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Antipsychotics and Neutropoenia: An Update

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Abstract

Introduction and Objectives: Drugs are a common reason for neutropenia. The objective of this article is to conduct a review of the scientific evidence of neutropenias associated with the use of antipsychotics.

Material and Method: A bibliographic review of the last 5 years was carried out, collected in Pubmed, Uptodate, antipsychotic data sheets and the main Clinical Practice Guidelines.

Results and Discussion: The frequency of neutropenias associated with the use of antipsychotics is 3%, and of agranulocytosis 1%. Neutropenias are more common in the first 3 months of treatment. Some of the risk factors are previous neutropenia, age, sex, the existence of comorbidities or genetic susceptibility. Mortality is extremely rare. Most of the cases of patients with neutropenia are asymptomatic and are a laboratory finding. However, when neutropenia is severe, the patient can even present with sepsis. It is recommended to carry out health education to the carers and patients of the alarm data. The use of clozapine has a specific management and monitoring protocol, which reduced the incidence of agranulocytosis and mortality.

Conclusions: The incidence of neutropenia with antipsychotics is low, although it is a potentially serious adverse effect. Serial monitoring blood counts are required during antipsychotic therapy. It is possible that drugs with great antipsychotic potential such as clozapine are underused due to difficulties in management and monitoring.

Keywords: Neutropenia; Agranuloytosis; Antipsychotic; Clozapine; Olanzapine

Introduction

Neutropenia is a decrease, below the values considered normal in the peripheral blood count of neutrophils. In adults, the normal number of neutrophils ranges from 1,800 to 8,100 neutrophils / mm3.Most of the neutropenias in adults are acquired and due to an increase in the destruction of granulocytes. Drugs are a common reason for central neutropenia. The risk of neutropenias and other blood dyscrasias associated with multiple commonly used drugs is known. Despite this, the use of these drugs is considered acceptable if the clinical benefit to the patient is documented and side effects are controlled [1]..

Among these drugs we have, among others, chemotherapeutic agents against cancer, metamizole, antithyroid drugs, sulfasalazine or trimethopin / sulfamethoxazole. Psychotropic drugs are a common reason for neutropenia such as tricyclic antidepressants, phenothiazines,carbamazepine, valproate, or lamotrigine. Within the group of neuroleptics we will especially point out clozapine and olanzapine and to a much lesser extent risperidone, quetiapine or paliperidone [2-4].

The objective of this article is to carry out an updated review of the available scientific evidence regarding neutropenias associated with the use of antipsychotics and their clinical management in psychiatry.

Material and Methods

A bibliographic review was carried out in the Pubmed database for the last 5 years with the terms indexed in the MesH: neutropenia, agranuloytosis, antipsychotic, clozapine, olanzapine. We analyze the recommendations referenced on the subject in the chapters of Uptodate: Drug-induced netropenia and agranulocytosis; Second generation antipsychotic medication: pharmacology, administration and side effects; Guideliness for prescribing clozapine in schizophrenia. We review the technical sheets of the medicines and the recommendations of the Spanish Agency for Medicines and Health Products (AEPMs). We consulted the British Association for Psychopharmacology clinical practice guidelines, Resistant Schizophrenia Task Force Guide (TRRIP), FDA Guide, NICE Guide,

Results and Discussion

Definitions, prevalence and risk factors

Definitions

White blood cells can be classified according to the presence of granules in the cytoplasm into: granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (lymphocytes and monocytes). Neutropenia is defined as an absolute peripheral blood neutrophil count of less than 1500 / microL. The risk of infection increases when the total neutrophils falls below 1000 / microL. The term agranulocytosis is used for severe neutropenias below 500 / microL [1].

Prevalence

It is estimated that neutropenias associated with antipsychotics are around 3% according to the different series and agranulocytosis 1%. Neutropenias are more frequent in the first 3 months of treatment, reaching 84% of the total number of cases referenced in the bibliography. Approximately 75% of patients who develop mild neutropenia will not progress to moderate or severe neutropenia. Mortality is extremely rare, equivalent to 1 death for every 7,700 patients treated [5-7].

Data from the UK Clozapine Pharmacovigilance Program show an incidence per 100,000 person / week of treatment of:

Week 0-18: incidence 32%

Week 19-52: incidence 2.3%

Week 53 onwards: incidence 1.8%

The cumulative incidence of agranulocytosis in this registry is 0.78%. Most cases occurred during the first 18 weeks of treatment [8].

Risk factor's

The literature identifies several risk factors for developing neutropenias associated with psychotropic drugs that are [5,9]:

Age: more than 50% of cases occur in people over 50 years of age.

Sex:more cases are identified in women than in men. It is thought that it is because they have a higher consumption of psychotropic drugs.

Patients with previous neutropenia.

Patients with previous blood dyscrasias due to other drugs.

Coexistence of infectious mononucleosis, kidney failure, autoimmune diseases, cryoglobulinemia.

Concomitant use of ACE inhibitors or interferon.

There are populations with genetic susceptibility to neutropenias such as Yemenite Jews with association to HLA B38 and Japanese with association to HLA DRB1.

Neutropenias associated with psychotropic drugs have a worse prognosis in people over 60 years of age, with counts of less than 100 neutrophils / microL, coexistence of septicemia and previous morbidities, mainly renal, cardiac or respiratory [10,11].

Pathogenesis of antipsychotic-associated neutropenia

The formation of the nitrenium cation through monooxygenase 3 in the leukocyte system is known to be the initial step in the hematologic toxicity of antipsychotics. It should be remembered that the majority of patients who initiate treatment with clozapine experience a benign leukocytosis that is due to the mobilization of leukocytes from the marginal pool and bone marrow. The appearance of a decrease in white blood cells would therefore be due to the reduction in the production of new neutrophils. This could be mediated by an immune mechanism against neutrophils, mitochondrial oxidative stress that would cause apoptosis of neutrophils, or direct toxicity of the drug to the bone marrow [2].

Neutropenia Clinic

Most of the cases of patients with neutropenia are asymptomatic and are a finding after analytical control. Oral ulcers can be a clinical manifestation, as well as nonspecific symptoms such as malaise and anorexia. On other occasions, especially when the neutropenia is severe, the patient presents with a fever and may even present with sepsis. In these cases, hospitalization for intravenous antibiotic therapy is necessary..The clinician must be attentive to the appearance of flu symptoms or odynophagia and it is recommended to carry out health education to caregivers and patients of the alarm data. If neutropenia is severe (below 500 / microL) and prolonged in time, the risk of bacterial infection is added to the risk of fungal infection [9].

Prevention: pre-treatment evaluation with clozapine

There are a number of circumstances that contraindicate the initiation of clozapine treatment [12-14]:

✓ Treatment should not be initiated in patients who cannot have regular blood tests.

✓ History of toxic or idiosyncratic agranulocytosis (with the exception of granulocytopenias caused by previous chemotherapy): an initial white blood cell count above 3500 / microL and a neutrophil count above 2000 / microL is usually required. Although the FDA lowers it to 1500 / microL. In benign ethnic neutropenia (African or Middle Eastern people usually have lower neutrophil counts without infections)> 1000 / microL neutrophils and the opinion of the hematologist are recommended.

✓ A previous history of clozapine agranulocytosis would be a contraindication. Although, if its benefits outweigh the risks, the Food and Drug Administration (FDA) considers it a relative contraindication and accepts its handling with extreme caution and supervision of the hematologist.

Before starting treatment with clozapine should be performed [12]:

✓ Complete history and medical examination including weight, height, muscle mass index, and blood pressure.

✓ Electrocardiogram: patients with a history of heart disease or alterations in the tracing should be referred to the cardiologist.

✓ Complete blood count.

✓ It is also advisable to determine blood glucose, lipids for high frequency of metabolic syndrome.

✓ Some Guidelines also recommend carrying out a pregnancy test in fertile women, C-reactive protein, troponin, and completing a scale for quantifying abnormal involuntary movements.

Clozapine treatment monitoring

Neutrophil count monitoring in patients taking clozapine reduced the incidence of agranulocytosis by one Relative Risk (RR) from 2 to RR: 0.38, mortality was reduced to 0.013%. However, some authors point out that the benefits of screening may be overestimated due to the low incidence of agranulocytosis [6,9,15].

There is consensus in carrying out [12,114,16,17]:

✓ A weekly blood count for the first 18 weeks.

✓ A monthly blood count for the duration of treatment.

✓ A hemogram 4 weeks after stopping clozapine treatment (since neutropenias have been described in this period).

Currently, it is considering reducing the monitoring from the first year of treatment since the cost-benefit balance is doubtful in patients who did not develop previous neutropenia [6].

There are alternatives such as capillary blood tests that can help improve monitoring compliance. Moderate physical ex-

ercise should be promoted as it produces an elevation of the white series. It must be taken into account that sometimes the antipsychotic is not the cause of neutropenia, and assess whether other drugs that the patient is receiving are involved, especially if there is concomitant use of metamizole or B-lactams [2].

In the event of neutropenia in which a causative drug is suspected, a bone marrow aspiration / biopsy is not indicated. This is carried out if with the suspension of the drug, with or without treatment with granulocyte colony stimulation factors (G-CSF), no recovery of the count is observed in a reasonable time, or in the case of other alterations peripherals that may suggest a non-pharmacological central cause [9].

Clinical management of neutropenias

For monitoring we must take into account the absolute neutrophil count. If they are descended, we must confirm it with a second determination. Performing a peripheral blood smear that shows a normal morphology of blood cells and the absence of accompanying cytopenias will help us rule out other pathologies that may be the cause of neutropenia. It is estimatedthat clozapine-associated neutropenias have an average duration of between 12-21 days after drug withdrawal. Table 1 summarizes the most frequently recommended therapeutic approach in each case regarding this drug [12, 18-23]:

Table 1: Recommendations for the management of clozapine-associated neutropenia

Stratification of neutropenia	Absolute neutrophil count	Recommendation
Light	1499-1000 / microL	Continue with the treatment. Increase the frequency of monitoring to 2-3 times per week.
Moderate	999-500 / microL	Stop treatment. Consult with the hematologist. Daily monitoring until the count rises> 1000 / microL where restarting clozapine could be considered
Severe	<500 / microL	Stop treatment. Consult with the hematologist. Reintroduction of treatment is not recommended unless the benefit outweighs the risks and with the agreement of the hematologist.

Some entities are more restrictive and recommend stopping clozapine if the neutrophil count is less than 1500 / microl [14].

For the treatment of established drug neutropenia, the G-CSF (Filgastrim), although these agents, apart from neutropenias due to oncological agents, do not have solid evidence. They are commonly used when neutropenia is severe. Lithium also raises leukocytes by inhibiting myeloperoxidase, it has been used to prevent neutropenia in patients with clozapine [2,3,9].

The incidence of agranulocytosis with olanzapine is much lower than with clozapine. Possibly because the handling doses are lower. The haematological toxicity of olanzapine is dose dependent. Olanzapine has a similar structure to clozapine, therefore it has been recommended as an alternative in patients with clozapine-induced neutropenia. Although this safety is uncertain because olanzapine metabolites are toxic in vitro against neutrophils [24,25].

With regard to the rest of second and third generation antipsychotics, the possibilities of hematological alterations are rare. Leukocytosis and neutropenia have been reported with risperidone in 4% of patients. 2% with quetiapine or paliperidone. No frequency of hematological monitoring has been recommended with these drugs [5].

In general, the use of clozapine in children or adolescents is not recommended as there is little data on its safety and efficacy. Despite this, the short series published show that neutropenia was not more prevalent than in adults. The use of lithium has been reported successfully in children with aripiprazole-associated clozapine neutropenias [2].

Conclusions

• The incidence of neutropenia with antipsychotics is low, although it is a potentially serious adverse effect.

• Serial hemograms should be done when we use clozapine, pending a consensus in the future to adjust the monitoring according to the risk of each patient.

• The risk of neutropenias with second or third generation atypical antipsychotics is much lower than with clozapine, but there is no consensus on its monitoring.

• It is important to educate patients and their families about clinical signs and symptoms of alarm, to alert the doctor to a possible neutropenia

In view of these results, we can conclude that a prudent management of antipsychotic drugs is necessary, knowing the monitoring strategies and the alarm signals to which we must pay attention, to avoid iatrogenesis, which in the worst cases can even

lead to death . In this sense, the European recommendations are more conservative, raising the demands and controls, being the most flexible standards in the US guidelines.

Once the risk-benefit of the use of antipsychotics has been assessed individually in each patient, we can affirm that they are not more unsafe drugs than others in common use, such as B-lactams or Metamizole. Thus, it is possible that drugs with great antipsychotic potential such as Clozapine are underused due to the difficulties generated by the controls for the professional in clinical management and lack of patient adherence. In the future, it would be of interest to conduct more pharmacotherapeutic safety studies to identify the most efficient regimen for clozapine monitoring.

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