Odgovor prolaktina kod bolesnika sa shizofrenijom liječenim haloperidolom, klozapinom, risperidonom i olanzapinom

Prolactin response in patients with schizophrenia treated with haloperidol, clozapine, risperidone and olanzapine

Jelena Potkonjak[1], Dalibor Karlović[1], Željka Bukovec[2], Tihana Baričević[1]

[1]Klinika za psihijatriju, Klinička bolnica Sestre milosrdnice, Zagreb

[1]University Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb, Croatia

[2]Endokrinološki laboratorij, Klinička bolnica Sestre milosrdnice, Zagreb

[2]Laboratory of Endocrinology, Sestre milosrdnice University Hospital, Zagreb, Croatia

Sažetak

Uvod: Cilj ovog istraživanja bio je ispitati odgovor prolaktina (engl. *prolactine*, PRL) nakon specifične probe s lijekom sulpiridom, koji djeluje na dopaminergične receptore, kao i nakon probe s lijekom klomipraminom, koji djeluje na serotoninske receptore, kod bolesnika sa shizofrenijom liječenim klozapinom, olanzapinom, risperidonom i haloperidolom.

Materijali i metode: Ispitivanje je obuhvaćalo muškarce (N = 44) kojima je shizofrenija dijagnosticirana prema dijagnostičkim kriterijima DSM IV. U sklopu neuroendokrine procjene određena je koncentracija PRL nakon probe sa sulpiridom koji djeluje na dopaminergične receptore te nakon probe s klomipraminom, koji djeluje na serotoninske receptore.

Rezultati: Srednja bazalna koncentracija PRL znatno se razlikovala među skupinama ($P < 0,001$). *Post hoc* Schefféov test pokazao je postojanje statistički značajne razlike između skupine liječene haloperidolom i ostalih triju skupina (klozapin, olanzapin i risperidon). Nadalje, srednja se vrijednost koncentracije ΔPRL nakon uzimanja sulpirida ($P < 0,001$) kao i klomipramina ($P < 0,001$) znatno razlikovala među skupinama bolesnika.

Zaključak: Postoji razlika u odgovoru PRL nakon probe sulpiridom koji djeluje na dopaminergične receptore, odnosno klomipraminom koji djeluje na serotoninske receptore, kod bolesnika sa shizofrenijom liječenih klozapinom, olanzapinom, risperidonom i haloperidolom. Ta se razlika u odgovoru u neuroendokrinom modelu pojavljuje vjerojatno zbog zasićenosti neuroprijenosničkog sustava različitim antipsihotičkim lijekovima.

Ključne riječi: dopamin; prolaktin; shizofrenija; serotonin; antipsihotički lijekovi

Abstract

Background: The aim of our study was to investigate the prolactin (PRL) response after specific dopaminergic probe with sulpiride as well as serotonergic probe with clomipramine in patients with schizophrenia treated with clozapine, olanzapine, risperidone, and haloperidol.

Materials and methods: Male patients (N = 44) diagnosed with schizophrenia according to DSM IV criteria were included in the study. Neuroendocrine assessment included the determination of PRL levels after specific dopaminergic probe with sulpiride and serotonergic probe with clomipramine.

Results: Mean basal PRL levels differed significantly between groups ($P < 0.001$). *Post-hoc* Scheffé test revealed significant difference between haloperidol group *vs*. all three other subgroups (clozapine, olanzapine, and risperidone). Furthermore, mean ΔPRL level after sulpiride ($P < 0.001$) as well as after clomipramine ($P < 0.001$) induction also differed significantly between patient subgroups.

Conclusions: There is a difference in PRL response after dopaminergic and serotonergic probe in patients with schizophrenia treated with clozapine, olanzapine, risperidone and haloperidol. We hypothesize that this different response in neuroendocrine model might probably be due to neurotransmitter systems being occupied by different antipsychotic drugs.

Key words: dopamine; prolactin; schizophrenia; serotonin; antipsychotics drugs

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Uvod

Moderno doba psihofarmakološkog liječenja shizofrenije započelo je opažanjem da klorpromazin, koji se zapravo započeo ispitivati zbog svojih sedativnih učinaka, ima sposobnost liječenja iluzija i halucinacija (1). Kasnije se, zahvaljujući hipotezi koja pretpostavlja da je antipsihotičko djelovanje klorpromazina uzrokovano njegovom sposobnošću blokiranja stimulacije moždanih receptora dopamina, u tu svrhu sintetiziralo mnogo novih supstanci kao što su npr. butirofeni ili fenotianizini (2,3). Ta skupina antipsihotičkih lijekova, nastalih kao rezultat dopaminske hipoteze o shizofreniji, ne samo da je oblikovala liječenje, već i osnovni koncept tijeka bolesti (4). Daljnja su istraživanja pokazala da nisu samo produktivni simptomi shizofrenije u interesu rehabilitacije bolesnika, već da su i kognitivni simptomi procesa shizofrenije prepoznati kao važne komponente za mnoge bolesnike (5,6). Ti koncepti bacaju novo svjetlo na etiologiju kao i na psihofarmakologiju shizofrenije; dopaminergični sustav nije ništa važniji od ostalih simptoma, posebno od serotoninskog sustava u patofiziologiji shizofrenije (7,8). Taj koncept pruža nove psihofarmakološke strategije i današnje nove antipsihotičke lijekove, nazvane atipičnima, svrstava među lijekove prvog izbora u liječenju shizofrenije (9).

No, prema suvremenoj klasifikaciji, antipsihotici se dijele na dvije skupine: na tipične, dopaminske antagoniste i atipične antipsihotike koji djeluju na više neuroprijenosničkih sustava, najčešće na dopaminergični i serotoninski (10). Postavlja se pitanje jesu li atipični antipsihotici zaista farmakološki slični, ili među njima postoji značajna razlika. Velike razlike između atipičnih i tipičnih antipsihotika vidljive su u rasponu nuspojava, pa tako tipični antipsihotici mogu proizvesti ekstrapiramidalne simptome, kao i povećanu koncentraciju prolaktina (engl. *prolactine*, PRL) (2,11,12). Povećanje koncentracije PRL u krvi bolesnika liječenih tipičnim antipsihotičkim lijekovima uzrokovano je njihovim antagonističkim djelovanjem, dok je dopamin snažan inhibitor PRL (13). Hiperprolaktinemija se kod bolesnika sa shizofrenijom dosad vezala za različite zdravstvene probleme, kao npr. seksualnu disfunkciju i neplodnost (14), galaktoreju, nepravilnosti u menstrualnom ciklusu (15), smanjenje gustoće kostiju koje dovodi do osteopenije i osteoporoze (16). Također je postojala teza da bi hiperprolaktinemija mogla biti povezana s metaboličkim poremećajima kod bolesnika sa shizofrenijom (17).

Cilj ovog istraživanja je ispitati odgovor prolaktina (PRL) nakon specifične probe sa sulpiridom koji djeluje na dopaminske receptore, kao i nakon probe s klomipraminom koji djeluje na serotoninske receptore kod bolesnika sa shizofrenijom liječenih klozapinom, olanzapinom, risperidonom i haloperidolom.

Introduction

The modern era in the psychopharmacological treatment of schizophrenia started with the observation that chlorpromazine, originally studied for its sedative effects, had the ability to treat delusions and hallucinations (1). Later, due to the hypothesis that suggested that the antipsychotic action of chlorpromazine was caused by its ability to block the stimulation of brain dopamine receptors, many other substances like butyrophenes or phenothiazines were synthesized for that purpose (2,3). Not only did that group of antipsychotic drugs, resulting from the dopamine hypothesis of schizophrenia, shape the treatment of schizophrenia but also the basic concept of the process of the disease (4). Further investigations showed that productive symptoms of schizophrenia are not only of interest for the patients' rehabilitation, but cognitive symptoms of the schizophrenic disease process are also recognized as important components for many patients (5,6). These concepts bring new light on the etiology as well as psychopharmacology of schizophrenia; the dopaminergic system is not more important than other symptoms, especially serotonergic system in the pathophysiology of schizophrenia (7,8). This concept provides new psychopharmacologic strategies and today's new antipsychotics, also called atypical, are the first line of drugs for the treatment of schizophrenia (9).

However, current classification divides the antipsychotics only in typical, dopaminergic antagonists and atypical antipsychotics with action on multiple neurotransmitter systems, mostly dopaminergic and serotonergic (10). The question is whether the atypical antipsychotics are indeed pharmacologically similar, or there exist some substantial differences among them. Cardinal differences between atypical antipsychotics and typical antipsychotics are in the range of side effects, considering that typical antipsychotics can produce extrapyramidal symptoms as well as elevated prolactin (PRL) levels (2,11,12). The elevation of blood PRL levels in patients treated with typical antipsychotics is a consequence of their antagonistic dopaminergic activity, since dopamine is a strong PRL inhibitory factor (13). Hyperprolactinemia in patients with schizophrenia has been linked to various health issues such as sexual dysfunction and infertility (14), galactorrhea, menstrual irregularities (15), bone mineral density loss leading to osteopenia and osteoporosis (16). There has also been recognition that hyperprolactinemia may be associated with metabolic disturbances in patients with schizophrenia (17).

The aim of our study was to investigate the prolactin (PRL) response after specific dopaminergic probe with sulpiride as well as serotonergic probe with clomipramine in patients with schizophrenia treated with clozapine, olanzapine, risperidone, and haloperidol.

Ispitanici i metode

Ispitanici

U ovo prospektivno istraživanje uključili smo 124 uzastopna muškarca sa shizofrenijom koji su zaprimljeni na Kliniku za psihijatriju Kliničke bolnice Sestre milosrdnice u Zagrebu u vremenskom razdoblju od siječnja 2007. do rujna 2007. godine. Odlučili smo selektivno odabrati samo muškarce zbog njihovih nižih i konstantnih koncentracija PRL u krvi u usporedbi s koncentracijama PRL kod žena.

Kriterij uključivanja u istraživanje bio je monoterapija antipsihotikom na koji su bolesnici dobro reagirali, da nisu uzimali niti jedan drugi lijek osim benzodiazepina, te da nisu imali niti jedan drugi psihijatrijski ili medicinski problem ne računajući shizofreniju. 44 bolesnika srednje starosti od 34 ± 6 godina ispunilo je kriterije uključivanja, te su uključeni u istraživanje. Svi su bolesnici ispunili kriterije DSM IV za shizofreniju (18). 34 bolesnika imalo je paranoidno halucinantni oblik, 5 dezorganizirani, jedan katatoni i 4 bolesnika nediferencirani oblik shizofrenije. Srednja vrijednost trajanja bolesti bila je 9 ± 4 godine. Bolesnici su bili podijeljeni u skupine prema svojoj terapiji antipsihotičkim lijekovima: haloperidol (N = 11), klozapin (N = 12), risperidon (N = 11) i olanzapin (N = 10). Doza haloperidola bila je 15 mg, klozapina 300 mg, risperidona 6 mg i olanzapina 20 mg dnevno za svakog bolesnika. Te su doze jednake ekvivalentima klorpromazina. Trajanje psihofarmakoterapije bilo je manje od pet tjedana prije početka ovog istraživanja.

Etičko povjerenstvo Kliničke bolnice Sestre milosrdnice odobrilo je ovo istraživanje i svi su bolesnici dali svoj informirani pristanak za sudjelovanje u istraživanju.

Endokrinološka mjerenja

U 8 sati ujutro, natašte, bolesnicima je venskim kateterom u venu na ruci ubrizgana infuzija fiziološke otopine. Nakon 15-minutnog odmora bolesnicima je intramuskularno dano 100 mg sulpirida. Uzorci krvi uzimali su se 0, 30, 60, 120, 180 i 240 minuta nakon infuzije. Nakon sedam dana ponovljen je isti postupak s klomipraminom u dozama od 75 mg intramuskularno i vremenom prikupljanja uzoraka krvi od 0, 30, 60, 120, 180 i 240 minuta nakon injekcije klomipramina. Svi su stimulacijski testovi napravljeni prema standardiziranim protokolima opisanim u prethodno objavljenoj literaturi (19). Svi uzorci krvi centrifugirani su 15 minuta na 2500 okr./min. Serum je alikvotiran i spremljen na –20°C do analize. Koncentracija PRL određena je fluoroimunom metodom (engl. *fluoroimmunoassay*, FIA) s komercijalnim reagensom Delfia prolactin (Wallac Oy, Turku, Finska). Svi su testovi napravljeni u duplikatu. Prema uputama proizvođača, osjetljivost testa bila je 0,04 ng/mL, koeficijent varijacije u seriji bio je 2,6% a onaj iz dana u dan 3,4%.

Subjects and methods

Subjects

We prospectively recruited a consecutive series of 124 male patients with schizophrenia admitted to the Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb, Croatia, from January 2007 to September 2007. We decided to selectively include only male patients, because they have lower and constant blood PRL concentrations in comparison to female patients.

Inclusion criteria were: patients who had only one antipsychotic in their therapy and had good therapeutic response to that drug, did not take any other drugs except for benzodiazepine and that they did not have any other psychiatric or medical problem besides schizophrenia. Forty-four male patients with a mean age of 34 ± 6 years fulfilled the inclusion criteria and were included in the study. All patients fulfilled DSM IV criteria for schizophrenia (18). There were 34 patients with a paranoid-hallucinatory, 5 with a disorganized, 1 with a catatonic and 4 with an undifferentiated form of schizophrenia. Mean duration of illness was 9 ± 4 years. Patients were divided into the following study subgroups according to their antipsychotic therapy: haloperidol (N = 11), clozapine (N = 12), risperidone (N = 11) and olanzapine (N = 10). The haloperidol dose was 15 mg, the clozapine dose 300 mg, the risperidone dose 6 mg, and the olanzapine 20 mg per day for each patient. These doses were equal to chlorpromazine equivalents. The duration of that psychopharmacotherapy was less than five weeks prior to this experiment.

The ethical committee of the Sestre milosrdnice University Hospital approved this research and all patients gave informed consent in order to participate in the study.

Endocrine measurement

At 8 a.m., after an overnight fast, an indwelling venous catheter was inserted into a forearm vein, maintaining normal saline infusion. After a 15-minute-rest subjects were administered 100 mg of sulpiride intramuscularly. Blood samples for PRL concentration were drawn at 0, 30, 120 and 180 minutes after the infusion.

Seven days after, the same procedure was repeated with clomipramine in doses of 75 milligrams intramuscularly, and blood samples were collected at 0, 30, 60, 120, 180, and 240 minutes after clomipramine injection. All stimulation tests were performed according to standardized protocols previously described in literature (19).

All blood samples were centrifuged for 15 minutes at 2500 rpm. Serum was aliquoted and stored at –20 °C until analysis. PRL concentration was determined by fluoroimmunoassay (FIA) using the Delfia prolactin commercial kit (Wallac Oy, Turku, Finland). All tests were run in duplicate. As declared by the manufacturer, assay sensitivity, intra-

ΔPRL je izračunata kao vršna koncentracija PRL nakon ubrizgavanja sulpirida nakon 30 minuta ili klomipramina nakon 180 minuta, umanjena za bazalnu koncentraciju PRL. Referentni interval koncentracije PRL našeg laboratorija za bolesnike (muškarce) iznosi 2,3–11,5 ng/mL.

Statistička analiza

Podaci su izraženi kao srednja vrijednost ± SD. Odstupanja između raspodjele podataka i normalne raspodjele ispitana su Kolmogorov-Smirnovljevim testom u svakoj skupini. Usporedbe bazalne koncentracije PRL i ΔPRL između skupina koje su primile haloperidol, klozapin, risperidon i olanzapin procijenjene su analizom varijance (ANOVA). *Post hoc* Schefféovom metodom ispitane su razlike u koncentracijama između pojedinih podskupina. Razina statističke značajnosti postavljena je na 0,01. Sve su analize podataka napravljene pomoću statističkog programskog paketa SPSS 8.0 (SPSS for Windows 8.0, SPSS., Chicago, IL, SAD).

Rezultati

Bazalne koncentracije PRL

Srednje vrijednosti koncentracije PRL bile su 32,0 ± 7,8 ng/mL u skupini koja je primila haloperidol, 4,7 ± 1,1 ng/mL u skupini na klozapinu, 10,1 ± 1,6 ng/mL u skupini na risperidonu i 6,4 ± 2,4 ng/mL u skupini na olanzapinu. Postojala je statistički značajna razlika u srednjoj vrijednosti bazalne koncentracije PRL između ovih skupina bolesnika ($P < 0,001$). *Post hoc* Schefféov test pokazao je da je razlika između skupine koja je primila haloperidol i ostalih triju skupina (klozapin, olanzapin i risperidon) statistički značajna (Tablica 1.). Koncentracije prolaktina u tim trima skupinama (klozapin, risperidon i olanzapin) međusobno se nisu statistički značajno razlikovale. Srednja vrijednost koncentracije PRL u skupini koja je primila haloperidol bila je iznad referentnog intervala, dok je u skupinama na klozapinu, olanzapinu i risperidonu srednja vrijednost koncentracije PRL bila unutar referentnog intervala.

PRL u probi sa sulpiridom

Srednje vrijednosti promjene izmjerene koncentracije prolaktina (ΔPRL) nakon ubrizgavanja injekcije sulpirida bile su 8,2 ± 1,7 ng/mL u skupini koja je primila haloperidol, 94,3 ± 8,7 ng/mL u skupini na klozapinu, 5,3 ± 1,3 ng/mL u skupini na risperidonu i 46,6 ± 16,0 ng/mL u skupini na olanzapinu. Primijećena razlika srednje vrijednosti ΔPRL nakon injekcije sulpirida bila je statistički značajna između skupina bolesnika ($P < 0,001$). *Post hoc* Schefféov test pokazao je da su srednje vrijednosti ΔPRL nakon injekcije sulpirida bile više u skupinama koje su primile klozapin i olanzapin nego kod onih na haloperidolu i risperidonu, dok razlika u vrijednostima ΔPRL nakon injekcije

assay coefficient of variation and inter-assay coefficient of variation were 0.04 ng/mL, 2.6% and 3.4%, respectively. ΔPRL was calculated at the maximum rise in PRL level after an injection of sulpiride after 30 minutes, or clomipramine after 180 minutes, minus basal PRL level. Our laboratory PRL reference interval for male patients is 2.3–11.5 ng/mL.

Statistical analysis

Data were expressed as mean ± SD. The discrepancies between data distribution and normal distribution were examined by the Kolmogorov-Smirnov test for each group. Comparisons of basal and ΔPRL between haloperidol, clozapine, risperidone, and olanzapine groups were evaluated by the analysis of variance (ANOVA). We used the *post-hoc* Scheffé method for pair-wise comparisons. Statistical significance was set at the level of 0.01. All data analyses were conducted using the statistical package SPSS 8.0 (SPSS for Windows 8.0, SPSS., Chicago, IL, USA).

Results

Basal PRL levels

Mean basal PRL values were 32.0 ± 7.8 ng/mL in haloperidol group, 4.7 ± 1.1 ng/mL in clozapine group, 10.1 ± 1.6 ng/mL in risperidone group, and 6.4 ± 2.4 ng/mL in olanzapine group. The observed difference in mean basal PRL levels between patient subgroups was statistically significant ($P < 0.001$). *Post-hoc* Scheffé test revealed that the difference was significant between haloperidol group vs. all three other subgroups (clozapine, olanzapine, and risperidone) (Table 1.). Clozapine, risperidone and olanzapine subgroups did not differ among each other. The mean PRL concentration in the haloperidol subgroup was above the reference interval, whereas clozapine, olanzapine and risperidone subgroups had mean PRL concentration within the reference interval.

PRL in dopaminergic probe

Mean ΔPRL values after the sulpiride injection were: 8.2 ± 1.7 ng/mL in haloperidol, 94.3 ± 8.7 ng/mL in clozapine, 5.3 ± 1.3 ng/mL in risperidone and 46.6 ± 16.0 ng/mL in olanzapine patient subgruop. The observed difference in mean ΔPRL levels after sulpiride injection was statistically significant among patient subgroups ($P < 0.001$). *Post-hoc* Scheffé test showed that mean DPRL levels after sulpiride injection were substantially higher in clozapine and olanzapine subgroups compared to haloperidol and risperidone groups. There was no statistically significant difference between haloperidol and risperidone groups in ΔPRL value after sulpiride injection (Table 1).

Tablica 1. Analiza varijance (ANOVA) i *post hoc* Schefféov test u analizi razlike bazalnih koncentracija prolaktina (PRL) nakon probe lijekovima sulpirid i klomipramin

Table 1. Analysis of variance (ANOVA), and Post-hoc Scheffé test in the analysis of difference in prolactin (PRL) basal levels, and after sulpiride and clomipramine probe.

Basal PRL levels	ΔPRL levels sulpiride test	ΔPRL levels clomipramine test
P (haloperidol *vs*. clozapine) = **0.001**	P(haloperidol *vs*. clozapine) = **0.001**	P(haloperidol *vs*. clozapine) = **0.001**
P(haloperidol *vs*. risperidone) = **0.001**	P(haloperidol *vs*. risperidone) = 0.94	P(haloperidol *vs*. risperidone) = **0.001**
P(haloperidol *vs*. olanzapine) = **0.001**	P(haloperidol *vs*. olanzapine) = **0.001**	P(haloperidol *vs*. olanzapine) = **0.001**
P(clozapine *vs*. risperidone) = 0.106	P(clozapine *vs*. risperidone) = **0.001**	P(clozapine *vs*. risperidone) = 0.88
P(clozapine *vs*. olanzapine) = 0.88	P(clozapine *vs*. olanzapine) = 0.56	P(clozapine *vs*. olanzapine) = 0.86
P(risperidone *vs*. olanzapine) = 0.389	P(risperidone *vs*. olanzapine) = **0.001**	P(risperidone *vs*. olanzapine) = 0.98
P(total group) = 0.001	**P(total group) = 0.001**	**P(total group) = 0.001**

je sulpirida između skupine na haloperidolu i risperidonu nije bila statistički značajna (Tablica 1.).

PRL u probi s klomipraminom

Srednje vrijednosti promjene izmjerene koncentracije prolaktina (ΔPRL) nakon ubrizgavanja injekcije klomipramina bile su 12,7 ± 4,7 ng/mL u skupini koja je primila haloperidol, 0,8 ± 0,3 ng/mL u skupini na klozapinu, 1,5 ± 0,7 ng/mL u skupini na risperidonu i 1,9 ± 1,1 ng/mL skupini onoj na olanzapinu. Primijećena razlika srednje vrijednosti ΔPRL nakon probe injekcijom klomipramina bila je statistički značajna između skupina bolesnika ($P < 0,001$). *Post hoc* Schefféov test pokazao je da su srednje vrijednosti ΔPRL nakon injekcije klomipramina bile znatno više u skupini koja je primila haloperidol nego kod ostalih skupina (klozapin, olanzapin i risperidon), dok među tim trima skupinama nije bilo statistički značajne razlike (Tablica 1.).

Rasprava

Temeljem dobivenih rezultata možemo primijetiti da postoji razlika u farmakološkim karakteristikama atipičnih antipsihotika risperidona, olanzapina i klozapina. Sulpirid testom u okviru neuroendokrine probe željeli smo istražiti dopaminergičnu aktivnost zbog njene snažne antagonističke aktivnosti na dopaminske receptore tipa 2 (D_2) i dobrog otpuštanja PRL nakon primjene sulpirida (20). Drugi test koji smo napravili bio je klomipraminski test. Odlučili smo se za klomipramin zbog njegova jake selektivne serotoninske inhibicije (21). U drugim je istraživanjima klomipramin također pokazao dobar utjecaj na oslobađanje PRL (22).

Bolesnici liječeni tipičnim antipsihoticima često imaju povišenu koncentraciju PRL zbog njihove jake antagonis-

PRL in serotonergic probe

Mean ΔPRL values after the clomipramine injection were: 12.7 ± 4.7 ng/mL in haloperidol, 0.8 ± 0.3 ng/mL in clozapine, 1.5 ± 0.7 ng/mL in risperidone and 1.9 ± 1.1 ng/mL in olanzapine subgroup. The observed difference in mean ΔPRL levels after serotonergic probe with clomipramine injection was statistically significant between patient subgroups ($P < 0.001$). *Post-hoc* Scheffé test revealed that mean ΔPRL levels after clomipramine injection were substantially higher in haloperidol compared to clozapine, risperidone and olanzapine subgroups. The mean ΔPRL values after a serotonergic probe with clomipramine did not differ among clozapine, risperidone, and olanzapine subgroups (Table 1).

Discussion

Our results suggest that there is a difference in pharmacological characteristics of atypical antipsychotics risperidone, olanzapine, and clozapine. We used the sulpiride test in our neuroendocrine probe to investigate the dopaminergic activity because of its strong antagonist dopaminergic receptor type 2 (D_2) activity, and good PRL release after the sulpiride application (20). The second test we performed was the clomipramine test. We chose clomipramine because of its strong selective serotonin inhibitor (21), and because clomipramine in other studies showed a favorable effect on PRL release (22).

Patients treated with typical antipsychotics often have elevated PRL levels because of their strong antagonistic activity on dopaminergic receptors (23). In our assessment, patients with schizophrenia treated with haloperidol also showed elevated basal PRL levels. Patients with schizophrenia treated with atypical antipsychotics, clozapine and olanzapine, had basal PRL levels within a normal

tičke aktivnosti na dopaminske receptore (23). U našem istraživanju bolesnici sa shizofrenijom liječeni haloperidolom imali su još i povišenu bazalnu koncentraciju PRL. Bolesnici sa shizofrenijom liječeni atipičnim antipsihoticima klozapinom i olanzapinom imali su koncentracije PRL unutar granica referentnog intervala, dok su koncentracije PRL bolesnika iz skupine koja je dobivala risperidon bile lagano povišene. Potencijal risperidona u serotoninskoj aktivnosti sličan je potencijalu klozapina i olanzapina, dok je u dopaminergičnoj aktivnosti njegov potencijal sličan potencijalu tipičnog antipsihotika, haloperidolu. Ovi rezultati daju risperidonu (kao atipičnom antipsihotiku) novo mjesto na granici između stvarnih tipičnih i stvarnih atipičnih antipsihotika te isto tako prikazuju u novom svjetlu klasifikaciju antipsihotika.

U drugim je istraživanjima risperidon klasificiran kao atipični antipsihotik zbog svoje jake serotoninske aktivnosti (10). No, kad smo analizirali klinički učinak risperidona u usporedbi s ostalim atipičnim antipsihoticima, posebno klozapinom, njegov bi se učinak na simptome shizofrenije prije mogao nazvati „tipičnim" nego „atipičnim". S druge strane, analizom kliničkog učinka risperidona u usporedbi s tipičnim antipsihoticima ustanovilo se da on ima bolji učinak na negativne simptome, što je karakteristika atipičnih, a ne tipičnih antipsihotika (24).

Raspon nuspojava risperidona više sliči nuspojavama tipičnih antipsihotika, posebno u segmentu ekstrapiramidalnih simptoma kao i povećanoj koncentraciji PRL (25). Stoga drugi autori kao i autori ovog istraživanja ističu nužnost preformuliranja koncepta antipsihotika, posebno onog segmenta koji se odnosi na podjelu na „tipične" i „atipične" antipsihotike.

Prema ranije objavljenoj literaturi, djelovanje antipsihotika donosi novu konceptualizaciju neuroprijenosničkih sustava uključenih u patologiju shizofrenije (26). U reduciranju nuspojava, poboljšavanju negativnih simptoma i terapijskim učincima liječenja, rezistentna je shizofrenija predstavljala jednu od faza u razvoju atipičnih antipsihotika (27). U tom konceptu na razvoj novih antipsihotika s dvostrukom dopaminergičnom i serotoninskom aktivnošću utjecala je nova hipoteza o serotoninsko-dopaminergičnoj neravnoteži kod shizofrenije (28).

Do danas objavljeni radovi ukazuju na postojanje mnogo više neuroprijenosnika osim serotonina i dopamina, koji su uključeni u neurokemiju shizofrenije. Istraživači, primjerice, ističu NMDA, GABA i druge sustave (29). Međutim, u budućnosti možemo očekivati nove lijekove koji bi djelovali terapijski, ne preko dopaniminskih ili serotoninskih, već preko drugih sustava (30,31). Smatramo da postoji potreba za analiziranjem djelovanja antipsihotičkih lijekova na kliničku sliku, tijek i rezultat simptoma shizofrenije, kao i za procjenom antipsihotičkog djelovanja na neuroprijenosnike.

range, while in the risperidone group the basal levels of PRL were slightly elevated or upper reference range values. The potential of risperidone for serotonergic activity equals that of clozapine and olanzapine, while in the dopaminergic activity its potential is similar to that of a typical antipsychotic, haloperidol. These findings put risperidone (as an atypical antipsychotic) in a new, borderline position between true typical and true atypical antipsychotics, and they also shed a new light on the classification of antipsychotics.

In other studies, risperidone is classified as an atypical antipsychotic because of its strong serotonergic activity (10). But when we analyzed the clinical effect of risperidone in comparison to other atypical antipsychotics, especially clozapine, risperidone's activity on the symptoms of schizophrenia could be marked more as "typical" then "atypical". On the other hand, while analyzing the clinical effects of risperidone compared to typical antipsychotics, risperidone had better effects on negative symptoms,which is a characteristic of atypical antipsychotics rather than the typical ones (24).

Risperidone's range of side effects is more similar to those of typical antipsychotics, especially regarding extrapiramidal symptoms and the rise of PRL level (25). Thus, other authors as well as our investigation pointed out that it is necessary in the future to reformulate the concept of antipsychotics, especially regarding what is "typical" or "atypical".

With respect to history data, antipsychotic activity introduces new conceptualization of neurotransmitter systems involved in pathology of schizophrenia (26). In reduction of side effects, improvement of negative symptoms, and therapeutic effect of treatment, resistant schizophrenia was a point in the development of atypical antipsychotics (27). In this concept, the development of new antipsychotics with dual dopaminergic and serotonergic activity was influenced by a new hypothesis of serotonergic/dopaminergic disbalance in schizophrenia (28).

Nowadays the literature suggests that many neurotransmitters are involved in the neurochemistry of schizophrenia other than serotonin and dopamine. For example, researchers especially pointed out NMDA, GABA and other systems (29). However, in the future we can expect new drugs which would act therapeutically through other systems rather than dopamine or serotonin ones (30,31). We think there is a need for analyzing the effects of antipsychotic drugs on the clinical picture, the course, and outcome of schizophrenic symptoms, as well as for assessing the antipsychotic action on neurotransmitters.

Our study had several limitations. Firstly, our study groups were too small. In further studies we need to increase the number of patients in the groups and expand research on some other antipsychotics, i.e. quetiapine, and aripiprazole. Also, we did not compare prolactin response

Naše istraživanje ima nekoliko ograničenja. Kao prvo, naša je eksperimentalna skupina bila premalena. U daljnjim istraživanjima trebamo povećati skupinu bolesnika i proširiti istraživanje na neke druge antipsihotike, npr. kvetiapin i aripiprazol. Također, nismo usporedili odgovor prolaktina i kliničku ozbiljnost simptoma shizofrenije koje kontroliraju psihijatrijske ljestvice kao npr. PANSS.
Zaključno, postoji razlika u odgovoru PRL nakon probe lijekovima koji djeluju na dopaminergične, odnosno serotoninske receptore kod bolesnika sa shizofrenijom liječenih klozapinom, olanzapinom, risperidonom i haloperidolom. Smatramo da se taj različiti odgovor u neuroendokrinom modelu događa zbog zasićenosti neuroprijenosničkog sustava različitim antipsihotičkim lijekovima. Daljnje su analize s drugim atipičnim antipsihoticima neophodne kako bi se revidirala sadašnja klasifikacija antipsihotičkih lijekova i eventualno formulirala nova.

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and clinical severity of schizophrenia symptoms controlled by the psychiatric scale such as PANSS.
In conclusion, there is a difference in PRL response after dopaminergic and serotonergic probe in patients with schizophrenia treated with clozapine, olanzapine, risperidone, and haloperidol. This different response in neuroendocrine model is due to neurotransmitter systems being occupied by different antipsychotic drugs. Further analyses with other atypical antipsychotics are necessary to revise current classification of antipsychotics and possibly introduce a new classification of these drugs.

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Adresa za dopisivanje:

Dalibor Karlović
Klinika za psihijatriju
Klinička bolnica Sestre milosrdnice
Vinogradska cesta 29
10 000 Zagreb
e-pošta: dalibor.karlovic@gmail.com

Corresponding author:

Dalibor Karlović
University Department of Psychiatry
Sestre milosrdnice University Hospital
Vinogradska cesta 29.
10 000 Zagreb
Croatia
e-mail: dalibor.karlovic@gmail.com

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