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Frequency of drug-associated hyperprolactinaemia: a single-center retrospective study

Elif Güneş[1], Mutlu Güneş[2]

[1]Department of Endocrinology, Metabolism Diseases and Diabetes, University of Health Sciences, Bursa City Hospital, Bursa, Turkey; [2]Department of Endocrinology and Metabolic Diseases, University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objectives: One of the causes of hyperprolactinaemia (HP) is drug-associated HP (DAHP). In this study, it was planned to investigate the frequency of DAHP.

Methods: In this study, a retrospective review of 296 individuals referred to the endocrinology outpatient clinic between June 2013 and March 2018 due to elevated prolactin (PRL) was performed.

Results: Of the 296 patients included in the study, 140 (47.3%) had HP (+), 80 (27.0%) had HP (-), 27 (9.1%) had DAHP and other causes (16.6%). The causes of DAHP were as follows; sulpiride in 7 (25.9%) patients, risperidone in 6 (22.2%), amisulpride in 4 (14.8%), domperidone in 3 (11.1%), haloperidol in 2 (7.4%), paliperidone, olanzapine, escitalopram, duloxetine and otilonium bromide in one patient each. PRL levels in the DAHP group were higher than in the HP (-) group (respectively; median 114.6 [interquartile range (IQR): 144.0], median 35 [IQR 37.3], $p < 0.001$). Patients with DAHP had an increased frequency of symptoms compared to the HP (-) group (oligomenorrhoea; 42.3%, 16.4%, $p = 0.007$, galactorrhoea; 53.8%, 30.1%, $p = 0.028$, respectively). PRL levels were higher and the frequency of clinical signs was higher in sulpiride than risperidone (PRL; median 195.0 [IQR 99.0], median 72.0 [IQR 57.9], $p = 0.022$, oligomenorrhoea; 100%, 20%, $p = 0.010$, respectively).

Conclusions: One of the 3 most common causes of patients referred for HP is DAHP and the most common cause of DAHP is anti-psychotic drugs. Sulpiride causes a higher rate of elevated PRL and frequency of clinical findings compared to other drugs.

Keywords: Hyperprolactinaemia, drug-associated hyperprolactinaemia, anti-psychotic drug

Prolactin (PRL) is a protein hormone produced from lactotroph cells in the pituitary (1). PRL release from lactotroph cells is under the control of negative and positive factors (1). The main factors that increase PRL production are suction, estrogen increase and stress (1). PRL production shows circadian production and is mainly under tonic control of inhibitory factors (1). The most important inhibitory factor is dopamine (DP) and it provides tonic control of PRL production via dopamine receptor 2 (DPR2) [1, 2]. The presence of sufficient amount of DP in the pituitary portal circulation suppresses production and pro-

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Address for correspondence: *Mutlu Güneş, MD., University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Department of Endocrinology and Metabolic Diseases, Mimarsinan Mah., Emniyet Cad., 16330 Yıldırım, Bursa, Turkey. E-mail: drmutlugunes@gmail.com, Phone: +90 224 295 50 00 ext. 1110*

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vides control of PRL synthesis (1, 2). This mechanism of action explains the effect of positive or negative dopaminergic effects of some drugs on PRL synthesis [3].

The most prominent drug group with anti-dopaminergic effects are anti-psychotic drugs (APD) and they constitute an important part of referrals due to hyperprolactinaemia (HP) [4-6]. Typical APD or 1st generation block DPR2 in all regions of the brain without any selectivity [7] and provide control of schizophrenic symptoms in this way [7]. On the other hand, 2nd generation or atypical APDs bind to serotonin 2 receptor (5HTR2) at a higher rate and DPR2 at a lower rate [7]. In addition, they show different effects in different regions of the brain (8). For example, 2nd generation APDs have a higher selectivity for the mesolimbic region than the striatal region [8]. Furthermore, while first generation neuroleptics have low affinity for DPR1, they show stronger antagonist effect against DPR2 [8]. All these mechanisms lead to the emergence of different effects of drugs on PRL.

On the other hand, increased PRL levels with APD cause drug-associated HP (DAHP). It is thought that increased PRL levels in DAHP disrupt the pulsatility of gonatotropins and lead to irregularities in menstrual cycles [9]. However, while this effect is observed in Caucasians, it is not observed in people of African descent [10], which leads to the questioning of the clinical significance of elevated PRL levels occurring in DAHP. The presence or absence of clinical findings in HP is one of the most important factors affecting the treatment approach [11, 12].

In this study, it was planned to determine the frequency of DAHP in patients referred with a prediagnosis of HP and to investigate whether there is an increase in the frequency of clinical findings in patients with DAHP.

METHODS

The study was conducted as a retrospective data analysis and individuals aged 18 years and over who were referred to the endocrinology, diabetes and metabolic diseases clinic of the Ministry of Health Çekirge State Hospital between June 2013 and March 2018 due to elevated PRL were included in the study.

The diagnosis and differential diagnosis of HP were made in accordance with the guidelines [11, 12].

Information about PRL, macro PRL (mPRL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), thyroid stimulating hormone (TSH), age, oligomenorrhoea, galactorrhoea, hirsutism, headache, erectile dysfunction, pituitary magnetic resonance imaging (MRI) and drug use were obtained from patient files. PRL levels were analysed with the "Abbott ARCHITECT Prolactin Reagen B7K76T Kit system" between the specified dates, covering 90% of the expected normal range in women and the entire expected normal range in men; median 6.99 ng/ml, range 3.46-19.40 ng/ml in men, median 10.29 ng/mL, range 5.18-26.53 ng/ml in women. Those with prolactin levels above normal limits for gender were defined as HP (+) and those with prolactin levels within normal limits for gender were defined as HP (-).

The present study was approved by the ethics committee of the University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital (011-KAEK-25 2022/02-11). In light of the retrospective nature of the study, all procedures were performed as part of routine care. The researchers affirm that they adhered to the Declaration of Helsinki. If the manuscript is accepted, it will not be published elsewhere in the same form in English or any other language without your consent.

Statistical Analysis

IBM® Statistical Package for the Social Sciences (SPSS) statistics 20 (IBM® Corp., Armonk, NY, USA) was used to compare the data. After the normal distribution was determined, an independent samples t-test was applied to data with a normal distribution, and the Mann-Whitney U test was applied to compare the data that did not have a normal distribution. The Pearson's chi-squared test was used to compare ratios. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 296 patients (264 females and 32 males) were referred, the mean age of females was 37.0 ± 9.3 years and the mean age of males was 43.8 ± 13.6 years. Of the 296 patients included in the study, 140 (47.3%) had HP (+), 80 (27.0%) had HP (-), 27 (9.1%) had DAHP, 41 (13.9%) had mPRL-related HP and the remaining 8 (2. 7%) patients had HP due to other

Table 1. Demographic and laboratory characteristics of patients

	HP (+) (n = 140)	*p* value[a]	HP (-) (n = 80)	*p* value[b]	DAHP (+) (n = 27)	*p* value[c]
Age (year)	38.8 ± 10.6	**< 0.001**	34.4 ± 7.0	**< 0.001**	42.2 ± 9.6	0.08
Gender (F/M)	123/17	0.50	73/7	0.6	26/1	0.70
Cr (mg/dL)	0.73 ± 0.15	0.47	0.71 ± 0.15	0.41	0.76 ± 0.14	0.17
TSH (µIU/mL)	2.01 (IQR25-75:1.42)	0.16	2.10 (IQR25-75:1.00)	0.92	2.10 (IQR25-75:1.79)	0.35
AST (U/L)	19.9 (IQR 25-75:6.0)	0.6	17.7 (IQR25-75:7.8)	0.13	19.4 (IQR25-75:9.5)	0.98
ALT (U/L)	16.5 (IQR25-75:11.0)	**0.002**	16 (IQR25-75:7.8)	0.97	16.0 (IQR25-75:9.5)	0.78
rPRL(µg/L)	101.5 (IQR25-75:102.4)	**0.001**	50.6 (IQR25-75:25.4)	**< 0.001**	132.7 (IQR25-75:100.5)	**0.004**
PRL (µg/L)	133.2 (IQR25-75:91.5)	**0.001**	35 (IQR25-75:37.3)	**< 0.001**	114.6 (IQR25-75:144.0)	0.38

*Median and interquartile range (IQR) 25-75 as not normally distributed, HP = hyperprolactinemia, DAHP = drug-associated HP, F = female, M = male, TSH = thyroid stimulating hormone, AST = aspartate aminotransferase, ALT = alanine aminotransferase, PRL = prolactin, rPRL = referral PRL

[a]Comparison of HP (+) and HP (-) group,

[b]Comparison of HP (-) and DAHP (+) group,

[c]Comparison of HP (+) and DAHP (+) group

causes (acromegaly + prolactinoma in 1 patient, polycystic ovary syndrome (PCOS) in 2 patients, pregnancy-related HP in 2 patients, HP as a result of pituitary stalk incision due to pituitary operation in 2 patients and HP due to hypothyroidism in 1 patient).

Demographic and laboratory characteristics of the study patients are shown in Table 1. During the period when the study was designed, mPRL was not a routine test and was ordered in case of clinical inconsistency. Therefore, the number of patients with mPRL was 83,

Table 2. Distribution of symptoms and findings

	HP (+)	*p* value[a]	HP (-)	*p* value[b]	DAHP (+)	*p* value[c]
Female, n (%)						
Oligomenorrhea,	52/123 (42.3)	**< 0.001**	12/73 (16.4)	**0.007**	11/26 (42.3)	0.99
Galactorrhea	84/123 (68.3)	0.06	22/73 (30.1)	**0.028**	14/26 (53.8)	0.16
Hirsutism	25/123 (20.3)	**< 0.001**	19/73 (26.0)	**0.050**	2/26 (7.7)	0.13
Headache	6/123 (4.9)	0.36	0/70 (0)	0.019	2/26 (7.7)	0.57
Male, n (%)						
ED	13/16 (81.3)	**0.032**	2/6 (33.3)	0.69	0/1 (0)	0.63
Headache	1/16 (6.3)	0.53	1/7 (14.3)	0.50	0/6 (0)	0.80

HP = hyperprolactinemia, ED = erectile dysfunction, DAHP = drug-associated HP

[a]Comparison of HP (+) and HP (-) group,

[b]Comparison of HP (-) and DAHP group,

[c]Comparison of HP (+) and DAHP group

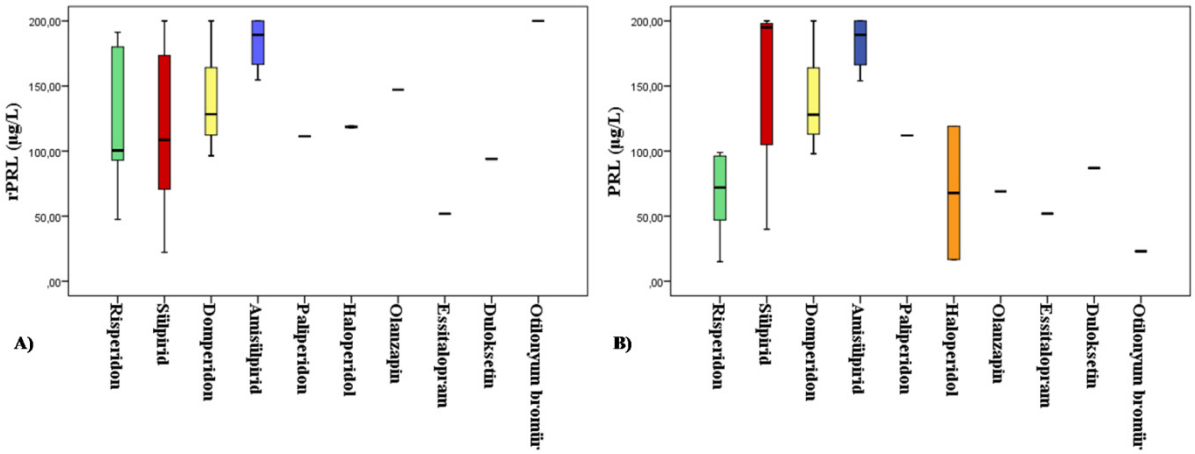

Fig. 1. rPRL (A) and admission PRL levels (B) according to etiological causes in drug-associated hyperprolactinemia. PRL = prolactin, rPRL = referral PRL.

the number of positive tests was 41, and the frequency of mPRL was 49.4% in ordered patiens group.

Clinical findings

The distribution of clinical findings according to the etiological causes of the patients in the study group is shown in Table 2. The frequency of symptoms increased in patients with DAHP compared to HP (-) group ($p = 0.028$).

Imaging data of 76 of 140 patients with HP (+) were available. Of the 76 patients whose imaging data were obtained, 65 were female and 11 were male. Of the 57 female patients with adenoma, 49 (75.4%) had microadenoma, 8 (12.3%) had macroadenoma, and 8 (12.3%)patients had no adenoma. Of the 11 male patients, 7 (63.6%) had microadenoma and 4 had macroadenoma (36.4%).

DAHP and Its Etiological Causes

The distribution of 27 patients with DAHP was as follows; sulpiride in 7 (25.9%), risperidone in 6 (22.2%), amisulpride in 4 (14.8%), domperidone in 3 (11.1%), haloperidol in 2 (7.4%), paliperidone, olanzapine, escitalopram, duloxetine and otilonium bromide in one patient each. 26 of 27 patients were female and 1 was male (Risperidone). The distribution of rPRL and PRL according to the etiological causes of DAHP is shown in the graph below (Fig. 1). While 21/27 (77.8%) of the patients had APD, the frequency of HP due to antidepressants was 7.4% (2/27) in the group with DAHP.

Age, rPRL and PRL levels of the three most common drugs are shown in Table 3. Amisulpiride, sulpiride, domperidone and haloperidol cause more severe HP compared to other agents.

Although all drugs increased PRL via dopamine in DAHP, the distribution of clinical findings was not the same (Table 4). Sulpiride causes more severe HP and the frequency of clinical findings is higher than risperidone ($p = 0.010$). Although more severe HP developed in domperidone users, the frequency of clinical findings was relatively less; two patients on haloperidol both had oligomenorrhoea and galactorrhoea (one of whom was postmenopausal), in dom-

Table 3. Characteristics of the three most common drugs causing DAH

	Age (years)	rPRL (µg/L)	PRL (µg/L)
Sülpirid (n = 7)	49.9 (IQR 25-75: 5.0)	108.6 (IQR 25-75: 160.0)	195.0 (IQR 25-75: 99.0)
Risperidon (n = 6)	38.0 (IQR 25-75: 12.8)	100.5 (IQR 25-75: 101.2)	72.0 (IQR 25-75: 57.9)
Amisülpirid (n = 4)	38.0 (IQR 25-75: 12.0)	189.3 (IQR 25-75: 39.4)	189.3 (IQR 25-75: 39.9)

Median and interquartile range (IQR) 25-75 as not normally distributed. DAHP = drug-associated hyperprolactinemia, PRL = prolactin, rPRL = referral PRL

Table 4. Distribution of clinical findings of the three most common drugs causing DAHP

	Oligomenorrhea	Galactorrhea
Sülpirid (n = 7)	7/7	4/7
Risperidon (n = 6)	1/5*	1/5*
Amisülpirid (n = 4)	2/4	3/4

DAHP = drug-associated hyperprolactinemia.
*In the risperidone group, there were 5 female patients and 1 male patient

peridone users; oligomenorrhoea was detected in 1/3 patients, that one patient with oligomenorrhoea was also postmenopausal, none of had galactorrhoea. Sulpiride, amisulpiride and haloperidol also cause severe HP and clinical findings are observed in most of the patients. Patients were premenopausal except for 2 patients using sulpiride (64 years) and domperidone (57 years).

DISCUSSION

It is observed that there is an increase in HP-related symptoms in DAHP compared to the HP-negative group. However, APDs causing DAHP have different mechanisms of action and clinical findings associated with HP at different frequencies.

In our study, DAHP constituted 9.1% of all admissions due to elevated PRL. In the PROLEARS study [13], which is one of the largest studies on the etiology of HP, the frequency of DAHP was found to be 45.9%. The study is a very large-scale investigation covering 20 years in Tayside, Scotland, where 400.000 inhabitants live and 1301 patients with HP were included [13]. The fact that it reflects community data is also an important aspect of the study. In the PROLEARS study, the frequency of DAHP was found to be considerably higher compared to our study. Possible reasons for this may be as follows; firstly, the frequency with which APDs are used may vary depending on the community concerned. and from region to region in the same community. In the literature review (PROSPERO) conducted by Junqueira *et al*. [14], in observational studies, APDs constituted a significant proportion of DAHP (90%), whereas antidepressants constituted 3%, prokinetic agents 5% and oral contraceptives 5%. In our study, APDs constituted 77.8% of DAHP, whereas antidepressants constituted 7.4%. As it is clearly seen in our study and previous studies, a significant proportion of DAHP are caused by APDs, whereas antidepressants constitute a very small proportion of DAHP (7.4%), although antidepressant use is very common in the in the community. In the study of Vilar *et al*. [15], the prevalence of DAHP was found to be 14.5% and the prevalence of prolactinoma was found to be 56.2%. In our study, the prevalence of DAHP was 7.4%, which is lower than that of Vilar *et al*. [15] and PROLEARS study [13]. The potential reason for this may be that the drugs were not questioned sufficiently. In our study, pituitary MRI imaging was requested from all patients who were thought to have HP, but MRI data of all patients could not be accessed. The prevalence of prolactinoma was 89.5%, and patients with HP constituted 47.3% of all presentations, so it can be assumed that the prevalence of prolactinoma was 42.3% in the whole study group. DAHP is one of the 3 most common causes of HP in clinical practice. Since mPRL was not requested from all patients, it is not possible to give a definite number in our study, but it is possible to say that it is more frequent than DAHP considering the positive rate in the requested patients.

DAHP consists of a very wide range of patient population including many different drug groups. Drugs in this group cause HP by different mechanisms. In general, APDs act by antagonising the effect of dopamine [16]. The anti-psychotic effect of APDs is by affecting DPR2 and DPR4 receptors in the mesolimbic area in the brain. Its effect on PRL secretion is again mediated by dopamine, blocking the effect of DPR2 receptors in the tuberoinfundubular area in the hypothalamus and removing the dopamine tonic inhibition on lactotrophs and thus PRL secretion increases [16]. DPR2 binding and selectivity of drugs show considerable variability [7, 17]. Old drugs, namely typical APD, phenothiazines (chlorpromazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, perphenazine), thioxanthenes (thiothixene), butyrophenones (haloperidol), and dibenzoxazepine (loxapine) are agents with very strong anti-psychotic effects [16]. Strong anti-psychotic effect also means strong anti-dopaminergic effect and strong HP-constructive effect [16, 17]. As their effects on DPR are different, DPR binding potentials in all regions of the

brain are not the same [16, 17]. New generation APDs such as clozapine, olanzapine, quetiapine, ziprasidone and aripiprazole act on DPR in different parts of the brain at different levels and lead to HP to a lesser extent [16-22]. In the study of Turrone *et al*. [20], it was found that olanzepine, an atypical APD, caused a slight increase in PRL levels, but this change was not significant. Since atypical APDs show anti-dopaminergic effect by transiently and mildly binding to DPR2, it is thought that the HP effect in these drugs is much milder and transient compared to typical APDs [16]. In a study conducted in individuals taking clozapine or olanzapine, PRL levels start to increase 2 to 4 hours after drug intake, the increase is generally limited to 1.5 to 2.5 times, and returns to baseline levels 8 hours after onset [20]. On the other hand, this effect starts at a similar time in Risperidone, but the effect of the drug lasts longer than 24 hours [209. However, this effect is not seen in 100% of patients, why does not PRL rise in all patients even though they are all taking the same drug? The answer to this question may be polymorphisms in the Taq1 A gene encoding DPR2 [23]. A decrease in DPR2 activity and number was found in individuals with A1 polymorphism, and APDs probably cause more HP in individuals with A1 polymorphism [23]. In general, HP caused by APDs returns to baseline levels 3-4 days after the drug is discontinued [16, 17]. In our study, PRL increase was higher in amisulpride, sulpiride and haloperidol compared to other drug groups, and mild HP was found in a patient using olanzepine. The findings were compatible with the general literature data.

As the HP-causing effects of APDs are different, there are also differences in the emergence of clinical findings [10]. In our study, oligomenorrhoea and galactorrhoea were found in 1 of 5 female patients using risperidone, whereas oligomenorrhoea was found in 7 of 7 patients and galactorrhoea was found in 4 of 7 patients using sülpirid, which increased PRL at similar levels. The number of patients in our study is not suitable for generalisation, the findings may be completely coincidental or the drugs may cause different frequencies of clinical findings at the same PRL levels. In the literature, oligomenorrhoea was found in 80% and galactorrhoea in 74% of the patients [14]. However, whether different drugs cause different clinical findings at the same PRL levels was not analysed in the studies [14]. Our study differs from the literature in this respect. This subject needs to be analysed and prospective and controlled studies in this field will contribute to a better understanding of the subject.

Limitations

Our study has some limitations. Firstly, since the study was conducted in retrospective design, there were problems in accessing some data. Again, it is likely that the same standard was not applied in the questioning of drugs, which are the most common causes of HP, and this attitude may have caused some unintentional errors to occur.

CONCLUSION

In our study, it was revealed that drugs were one of the three most common causes of HP and APDs was the most common cause of DAHP. It was observed that the frequency of clinical findings was higher in the DAHP group compared to the HP negative group. There is a strong suspicion that the effects of different drug groups on the frequency of clinical findings at similar PRL levels are also different, but further studies are needed in this regard.

Authors' Contribution

Study Conception: MG; Study Design: EG, MG; Supervision: MG; Funding: MG, EG; Materials: MG; Data Collection and/or Processing: EG, MG; Statistical Analysis and/or Data Interpretation: MG, EG; Literature Review: MG, EG; Manuscript Preparation: EG and Critical Review: MG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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