CASE REPORT

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Zuclopenthixol decanoate in pregnancy: successful outcomes in two consecutive offsprings of the same mother

Zuklopentiksol dekanoat u trudnoći: uspešan ishod dve uzastopne trudnoće iste majke

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Abstract

Introduction. Almost all individual antipsychotics are classified into the intermediate pregnancy risk category as no or limited data exist about human pregnancy outcomes. We presented the case of zuclopenthixol decanoate using in two successive pregnancies of the same woman, which had not been published in the available peer-reviewed literature. **Case report.** A middle-age female subject who suffered from schizophrenia received zuclopenthixol decanoate injection during her two consecutive pregnancies. About four and a half months before diagnosis of the first pregnancy (~3.5 years after psychosis emergence), zuclopenthixol decanoate (400 mg every other week, *im* injection) was introduced to the treatment protocol (due to previous non-compliance with haloperidol and risperidone). A significant clinical improvement was achieved and the dose during pregnancy was reduced to 200 mg once monthly and maintained to date. In both pregnancies the women gave birth to healthy girls who have been developing normally until now, at their ages of 6 months and of 3.5 years. During pregnancy and after giving birth to children the mothers' psychiatric status and her social functioning were significantly improved and are still stable. Close monitoring of the mother's health, a multidisciplinary approach to both her treatment and the monitoring of pregnancies as well as the complete compliance with the prescribed drug protocol were likely to be crucial for the therapeutic success. **Conclusion.** A favorable outcome of the present case suggests that the zuclopenthixol decanoate is a rational therapeutic option for pregnant women suffering from psychosis when the expected benefit exceed the potential risk, but a definitive evidence for its safety requires large, controlled studies.

Key words:
psychotic disorders; pregnancy; risk factors; psychotropic drugs; treatment outcome.

Apstrakt

Uvod. S obzirom na to da ne postoje ili su podaci o ishodu trudnoće u slučaju njihovog korišćenja oskudni, skoro svi antipsihotici su svrstani u kategoriju sa srednjim rizikom u slučaju trudnoće. Prikazano je korišćenje zuklopentiksol-dekanoata u dve uzastopne trudnoće iste žene, što do sada nije bilo objavljeno u dostupnoj recenziranoj literaturi. **Prikaz bolesnika.** Žena srednjih godina koja je bolovala od šizofrenije primala je injekciju zuklopentiksol-dekanoata tokom svoje dve uzastopne trudnoće. Oko četiri i po meseca pre dijagnoze prve trudnoće (~3,5 godine posle početka psihoze) u terapijski protokol je uveden zuklopentiksol-dekanoat (400 mg svake druge nedelje, *i.m.* injekcija) zbog prethodnog neredovnog uzimanja haloperidola i risperidona. Postignuto je značajno kliničko poboljšanje, pa je doza leka tokom trudnoća snižena na 200 mg jednom mesečno i održavana do sada. U obe trudnoće rođena je po jedna zdrava devojčica i normalno su se razvijale do uzrasta od šest meseci, odnosno 3,5 godine. Tokom trudnoća i posle rođenja dece psihijatrijski status i socijalno funkcionisanje majke bili su značajno poboljšani i do danas stabilni. Pomno praćenje zdravstvenog stanja majke, multidisciplinarni pristup njenom lečenju i praćenju trudnoća kao i potpuna komplijansa sa propisanim medikamentnim protokolom najverovatnije su bili presudni za terapijski uspeh. **Zaključak.** Povoljni ishodi prikazane bolesnice ukazuju da je kod trudnica obolelih od psihoze zuklopentiksol-dekanoat racionalna terapijska opcija, kada očekivana korist prevazilazi potencijalne rizik, ali su za definitivan dokaz o njegovoj bezbednosti potrebne kontrolisane studije sa velikim uzorkom.

Ključne reči:
psihotički poremećaji; trudnoća; faktori rizika; psihotropni lekovi; lečenje, ishod.

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Introduction

Pregnancy in a schizophrenic woman represents a considerable therapeutic challenge as there is a high risk of adverse outcomes [1]. Apart from obstetric complications, the changes in pharmacokinetics and drug response in pregnancy [2] and possible harmful effects of pharmaceuticals on developing fetus [3] could also make using antipsychotic medication difficult. Although clinical experience with the use of antipsychotic drugs in pregnant women is mostly encouraging [4, 5] almost all individual antipsychotics are classified into the intermediate pregnancy risk category as no or limited data exist about human pregnancy outcomes [6]. Zuclopenthixol belongs to an older, thioxanthene drugs but some professionals prefer it for agitated or aggressive patients [7]. Besides, a long-acting parenteral formulation of decanoate ester (depot) is still widely marketed, including many European countries [8]. Zuclopenthixol decanoate, having lower acquisition price in comparison with depot formulations of novel antipsychotics [9], might be convenient choice for decreasing frequency of relapses [10] and when shortages of the older depot antipsychotics happen [11]. However, we were unable to locate the published data dealing with both the use of zuclopenthixol during human or animal pregnancy and the consequent fetal outcomes.

Case report

A 35-old woman, suffered from schizophrenia (F20, ICD-10 code) from November 2003. The disease started with symptoms of disorganized behavior, delusions of control, tactile hallucinations, flat affect and social withdrawal. The patient was hospitalized and psychiatrist prescribed haloperidol, initially with 15 mg per day and then in maintenance daily dose of 10 mg. After four weeks the patient continued ambulatory treatment with the same drug but gradually reduced to 7.5 mg per day. The patient's condition significantly improved and the patient returned to her usual activities. However, in 2005, the second exacerbation appeared, almost immediately after the self-discontinuation of haloperidol due to the perceived adverse effects of the medication (rigidity, bradykinesia and "mind disturbances"). The patient's condition stabilized with risperidone, 4 mg daily, but after a 10-month treatment the patient went abroad, and presented to the psychiatrist again in February 2007 with another exacerbation characterized with delusions of control and persecution, psychomotor agitation and tangential thinking. The patient's status was rated "markedly ill", according to the Clinical Global Impression-Severity Scale (CGI-S).

Six months before the episode, the patient discontinued risperidone on her own, due to amenorrhea perceived by the patient to be "drug-induced". She refused the continuation of treatment with any drugs and intramuscular (*im*) injections of zuclopenthixol acetate and, then, decanoate was prescribed due to the expected compliance problems. The dose of zuclopenthixol acetate was 50 mg every third day, up to 150 mg and then long-acting, *im* depot injection of zuclopenthixol decanoate, 400 mg every two weeks. The psychiatric status significantly improved and rated as "borderline mentally ill" due to minimal residual symptoms (blunted affect, discrete suspiciousness).

The first unintentional pregnancy was diagnosed in the 13th week of gestation, about four and a half months after zuclopenthixol treatment initiation. The team consisting of a psychiatrists, clinical pharmacologists and gynecologists considered the case to be at high risk and took closely further care of both mother and fetus. They explained the risk of using zuclopenthixol during pregnancy to the patient and she freely decided to continue both the pregnancy and the drug treatment. The next drug dose was reduced to 200 mg administered in monthly intervals. The history of fluctuating disease course, noncompliance and frequent exacerbations favored the treatment decision. The same dose continued to be administered throughout further pregnancy.

In 2010 the patient conceived for the second time but again unintentionally and presented to the team from the 12th gestational week. Since the first delivery, the mother continuously received zuclopenthixol decanoate *im* injection, and she was stabilized on 200 mg monthly dose. The scenario from the first pregnancy repeated as both the pregnancy and the antipsychotic were continued.

Hospital pediatricians as well as primary care staff (pediatrician, general practitioner, and nurse) jointed during the end of pregnancies and postnatal periods. Both babies were healthy, mature girls at deliveries (Table 1). The first one was born in January 2008, and the second one in January 2011, without obvious congenital malformations. The brain ultrasound finding in the younger sister was normal and in the first child revealed some clinically-insignificant periven-

Table 1

The clinical and laboratory findings in both babies at deliveries

Variable	The first child	The second child
Gestation, delivery (weeks)	39th	40th
Apgar score (points)	9	9
Body weight, delivery (g)	3,750	3,700
Body weight, discharge (g)	3,650	3,530
Body height (cm)	55	53
Head circumference (cm)	35	35
Thoracic circumference (cm)	35	33
Amniotic fluid	clear	clear
Umbilical cord	normal	normal
Glycemia (mmol/L)	3.2	2.0 and 2.4
C-reactive protein (mg/L)	6.1	not done
Coombs' test	positive	negative

tricular hyperechogenicity. In both girls blood counts were normal and blood groups were ”0“ with positive Rh factor. The babies received vitamin K, BCG and hepatitis B vaccines. Breastfeeding was avoided and they were fed with the artificial alimentary formulas. At discharge, both children had normal general status, skeletal muscle tonus and reflexes as well as respiratory, cardiovascular and gastrointestinal functions. Skin was normal in the older girl and in the younger sister was slightly icteric but otherwise normal. Umbilical cords were dry, but still present, in both cases. The mother recovered uneventfully after both pregnancies.

During the summer 2011 we conducted the follow-up. We first visited the primary care department, discussed with pediatricians in charge of both children and reviewed their medical records. In general, the children were healthy with normal psychomotor developments, somatic, neurological and nutritive status and regularly vaccinated. The younger child had no somatic disease. The older girl experienced several transitory respiratory infections (pharyngitis, bronchitis, laryngitis), and a couple of episodes of mild-to-moderate diarrhea.

The mother’s psychiatric status during both pregnancy, after each delivery and during the follow up period was also favorable (continued to be rated as “borderline mentally ill”), with no exacerbations, receiving regularly 200 mg of zuclopenthixol decanoate *im* injections monthly. She experienced a moderate stressor episode (threat of a possible job loss) without obvious consequences. The mother’s social relationships were very well and pretty stable.

Discussion

Our paper probably represents the first case report on zuclopenthixol decanoate use during entire pregnancy in schizophrenic patients, particularly considering successive events in the same mother. Depot preparations of antipsychotics are rarely prescribed in pregnancy. The case of long-acting risperidone use with a successful outcome was described [12], but a newborn girl, whose mother had received perphenazine decanoate during the second and the third trimester, experienced postnatal extrapyramidal symptoms [13]. Therefore, possible benefits of antipsychotic treatment in pregnant women such as improvement of psychiatric status and social functioning must be carefully balanced against the potential risk from adverse pharmacological effects on the fetus.

It seems that the use of antipsychotics in pregnancy, in general, bears no or little additional fetal risk for congenital malformations. However, many consider the safety of this pharmacological class in pregnancy to be still an unresolved issue. The insufficient amount of sound, evidence-based data, possibility of immediate drug effects after the birth and concern about long-term disturbances of behavioral development make the authorities in the field still vigilant [4].

We counseled the mother to avoid breastfeeding during zuclopenthixol treatment. Some professionals considered that the risk from single antipsychotic agent was less than potential benefits from breastfeeding [5]. Indeed, antipsychotics, in general, enter the mother’s milk with low concentrations but they may have a long half-life and active metabolites. Due to the possibility of entering infant’s brain in measurable amounts and the insufficient data about neurodevelopmental, the delayed the effects American Academy of Pediatrics classified psychotropics, including antipsychotic agents, as “drugs for which the effect on nursing infants is unknown but may be of concern” [14].

The outcomes of the presented pregnancies suggest that the judicious prescribing of antipsychotics in pregnant psychiatric patients could be a safe and effective treatment option. It seems that assuring full drug compliance [9] and close supervision of health status with multidisciplinary approach [15] were crucial for the therapeutic success in our cases. However, the case reports bear many methodological limitations and we were unable to collect some valuable additional data such as zuclopenthixol serum concentrations and the insight into possible hidden malformations of children.

There are no studies in the field with a sufficiently large sample and, therefore, zuclopenthixol and probably any other antipsychotic should be used only if the expected benefits outweigh possible risks. Medical community still waits for the results of incentives based on the widest and the longest possible follow-up of drug use in pregnant women with mental disorders [16]. Until they appear we believe that our paper presents a fair and useful piece of evidence.

Conclusion

The use of zuclopenthixol decanoate in the presented case resulted in therapeutic success for the mother without adverse effects for the children. We need larger studies with the refined research designs in order to confirm our results.

Conflicts of interest and the source of funding

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