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Hyperprolactinemia after low dose of amisulpride

Miloslav Kopecek[1,2,3], Martin Bares[1,2], Jirí Svarc[1], Colleen Dockery [1,3] & Jirí Horácek [1,2,3]

[1] Psychiatric Centre Prague,
[2] Charles University, 3rd School of Medicine in Prague,
[3] Centre of Neuropsychiatric Studies in Prague, CZECH REPUBLIC

Correspondence to: Miloslav Kopecek MD
Psychiatric Centre Prague,
Ústavní 91, Prague 8 – Bohnice, CZECH REPUBLIC
PHONE: +420-2663360
FAX: +420-2663361
EMAIL: kopecek@pcp.lf3.cuni.cz

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Abstract

OBJECTIVES: Amisulpride in antipsychotic doses can induce hyperprolactinemia. The aim of this study was to prove whether the same is true for low doses of amisulpride.

METHODOLOGY: Plasma prolactin levels were measured in 5 males and 5 females with depressive symptoms who were treated with 50 mg of amisulpride per day as an augmentation to antidepressants (n=5), benzodiazepine anxiolytics (n=8) or in monotherapy (n=1). Six of these patients were assessed prior to onset of amisulpride treatment and after 10 days of amisulpride use. Four patients had been using amisulpride for more than a month.

RESULTS: There was a significant increase of prolactin levels from mean 16±6 ng/ml to 113±65 ng/ml (median 14.5 ng/ml to median 92 ng/ml; Wilcoxon matched pair test, p=0.027). All patients had hyperprolactinemia (30–200 ng/ml). The prolactinemia was significantly higher in females (mean 160±50 ng/ml; median 198 ng/ml) than in males (mean 48±12 ng/ml; median 48 ng/ml; Mann-Whitney U test, p=0.041).

CONCLUSION: Even low doses of amisulpride used as an augmentation to antidepressant treatment, benzodiazepines or in monotherapy seem to be associated with hyperprolactinemia. The co-medication of antidepressants and benzodiazepines can potentially increase intensity of prolactinemia.

Abbreviation and units:

ng	– nanogram
mg	– milligram
kg	– kilogram
ml	– milliliter
ICD –10	– International Classification of Diseases, 10th edition
SGA	– second generation of antipsychotics
MEIA	– Microparticle Enzyme Immunoassay
c.v.	– Coefficients of variation
CI	– Confidence interals

Introduction

Amisulpride (Deniban) is a substituted benzamide antipsychotic which blocks dopamine D2/D3 receptors. A high dose of amisulpride (≥ 400 mg) is effective in treatment of positive symptoms of schizophrenia [7]. A low dose of amisulpride is effective in treatment of negative symptoms of schizophrenia (50–300 mg) [5,7]. Low doses of amisulpride are also effective in treatment of dysthymia or major

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depression (50 mg) [8]. These different clinical effects are theoretically explained by preferentially blockade of D2 presynaptic autoreceptors after low doses (≤ 10mg/kg) of amisulpride that control dopamine synthesis and release in the rat, whereas at higher doses (40–80mg/kg), postsynaptic dopamine D2 receptors occupancy and antagonismus is apparent [10]. Even though amisulpride belongs to the second generation of antipsychotics (SGA), it increases prolactin levels more than other SGA (clozapine, quetiapine, olanzapine). Such simple intravenous doses as 20 or 100 mg of amisulpride can lead to increase of prolactin level [11]. Female patients taking amisulpride for dysthymia had side effects which included menstrual disorder (2% to 12.3%), galactorrhea (3.9% to 7.3%), breast pain/breast enlargement (0.9% to 7.5%) in 4 large clinical trials [8]. The aim of this study was to verify whether oral doses of low-dose amisulpride (50 mg per day), which can be use in therapy for depressive syndrome, lead to an increase of prolactin plasma levels and how often.

Material and methods

Prolactin levels were measured in 10 inpatients (5 males, 5 females) with depressive symptoms in different diagnoses according to ICD-10 (Table I) who were treated with 50 mg of amisulpride per day as an augmentation treatment to antidepressants (n=5), benzodiazepine anxiolytics (n=8) or in monotherapy (n=1). All of them were endocrinologically screened, and had normal plasma levels of thyroid hormones. The clinical characteristics of our sample are in Table I. The main age was 49±5.8 in females and 40.8±9.5 in males. No patients used any other compounds capable of blocking D2 receptors except amisulpride. Six of these patients were assessed prior to onset of amisulpride treatment and after 10 days of amisulpride use. The plasmatic half life of amisulpride is 12 hours [2] and so a 10-day interval of prolactin measure is sufficient to reflect a steady-state of amisulpride plasma level. Concomitant medication remained unchanged during a 10-day interval. Four patients had been using amisulpride for more than a month. The blood sample was taken always at 6 o'clock in the morning (22 hours after last dose of amisulpride) and then it was centrifuged to separate serum. Prolactin levels were determined by the Microparticle Enzyme Immunoassay (MEIA). The sensitivity of the assay is 0.6 ng/ml (intra-assay coefficients of variation (c.v.): 2.81–4.13%, inter-assay c.v. 1.11–2.76%. The normal range established for this assay is within 1.39–24.2 ng/ml. Informed consent was obtained from all subjects.

Due to the sample size the nonparametric statistical tests were used to determine the within group (Wilcoxon matched pair test, Sign test) and between group (Mann-Whitney U test) analyses with a 5% significance level.

Results

Five of six patients had normal baseline prolactinemia at the baseline, in 4 patients the prolactin was not established before amisulpride treatment. There was a significant increase of prolactin levels from mean 16±6 ng/ml (median 14.5 ng/ml) to mean 113±65 ng/ml (median 92 ng/ml) (Wilcoxon matched pair test, Z = 2.2; p=0.027). The prolactin levels increased in all patients (Sign test; Z = 2.04; p=0.041) and all patients reached hyperprolactinemia (30–200 ng/ml, 95%CI = 54–154) (Figure 1). The prolactin plasma levels induced by amisulpride were significantly higher in females (mean 160±50 ng/ml, median 198 ng/ml, 95%CI = 89–229) than in males (mean 48±12 ng/ml, median 48 ng/ml, 95%CI = 29–67; Mann-Whitney U test, Z=2.61; exact p=0.007). No patients complained of breast pain, galactorrhea or amenorrhea. Two patients were reassessed after withdrawal of amisulpride and both showed a normalization of prolactin plasma levels.

Discussion

We observed a significant increase of prolactin plasma levels after 50 mg of amisulpride used as an augmentation to antidepressant treatment, benzodiazepines or in monotherapy. All patients reached significant hyperprolactinemia (30–200 ng/ml). Kapur et al. [3] described hyperprolactinemia after first generation antipsychotic haloperidol in doses which lead to striatal dopamine D2 receptor occupancy more than 72%. The striatal D2 occupancy after amisulpride in doses from 200 to 600 mg were between 16–44% [12]. Although we used only 50 mg amisulpride, which probably lead to less than 50% striatal D2 occupancy, we observed hyperprolactinemia, which reflects significant antidopaminergic activity in the pituitary. This fact could be explained by the low lipophilicity of amisulpride, which consequently is dosed much higher than the other antipsychotics. Since the pituitary is outside the blood-brain barrier, amisulpride concentrations in the pituitary may be very high compared with more lipophilic compounds. Moreover, the amisulpride binds preferentially to the autoreceptors and the dopamine receptors in pituitary behave more like the autoreceptors [1,6]. These mechanisms should explain the dissociation between central (striatal) and peripheral (pituitary) dopamine D2 receptors effects after amisulpride administration [4]. In amisulpride, these dissociation results in lower occupancy of D2 receptors in the striatum and higher occupancy in the pituitary [4]. This concept is also in accordance with the fact that the amisulpride has high propensity producing hyperprolactinemia and very low risk of producing the extrapyramidal side effects [5].

We did not observe any significant clinical side effects. The absence of endocrinological side effects was explained by the short follow up period. Especially in females, plasma levels of prolactin were markedly high. Long-lasting hyperprolactinemia can lead potentionally to oligomenorrhea, amenorrhea, galac-

Table I. Clinical features of patients

Sex	Age	Diagnosis (ICD-10)	Plasma level of prolactin ng/ml (before-during-after*) amisulpride use	Concomitant medication (daily doses in mg)
F	41	F 60.4 F 41.2	x – 200 – 18	clonazepam 2
F	44	F 32.2	19 – 200 – x	maprotiline 75 clomipramine 75 clonazepam 3
F	51	F 60.4 F 41.2	x – 83 – x	amitriptyline 50
F	52	F 41.2	16 – 200 – x	alprazolam 0.75 ginkgo biloba 40
F	57	F 32.2	28 – 116 – x	dibenzepine 480 buspirone 15 clonazepam 3 promethazin 25
M	30	F 33.1 F 60.31	11 – 50 – x	none
M	32	F 32.2	13 – 68 – x	alprazolam 1.5
M	39	F 60.9	x – 30 – x	clonazepam 1
M	48	F 32.2	9 – 46 – x	reboxetine 12 alprazolam 1.5
M	55	F 33.1	x – 50 –11	clonazepam 1 citalopram 40 pindolol 7.5

Legend: F – female, M – male, F32.2 – Severe Depressive Episode Without Psychotic Symptoms, F 33.1 – Recurrent Depressive Disorder With Current Moderate Symptoms, F 41.2 Mixed Anxiety Depression, F 60.31 – Borderline Personality Disorder, F 60.4 – Histrionic Personality Disorder, F 60.9 – Personality Disorder – Unspecified, x-not assessed, * after 10 days of withdrawal.

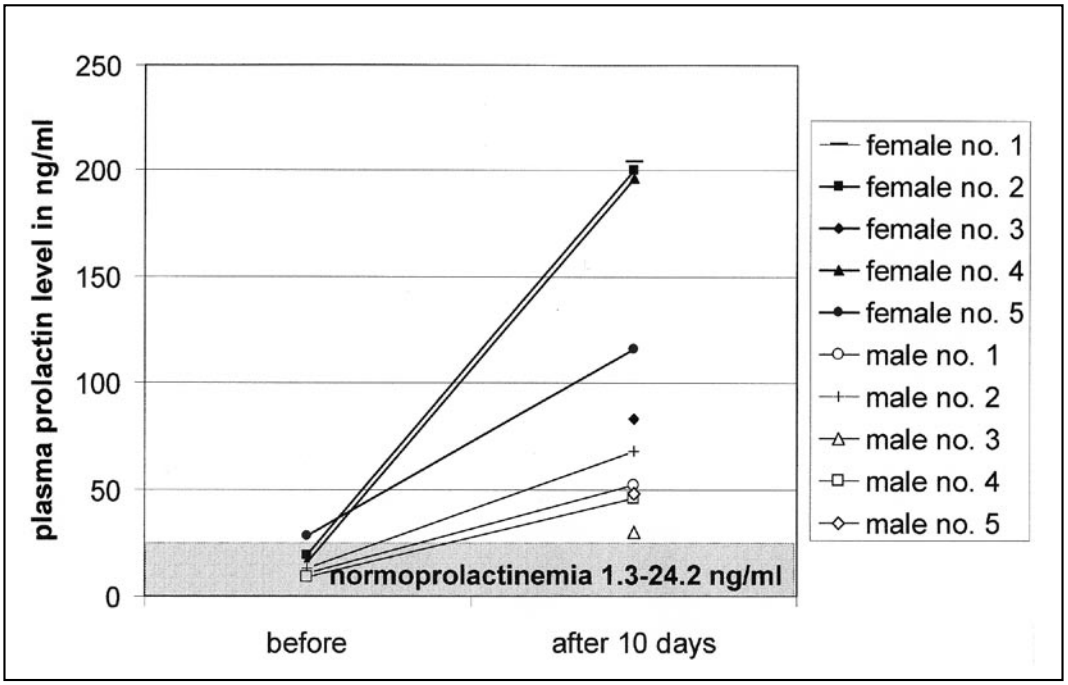

Figure 1. Plasma prolactin level before and after 10 days of 50 mg amisulpride daily administration.

torrhea, cessation of normal cyclic ovarian function, loss of libido, hirsutism or increased long-term risk of osteoporosis [9]. It seems necessary to be aware about these side effects, which are usually apparent after first generation of antipsychotics, even in low doses of amisulpride.

In two patients, which were treated with amisulpride for more than one month, we observed normalization of prolactin plasma levels 10 days after amisulpride withdrawal.

The co-medication of antidepressants and benzodiazepines can potentially increase the intensity of prolactinemia. In future studies it is preferential to follow low-dose amisulpride monotherapy only.

Conclusion

Even low doses of amisulpride used as an augmentation to antidepressant treatment, benzodiazepines or in monotherapy are associated with significant hyperprolactinemia. The psychiatrists should keep in mind the potential endocrinological side effects of low doses of amisulpride.

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