).

Prolactinaemia and blood glucose

The multidimensional regression analysis revealed no correlation between the endpoint prolactinaemia and blood glucose (t=–0.2786, p=0.7807).

Prolactinaemia and daily doses of SGA

The relation of prolactinaemia to daily doses of SGA was tested by linear regression analysis for all used SGAs.

In the group of 125 patients treated with olanzapine, 452 prolactinaemia values were collected. In the group of 93 patients treated with amisulpride, 386 values of prolactinaemia were collected. There were 306 values of prolactinaemia in the group of 84 patients treated with quetiapine, 301 values in 93 patients in the risperidone group and 117 values in 38 patients in the zotepine group. Prolactin values were compared with daily doses of a specific antipsychotic (in mg) administered a day before a prolactin check was performed.

A correlation between levels of prolactinaemia and a daily dose was found only for olanzapine ($p<0.00002$) – see Figure 5. The linear regression curve representing the dependence of serum prolactin levels on daily doses of quetiapine was somewhat flat and the correlation insignificant (p=0.81117). The same applies for amisulpride (p=0.62918). Due to the relatively small number of patients treated with higher doses of risperidone no significant relation between prolactinaemia and the daily dose of risperidone (p=0.14947) was identified. Prolactinaemia did not correlate with a daily dose of zotepine either (p=0.26987).

DISCUSSION

Studied antipsychotics have shown different effects on prolactinaemia in female in-patients in this 6-week trial. Amisulpride and risperidone increased prolactinaemia significantly compared with the baseline and compared to the other anitpsychotics: quetiapine, zotepine, and olanzapine. Amisulpride had a significantly more marked prolactin-elevating effect than risperidone. Quetiapine, zotepine and olanzapine reduced prolactinaemia significantly compared with the baseline. Quetiapine and zotepine had a similar prolactin-sparing effect and both differed significantly from olanzapine in this regard.

There was 100% prevalence of hyperprolactinaemia in the amisulpride and the risperidone group. These findings are consistent with the findings reported by Bushe *et al.* (2007), Melkersson (2005), Montgomery *et al.*(2004) and Kleinberg *et al.* (1999). The prevalence of hyperprolactinaemia associated with quetiapine therapy was very low, namely 9% in our patient group. It is also consistent with published data. In contrast with other published findings, the prevalence of hyperprolactinaemia associated with zotepine therapy was lower than with amisulpride or risperidone (60.5% vs. 100%, respectively). Similarly to zotepine, olanzapine had a less prolactin-increasing effect than amisulpride and risperidone (hyperprolactinaemia in 75.6% in the olanzapine group and 100% in the amisulpride and the risperidone group). The main difference between zotepine and olanzapine on the one hand, and amisulpride and risperidone on the other, consisted in the extent to which they elevated prolactinaemia. Prolactin levels over 2 000 mIU/l were observed in 87% of patients treated with amisulpride and in 74% of patients treated with risperidone while the rates were only 12.7% in the olanzapine group and 7.69% in the zotepine group.

A significant change in prolactinaemia occurred as early as the end of week 1 of therapy with amisulpride, risperidone, and quetiapine and at the end of week 2 of olanzapine therapy. These findings confirmed published data regarding the fast onset of hyperprolactinaemia during therapy with antipsychotics (Wieck and Haddad, 2003; Turrone *et al.*, 2002; Crawford *et al.*, 1997; Gruen *et al.*, 1978; and Meltzer and Fang, 1976). The 6-week therapy with amisulpride and risperidone did not induce even partial toleration to the prolactin-elevating effect of these drugs while olanzapine-induced hyperprolactinaemia was transient and serum prolactine levels decreased from week 4 of therapy again.

Our study did not find any correlation between changes in prolactinaemia and daily doses of amisulpride, risperidone, quetiapine and zotepine. This fact can be interpreted in the knowledge that any daily dose of amisulpride or risperidone elevates prolactinaemia. Olanzapine elevated serum prolactin levels only when higher daily doses were administered, with the initial transitory elevation.

Elevation of prolactinaemia correlated with body weight, presence of EPS, T4 and TSH serum concentrations. Significantly higher prolactinaemia was recorded in patients experiencing their first (as opposed to subsequent psychotic episodes) psychotic episode. In our study prolactinaemia did not correlate with the therapeutic efficacy of SGAs, in contrast to the findings of Goodnick *et al.* (2000) and Chou *et al.* (1998). No correlation between prolactinaemia and patient age, total cholesterol, triglycerides and blood glucose was found. In contrast to available studies (for a review see Haddad and Wieck, 2004), no significant difference in prolactinaemia in premenopausal and postmenopausal women was identified.

CONCLUSION

The findings suggest that amisulpride and risperidone have a significant prolactin-elevating effect. The implication is that during treatment with both these antipsychotics monitoring of prolactinaemia and the associated undesirable effects and risks is required on a more frequent basis than quetiapine, zotepine or olanzapine.

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