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Case Report

A Case Report: Risperidone-Induced Lactation Nonpuerperal in Bipolar Patient

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Abstract
Risperidone is an atypical antipsychotic for acute and chronic schizophrenia and mania. In this case report, we report a rare side effect of risperidone, namely nonpuerperal lactation, where the common side effects of risperidone are insomnia, anxiety, headaches, and extrapyramidal symptoms. Lactation nonpuerperal is one of the rare side effects of risperidone, with an incidence in adults < 1%. We report the case of a 21-year-old woman. This woman was diagnosed with bipolar affective disorder with major depression and got risperidone, fluoxetine, trihexyphenidyl, and valproic acid for treatment. The first visit was at a teaching hospital on April 21, 2022. She had to control it within a month. At the first control on July 1, 2022, her condition improved. She had no complaints. On August 4, 2022, she came to the hospital and told the doctor that she had nonpuerperal lactation. We do a causality analysis that the side-effect is due to risperidone. From Naranjo's analysis, we scored 6 for risperidone (probable). From the Liverpool algorithm, we concluded that risperidone probably caused lactation nonpuerperal. In this case, risperidone probably caused lactation nonpuerperal.

Keywords: atypical antipsychotic, lactation nonpuerperal, risperidone, side-effect

Laporan Kasus: Risperidon Menyebabkan Laktasi Nonpuerperal pada Pasien Bipolar

Abstrak
Risperidone adalah antipsikotik atipikal yang digunakan pada skizofrenia dan mania akut dan kronis. Kami akan melaporkan efek samping laktasi nonpuerperal pada penggunaan risperidone. Laktasi nonpuerperal adalah salah satu efek samping risperidone yang jarang terjadi, dengan insiden pada orang dewasa <1%, dimana efek samping risperidone yang umum terjadi adalah insomnia, kecemasan, sakit kepala, dan gejala ekstrapiramidal. Kami melaporkan kasus seorang perempuan berusia 21 tahun. Dia didiagnosis mengalami gangguan afektif bipolar dengan depresi berat. Terapi yang didapatkan adalah risperidone, fluoxetine, trihexyphenidyl, dan asam valproat. Pasien tersebut adalah pasien rawat jalan. Kunjungan pertama di sebuah rumah sakit pendidikan pada 21 April 2022. Pasien terjadwal harus kontrol setiap bulan. Pada kontrol pertama tanggal 1 Juli 2022, kondisinya membaik, tidak ada keluhan yang dirasakan. Pada tanggal 4 Agustus 2022, pasien datang ke rumah sakit dan mengatakan kepada dokter bahwa ia mengalami keluar air susu nya (laktasi nonpuerperal). Kami melakukan analisis kausalitas bahwa efek samping tersebut dan menduga hal tersebut disebabkan oleh risperidone. Dari analisis Naranjo, kami memberi skor 6 untuk risperidone (*probable*). Dari algoritma Liverpool, kami menyimpulkan bahwa risperidone mungkin menyebabkan laktasi nonpuerperal (*probably*). Dalam kasus ini, risperidone menyebabkan laktasi nonpuerperal dengan kausalitas *probable.*

Kata kunci: risperidone, antipsikotik atipikal, laktasi nonpuerperal, efek samping

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Introduction

Risperidone is an atypical antipsychotic or a second-generation antipsychotic. As an atypical antipsychotic, risperidone is relatively safer than first-generation antipsychotics. Indications for the use of risperidone include the treatment of acute and chronic schizophrenia, as well as for mania.[1] In 2003, risperidone received marketing authorization from the FDA to treat acute bipolar mania. Risperidone is included in the WHO list of effective and safe essential drugs.[2]

Risperidone is a selective monoamine antagonist with a high affinity for serotonin, dopamine, adrenergic and histaminergic receptors. Side effects that often appear include somnolence, headache, hyperkinesia, dyspepsia, and nausea, with an incidence rate > 10%. Other side effects include extrapyramidal, weight gain, and insomnia. While the severe side effects are tardive dyskinesia, cardiovascular effects, and neuroleptic malignant syndrome.[1,3]

Lactation nonpuerperal is the release of breast milk not due to breastfeeding, usually a side effect of drugs, especially antidepressants. Another term is galactorrhea. Case reports of the emergence of lactation nonpuerperal as a side effect of antidepressant use have been around since 1960. Serotonergic antidepressants are eight times more likely to cause side effects of lactation nonpuerperal.[4–6] We found the use of risperidone, which caused non-pureperal lactation in a case report in 2007, namely in a Caucasian female thyroid carcinoma patient. The patient developed anxiety on the third cycle of therapy and was treated with risperidone. Then, the prolactin levels increased by 123 ng/mL (normal values: 2.7-26 ng/mL) and returned to normal after risperidone was discontinued.[7]

Case Presentation

We present the case of a 21-year-old female patient diagnosed with Bipolar Affective Disorder, a Current Episode of Major Depression with psychotic symptoms. The patient came to the teaching Hospital on April 21, 2022. The patient's vital signs were as follows, blood pressure 116/83mm Hg, respiratory rate 20x/minute, heart rate 105x/minute. The patient's weight is 43.9 kg, with a height of 155 cm. There was no history of disease. The therapy given by a psychiatrist was valproic acid 250 mg, fluoxetine 20 mg, risperidone 2 mg, trihexyphenidyl 2 mg twice a day, respectively, and diazepam 5mg once a day. This outpatient patient must be controlled at the hospital once a month. In the first control, the patient did not come; hence the drug was cut off. The patient was then controlled again on July 1, 2022 and was in good health but still a little anxious. She gained weight to 46kg and heart rate 89x/min with blood pressure relatively stable at 118/82mmHg. The psychiatrist provides therapy when the patient arrives, i.e., valproic acid 250 mg, fluoxetine 20 mg, risperidone 2 mg, trihexyphenidyl 2 mg. On August 4, the patient returned to the teaching hospital for control. The patient began to complain of excessive anxiety. She also feels nausea when taking medication and breast milk even though she was not breastfeeding. The patient's blood pressure has increased to 128/92mmHg. The psychiatrist then reduced the dose of risperidone to half 2x1/2 tablets (2mg tablets). The other medications were still prescribed as before. In the next month of control (8 September 2022), the patient experienced increasingly severe depression to the point of suicidal ideation. On the one hand, the breast milk did not come out anymore. The therapy given did not change. The patient was routinely controlled every month, and there was no change in the

medication given. In November, she said that breast milk came out again, and then the psychiatrist stopped risperidone. The therapy given was valproate acid, fluoxetine, trihexy phenidil, diazepam, and added alprazolam 0.5mg. The patient went back to the hospital in December for standard care. After stopping risperidone, the patient did not report any more issues.

Discussion

The incidence of lactation nonpuerperal which is a side effect of risperidone has been reported in the early years of risperidone use. Risperidone is a selective monoaminergic antagonist with a strong affinity for serotonin, dopamine², alpha one and alpha two adrenergic, and histaminergic H1; therefore, it may have a similar effect on causing lactation nonpuerperal. In a more recent study of the efficacy and safety of risperidone and quetiapine in bipolar disorder, an increase in the hormone prolactin was found in the group of patients receiving risperidone.[8] Increasing prolactin is in line with a review by Peuskens et al. regarding the effect of antipsychotics on serum prolactin. This review discusses the mechanism of increasing prolactin by antipsychotics. The mechanism is thought to be due to effects on serotonin and dopamine.[1,9] Hyperprolactinemia may potentially be explained by antipsychotics' capacity to penetrate the blood-brain barrier and inhibit Dopamine 2 receptors. The faster it is detached from dopamine two receptors, the less the increase in prolactin in plasma. Risperidone metabolites include antipsychotics that increase Risperidone's major metabolite, 9-hydroxy risperidone (or paliperidone), plays a significant role in raising prolactin levels. The increased level of prolactin was known in many risperidone-treated patients.[9,10]

In the case that we found, the effect of milk secretion, which is identical to the increase in serum prolactin and is referred to as lactation nonpuerperal, appeared after the patient took risperidone for one month. The patient had previously received risperidone, which was discontinued because the patient was not in control. Side effects appeared one month after the patient retook risperidone. Dopamine is an important prolactin-inhibiting factor in the hypothalamus. The blockade of dopamine 2 receptors will result in the disinhibition of prolactin secretion. In comparison, serotonin is more complex in its activities through the hypothalamus and pituitary.[9] Several reports related to the increase in the hormone prolactin with the use of risperidone found that the effect occurred on average after eight weeks. The incidence of side effects in the form of non-lactation is risperidone dose-dependent.[1,12] The increase in serum prolactin is individualized, with differences between individuals varying. At a risperidone dose of 2mg/day, the mean serum prolactin increase for females was 76.14ng/ml, and for males was 24.53ng/ml. Risperidone long-acting can still cause an increase in serum prolactin, even though if used long-term, serum prolactin can decrease on its own. This condition is due to the reduced peak facilitation in long-acting risperidone.[13]

We performed a causal analysis of the occurrence of lactation nonpuerperal by risperidone with the Naranjo algorithm.[14] The results of the analysis can be seen in Table 1 (Naranjo analysis results in lactation nonpuerperal due to risperidone).

In Naranjo's analysis for question no 1 (Are there previous conclusive reports on this reaction?), we found several references regarding lactation nonpuerperal events caused by risperidone. Some evidence is ancient, and there has yet to be a new journal. Glocker et al. conducted a drug surveillance program that found that risperidone had an

Table 1 Naranjo analysis results in lactation nonpuerperal due to risperidone

No	Question	Yes	No	Don't Know	Score
1	Are there previous conclusive reports on this reaction?	1	0	0	1
2	Did the adverse event appear after the suspected drug was administered?	2	-1	0	2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	1
4	Did the adverse reaction reappear when the drug was readministered?	2	-1	0	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0	-1
6	Did the reaction reappear when a placebo was given?	-1	1	0	1
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	0
8	Was the reaction more severe when the dose was increased,or less severe when the dose was decreased?	1	0	0	1
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0
10	Was the adverse event confirmed by any objective evidence?	1	0	0	1
	Total				6

incidence of 52 cases, or 0.19% of all patients who received risperidone from 1993-2015.[15] In the second question point (Did the adverse event appear after the suspected drug was administered?), the answer is yes, because the patient experienced lactation nonpuerperal after taking risperidone for three months. For question no 3 (Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?), in this case, the psychiatrist did not stop the risperidone immediately but reduced the dose. The lactation nonpuerperal stopped; therefore, we gave a score of 1. Question 5 (Are there alternative causes (other than the drug) that could have caused the reaction on their own?) The answer to question 5 is "test" (score -1) because the patient also receives fluoxetine. But fluoxetine is the antidepressant with the slightest chance of causing non-puerperal lactation.[16] We answered question number 6 with a yes (score 1) because the patient was still receiving other drugs except risperidone. We could not answer questions 7 (checking blood levels of the drug) because they were not done; hence they were given a score of 0 (do not know). When the dose of risperidone decreased, the symptoms improved; thus, for question eight, we scored 1. For question nine, we also scored 0 because the patient had never experienced something similar. We offer question number 10 a score of 1 because there is evidence of milk escaping seen from the patient's condition, even though there is no prolactin-level examination.

To be more convincing, we also conducted a causality analysis using the Liverpool algorithm. The results of the analysis can be seen in Figure 1 (Results of causality analysis using Liverpool's algorithm).

In the Liverpool algorithm analysis, the initial question "Do you suspect an adverse drug reaction?" was answered "yes" because the patient experienced breast milk discharge not due to breastfeeding. "Did the event appear after the drug was administered or dose increased?" was answered "yes" because the patient experienced breast milk

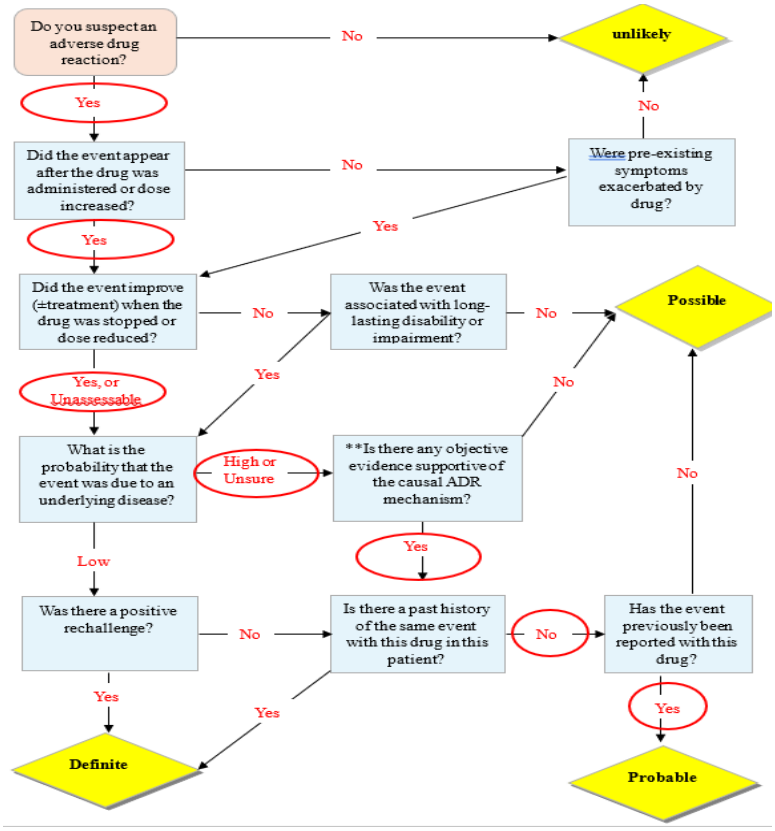

Figure 1 Results of causality analysis using Liverpool's algorithm[20]

*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants)
**Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

discharge after taking the suspected drug, risperidone. The next question was, "Did the event improve (± treatment) when the drug was stopped or dose reduced?" We answered with 'yes' because the doctor then lowered the dose of risperidone, and the patient was no longer breastfeeding. In the question "What is the probability that the event was due to an underlying disease?" the answer was "unsure" because there were no other diseases of the patient other than the primary diagnosis of Affective Bipolar Episode, Now Severe Depression with psychotic symptoms. In addition, the patient is not married and has no children. From the medical record data and patient interview, no other diseases were related to the emergence of non-puerperal lactation. The analysis continued by answering, "Is there any objective evidence supportive of the causal ADR mechanism."

The researcher answered 'yes' because several journals explain the mechanism of non-puerperal lactation (hyperprolactinemia) caused by risperidone.[9] The patient was experiencing this side effect for the first time, so the answer to the question, "Is there a past history of the same event with this drug in this patient?" was "No." Next, the arrow is directed at the question, "Has the event previously been reported with this drug?". The answer to this question is 'yes' because there are previous case reports. Thus, the

analyst's conclusion using the Liverpool algorithm is probable causality. Risperidone most likely results in lactation nonpuerperal because both causality analyses gave us a Probable status. For the other drugs taken by the patient (fluoxetine, trihexyphenidyl, and valproate acid), no adverse effect causality analysis was conducted, as no literature mentioned these three drugs causing non-puerperal lactation.

In some cases of non-puerperal lactation characterized by elevated serum prolactin, some therapies can be given. Several journals mention dopamine agonists as a therapeutic option, with the primary choice being cabergoline. A study conducted by Pollice et al. mentioned the efficacy of cabergoline in patients who had increased serum prolactin due to risperidone. No side effects were noted. This therapy can be a strategy to overcome the side effects of non-puerperal lactation in patients who are unlikely to stop risperidone.[17]

Cabergoline therapy is safer than bromocriptine, although there is still some controversy. There are several case reports of adverse effects of cabergoline on patient psychosis in the form of mania. In this patient, there was no problem with discontinuation of risperidone, so no further therapy was needed.[18,19]

This case report demonstrates the importance of monitoring the adverse effects of antipsychotics in patients with psychiatric disorders. Factors influencing patient compliance can be anticipated and addressed as early as possible, including side effects that make the patient uncomfortable. If this condition is not anticipated, it can cause problems with medication adherence, while the treatment of people with mental illnesses requires long-term therapy. The limitation of this case report is that the patient's serum prolactin was not measured. This situation was because there was already evidence of breastmilk release not only during the breastfeeding period but also due to the cost of the test. A solid team of psychiatrists, pharmacists, nurses, and even the patient's family plays an essential role in the treatment of patients with psychosis. Pharmacists can play a role by monitoring patient compliance, the incidence of side effects, and any drug-related problems. Psychosis patients also require more attention so that pharmacists can do drug counseling more personally for the success of therapy.

Conclusions

Risperidone causes lactation nonpuerperal in this patient with a Naranjo score of 6 and possible causality. Monitoring of side effects in patients with psychiatric disorders needs to be done to support the success of therapy.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Statement of Ethics

This research was conducted in accordance with the approval and recommendations of the Ethics Committee of PKU Muhammadiyah Gamping Hospital. Written

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