Extrapyramidal side effects as a consequence of treatment with neuroleptics

Efeitos extrapiramidais como conseqüência de tratamento com neurolépticos

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ABSTRACT

Objective: To check the occurrence of extrapyramidal side effects in patients receiving neuroleptic drugs, how these effects are treated, and to observe the occurrence of hallucinations caused by treatment of extrapyramidal symptoms. **Methods:** The present study analyzed medical records and interviewed 39 schizophrenic patients being treated in a public primary care clinic located in the southern part of the city of São Paulo, who had previously agreed to participate in the project. **Results:** Among 39 patients studied, 85% presented extrapyramidal symptoms. Of these, 69.7% were treated for the side effects, 73.9% were treated with biperiden and 26.09% had their neuroleptic drug reduced. Out of those patients treated with biperiden, 70.5% had side effects, such as hallucination and delusion, blurred vision, somnolence and verbal memory deficit. **Conclusions:** The majority of patients (85%) undergoing treatment with neuroleptic drugs developed motor side effects. When these extrapyramidal symptoms were treated with central action anticholinergic drugs (biperiden), hallucination and/or delusion occurred in 52.94% of patients – probably because of increased dopaminergic activity as a consequence of cholinergic activity reduction caused by biperiden in the mesocortical and mesolimbic pathways.

Keywords: Antipsychotic agents/adverse effects; Cholinergic antagonists; Biperiden/therapeutic use; Schizophrenia/drug therapy

RESUMO

Objetivo: Identificar a ocorrência de efeitos extrapiramidais (EPS) com o uso de neurolépticos, em pacientes esquizofrênicos, bem como verificar o possível aparecimento de alucinação secundária ao tratamento dos efeitos EPS. **Métodos:** Trinta e nove pacientes que estiveram em tratamento com neurolépticos em uma instituição pública de atenção primária em saúde mental, localizada na região sul da cidade de São Paulo, tiveram seus dados coletados do prontuário e participação por meio de entrevistas após concordarem, voluntariamente, em fazer parte da pesquisa. **Resultados:** Dos 39 pacientes esquizofrênicos em tratamento com neurolépticos analisados, 85% apresentaram efeitos EPS, enquanto 69,7% receberam tratamento para estes efeitos colaterais de movimento. Foram tratados com biperideno 73,91% dos pacientes, enquanto 29,06% tiveram redução da dose do neuroléptico. Dos pacientes que receberam biperideno, 70,50% apresentaram alucinação/delírio, visão embaçada, sonolência ou *deficit* de memória verbal. **Conclusões:** Grande parte dos pacientes que receberam neurolépticos (85%) apresentou efeitos colaterais motores e estes, quando tratados com anticolinérgico de ação central (biperideno), apresentaram alucinação e/ou delírio (52,94%) – provavelmente pelo aumento da atividade dopaminérgica decorrente da redução de atividade colinérgica nas vias mesocortical e mesolímbica.

Descritores: Agentes antipsicóticos/efeitos adversos; Antagonistas colinérgicos; Biperideno/uso terapêutico; Esquizofrenia/quimioterapia

INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by two distinct groups of positive and negative symptoms. Positive symptoms include hallucination, delusions and distorted reality. Negative symptoms are manifested as social isolation, flat affect and attention deficit[1].

Positive symptoms are those that usually respond to treatment with neuroleptic agents[2], while negative symptoms are relatively difficult to treat[1,3-4].

Neuroleptics are drugs used to treat schizophrenia and, as a mechanism of action, they block central dopaminergic receptors. They are classified as typical and atypical. The typical neuroleptic agents are represented by haloperidol, chlorpromazine,

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fluphenazine, thioridazinea, flupenthixol and loxapine, and the atypical group comprises clozapine, quetiapine, risperidone, olanzapine, sulpiride and sertindole[1,5].

Central nervous system (CNS) dopaminergic neurons are present in the mesolimbic, mesocortical, tuberoinfundibular and nigrostriatal pathways[6].

The mesolimbic pathway goes from the mesencephalon up to the limbic system. The mesencephalon is associated with sleep and awareness, whereas the limbic system is responsible for elaborating emotional reactions, punishment and reward behavior. The mesocortical pathway starts in the mesencephalon and ends in the cortex, which is linked to language, abstract thinking, motor activities, associative and visual functions[6].

While the tuberoinfundibular pathway extends from the hypothalamus to the medial eminence, the hypothalamus commands autonomic functions, elaborates specific functions such as thirst and hunger, appetite for specific nutrients such as salt and sugar, and it is also responsible for the individual's survival drive and propagation of the species (fighting/fleeing and sexual behavior). Finally, the nigrostriatal pathway goes from the mesencephalon to the corpus striatum, which is associated with central movement control[6].

Schizophrenic patients may have emotional, mystic and sexual delusions, auditory and olfactory hallucinations and reality distortions. These symptoms are associated with an increase in dopamine levels in the mesolimbic and mesocortical pathways. They are treated with neuroleptic agents that block central dopaminergic receptors[6].

Neuroleptic agents block dopaminergic receptors in the entire CNS; consequently, the tuberoinfundibular and nigrostriatal pathways are blocked, resulting in hormonal and extrapyramidal side effects (EPS), respectively[7].

Undesirable dopaminergic block in the tuberoinfundibular pathway causes collateral effects such as galactorrhea and the malignant neuroleptic syndrome. In the nigrostriatal pathway, it causes motor effects (EPS), such as akathisia, drug-induced parkinsonism, acute dystonia, perioral tremor and late dyskinesia[2,7-9].

The EPS may be treated by reducing the neuroleptic dose or with antiparkinson agents (anticholinergic and central muscarinic antagonists), such as biperiden, benzhexol, orphenadrine, benztropine, promethazine and amantadine. These drugs improve tremor and rigidity and reduce salivary secretion; however, they can cause side effects, such as mental confusion, urinary retention and blurred vision[1,5]. Since they are broadly used to treat EPS caused by neuroleptic agents, such as haloperidol, these central acting anticholinergic agents can still cause side effects, including hallucination, delusion[8,10-11] and verbal memory deficit[12-13].

There is a dose-dependant relation with the onset of EPS, especially with late dyskinesia[14]. Biperiden is a reference drug for treating EPS, and the dose prescribed is associated with that of the neuroleptic agent used.

EPS, as a consequence of using neuroleptic drugs, are the most important cause for patients not complying with the psychiatric treatment. This study aimed to assess these side effects.

OBJECTIVE

The goal of this investigation was to study patients under treatment with neuroleptic agents, as follows:

- to identify the neuroleptic agent most frequently used in psychiatric treatments and the occurrence of EPS resulting from these therapies;
- to check treatment modalities used to improve EPS and their adverse reactions;
- to propose possible strategies to improve Nursing care of these patients.

METHODS

This is an exploratory, quantitative, descriptive and field study.

According to resolution 196/1996, of the National Health Council, the project was submitted to approval by the National System of Information on Research Ethics involving Human Beings (Sisnep), of the Brazilian Health Ministry; by the Scientific Committee of Faculdade de Enfermagem of Hospital Israelita Albert Einstein (HIAE); Ethics Committee of HIAE; Research Ethics Committee of the Centro de Atenção Psicossocial (Caps) Jardim Lídia; Research Ethics Committee of the Secretaria Municipal de Saúde de São Paulo (SMS-SP). The researchers committed to use the data collected exclusively the present study.

The population of this study consisted of 39 patients who were being treated with neuroleptics in a public primary mental healthcare institution, located in southern part of the city of São Paulo.

Data collection was carried out after approval to search patients' charts, from where we gathered data, and through interviews with patients, who voluntarily agreed to participate in the study after signing an informed consent form, using questionnaire forms prepared by the researchers.

The data collected were grouped, submitted to statistical analysis and tabulated. The results were presented in absolute and percent numbers, as figures and tables.

RESULTS

Thirty-nine patients under treatment with neuroleptic agents met the inclusion criteria and participated in the study. In order to facilitate data analysis, we decided to group the results into three categories:

epidemiologic profile;
EPS as a consequence of neuroleptic treatment;
EPS treatment.

Epidemiological profile

Sex and age

Among 39 patients who participated in the study, 21 (53.85%) were males and 18 (46.15%) were females.

The age ranged between 18 (minimum age) and 54 (maximum age) years, with a mean age of 32.4 years and standard deviation of 9.71.

EPS as a consequence of treatment with neuroleptic drugs

In this category, we separated all drug combinations used among the 39 patients submitted to the study, checking for the presence of any EPS: akathisia, parkinsonism, acute dystonia and perioral tremor.

Table 1 was designed to associate the presence of EPS with the neuroleptic drugs used in each treatment.

Table 1. Presence of extrapyramidal side effects

Drugs used	Presence of extrapyramidal side effects
Olanzapine	4
Olanzapine + chlorpromazine	1
Olanzapine + haloperidol	4
Haloperidol	4
Haloperidol + chlorpromazine	4
Risperidone	6
Clozapine	3
Ziprasidone	0
Haloperidol decanoate	3
Haloperidol + olanzapine + chlorpromazine	1
Risperidone + ziprasidone	1
Haloperidol + risperidone	0
Chlorpromazine	1
Olanzapine + zisperidone	1
Total	33

Of the 39 patients studied, 33 (85%) had at least one extrapyramidal side effect, while six (15%) had no EPS.

Among the 33 patients submitted to the study, 27 (81.81%) had akathisia; 23 (69.70%), parkinsonism; four (12.12%), acute dystonia; and four (12.12%), perioral tremor. Figure 1 shows a comparison of the four EPS.

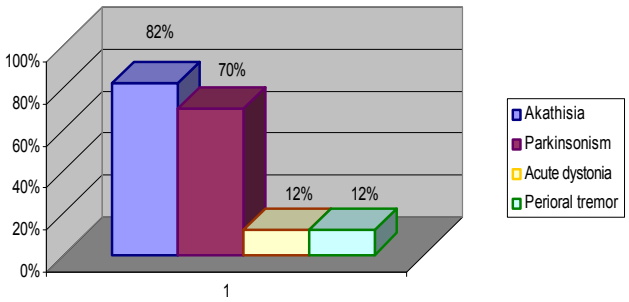

Figure 1. Comparative histogram for the variable frequency of extrapyramidal side effects

Treatment of EPS

Among the 33 patients submitted to the study and who presented some type of extrapyramidal side effect, 23 (69.70%) underwent treatment, while ten patients (30.30%) were not treated for EPS.

Of these 23 patients who underwent EPS treatment, 17 (73.91%) used central action anticholinergic, biperiden, and six patients (26.09%) reduced the neuroleptic dose (Figure 2).

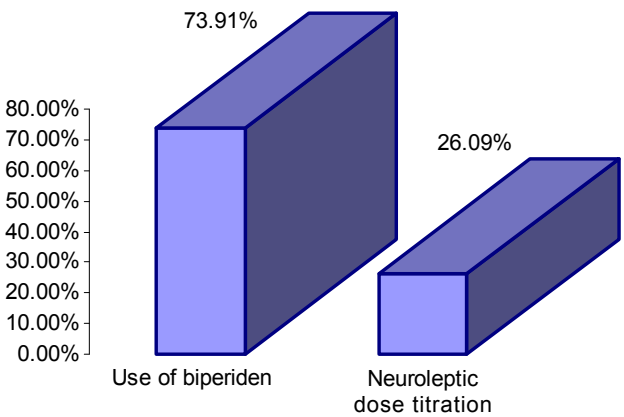

Figure 2. Graph for the variable type of extrapyramidal side effects treatment

Among patients treated with biperiden, the extrapyramidal effects induced by neuroleptic agents presented other side effects.

We analyzed the following side effects associated with biperiden: somnolence, hallucination/delusion, blurred vision and verbal memory deficit.

Among the 17 patients who used biperiden, 12 (70.58%) presented at least one side effect to this treatment, while five (29.42%) did not show any.

Of the 17 patients who were medicated with biperiden, three (17.65%) had somnolence; nine (52.94%), hallucination or delusion; four (23.53%) had blurred vision; and two (11.76%) had verbal memory deficit as side effects. Figure 3 shows a comparison of the four side effects associated with biperiden.

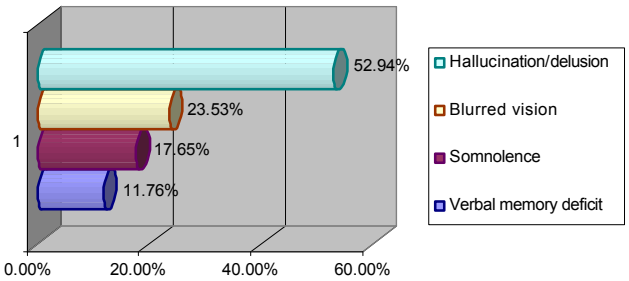

Figure 3. Graph comparing the incidence of side effects of biperiden

DISCUSSION

Schizophrenia is a psychiatric disorder in which we observe intense behavioral dysfunction, incapacity of having a coherent thought, distortions of reality and hallucinations[5].

The increase in dopamine in dopaminergic, mesolimbic and mesocortical pathways is associated with the psychiatric pathology[15].

The neuroleptic agents used to treat schizophrenia block dopamine receptors in the CNS, reducing dopaminergic activities in these pathways and thus improving disease symptoms[15].

The patients studied were treated with typical neuroleptic agents, such as chlorpromazine and haloperidol, and also atypical agents, such as clozapine, olanzapine, risperidone and ziprasidone, or a combination of these drugs.

Typical neuroleptics are the oldest agents and characterized for blocking central type D_2 dopaminergic receptors, which are also present in large amount in the movement pathway (nigrostriatal pathway), causing movement side effects (extrapyramidal effects)[7,15].

The main action of neuroleptic agents is to block central dopaminergic receptors. We observe the blockage of these receptors in the mesocortical and mesolimbic pathways, as well as the nigrostriatal pathway. The unnecessary blockage of these dopaminergic receptors in the nigrostriatal pathway generate side effects in the area responsible for movement control, which limits patient compliance to this treatment[15].

The dopaminergic pathways go parallel to the CNS cholinergic pathways. It is important to have a balance between dopaminergic and cholinergic activities in order to normalize the functions of these pathways[15].

Schizophrenia is characterized by an increase in dopaminergic activity in relation to the cholinergic activity of the mesolimbic and mesocortical pathways. By blocking dopamine receptors with a neuroleptic agent, one can balance the activity of dopaminergic and cholinergic neurons in these pathways. However, the dopaminergic blocking action of the neuroleptic agent on the nigrostriatal pathway, which controls a normally balanced movement in schizophrenic patients, is unbalanced (low dopaminergic activity in relation to the cholinergic activity)[15].

This causes movement disorders in patients, such as akathisia, acute dystonia, perioral tremor and drug-induced parkinsonism[5,7].

The akathisia is related to subjective feelings of malaise or discomfort and the uncontrollable need to be constantly moving[5,7].

Acute dystonia is clinically manifested by spasms in the tongue, face, neck and dorsum muscles[5,7].

In the natural course of Parkinson's disease, the dopaminergic neurons of the nigrostriatal pathway degenerate throughout the years. However, in drug-induced parkinsonism caused by neuroleptic drugs, there is a reduction in the activity of dopaminergic neurons, caused by neuroleptic block, leading to rigidity and tremors at rest[5,7].

Perioral tremor is also an extrapyramidal effect, causing mouth and nose movements in the patient, similar to oronasal movements in rabbits[5,7].

In the present investigation, these EPS were present in 85% of patients who used neuroleptic agents.

According to the intensity of these effects, it is necessary to carry out frequent assessments, neuroleptic dose reduction and/or continuous treatment for side effects of these patients.

The management of these patients requires Nursing care, and these professionals should understand the mechanism of action of this group of drugs and may be able to predict the possible side effects, thus contributing to treatment.

It is to improve Nursing care for these patients that we propose the use of assessment scales, because the periodic evaluation and active investigation of the side effects caused by these drugs is important to minimize them and allow better patient compliance to drug treatment at hand. The scales are as follows:

- Simpson and Angus[16] rating scale for extrapyramidal effects, comprising ten items in a scale from zero (absent) to four (severe). Each item brings instructions to assess and specify severity of each symptom;
- Barnes[17] akathisia scale, made up of three items with the following classifications:
  1. objective evaluation from zero (absent) to three (constant akathisia);
  2. subjective assessment that has two subitems, restlessness perception and discomfort associated with restlessness, from zero (absent) to three (severe);
  3. global akathisia evaluation from zero (absent) to five (severe).

Besides learning about neuroleptics, the nurses must also be attentive to the intensity of its side effects,

since they may become psychiatric emergencies, such as acute dystonia, which may cause laryngeal spasms and consequently glottis obstruction, which may evolve to a respiratory arrest.

Nurses must also know the mechanism of action of central-action anticholinergic drugs used to treat EPS, since these drugs act on ciliary muscles, and may increase intraoptic pressure, which can cause blindness in glaucoma patients.

The side effects of neuroleptic agents were treated in 69.7% of the patients, of whom 73.91% received biperiden and 29.06% were treated with neuroleptic dose reduction.

Among the patients treated with biperiden, 52.94% had hallucination/delusion and 11.76% had verbal memory deficit, which are characteristics of schizophrenia[16]. Moreover, 23.53% of these patients had blurred vision, maybe due to the anticholinergic peripheral activity associated with biperiden, relaxing the eye ciliary muscle, adapting the lens for far vision and making it difficult to see near objects. Somnolence was observed in 17.65% of patients, which may be due to antihistamine action of biperiden[5,17].

Since neuroleptics cause an unbalance in the pathway that controls movement (reduction of dopamine activity in relation to acetylcholine activity), the central cholinergic activity block caused by biperiden balances the dopaminergic/cholinergic activity in the nigrostriatal pathway, normalizing central motor function. However, by blocking acetylcholine receptors in other areas, such as the mesolimbic and mesocortical pathways, biperiden causes an increase in dopaminergic activity in relation to the cholinergic one, and such condition is very similar to what is observed in schizophrenia. Probably for this reason, 52.94% of patients who received biperiden had hallucination or delusion.

CONCLUSIONS

The data obtained confirm the onset EPS of even when using atypical neuroleptic agents.

EPS were treated with central action anticholinergic, biperiden (73.91%) or neuroleptic dose titration (29.06%).

The cholinergic block caused by biperiden on the nigrostriatal pathway balances the dopaminergic/cholinergic activity in this pathway; however, it causes an increase in dopaminergic activity in relation to the cholinergic one on the mesolimbic and mesocortical pathways.

Hallucination and delusion are typical symptoms of schizophrenia. After the action of central acting anticholinergic agents, these symptoms returned in 52.94% of patients who were treated with biperiden.

The strategy proposed in this article to improve Nursing care is the use of rating scales that assess the intensity of EPS, such as the Simpson and Angus and Barnes scales.

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