# Agranulocytosis and complications from the use of the drugs dypirone and clozapine

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**Resumo**

Agranulocitose é um tipo de discrasia sanguínea, caracterizada por baixos níveis de granulócitos totais no sangue periférico, que pode ser causada por diversos medicamentos, desde os de venda livre, como a dipirona, até substâncias controladas, como a clozapina. Por estar disponível e sem prescrição médica, a automedicação com dipirona é comum em todas as faixas etárias. A clozapina, por outro lado, é um antipsicótico de segunda geração usado para tratar a esquizofrenia em pacientes refratários a outros medicamentos. O uso de qualquer uma das drogas está associado à agranulocitose, um efeito colateral grave e potencialmente letal. Portanto, este estudo tem como objetivo discutir os dados epidemiológicos e os mecanismos pelos quais essas drogas podem induzir a ocorrência de agranulocitose. Para a elaboração desta revisão foram utilizados artigos científicos, escritos em inglês e português, encontrados através do uso dos descritores "agranulocytosis; dipyrone; clozapine" or "agranulocitose; dipirona; clozapina", nas bases de dados Pubmed, Scielo e Google Acadêmico. Os estudos mostram que há relatos de casos de agranulocitose associados à dipirona, porém, em geral, com baixa incidência. No que diz respeito a clozapina, este fármaco continua sendo a primeira escolha no tratamento farmacológico da esquizofrenia refratária e, além disso, os estudos mostram que a incidência de agranulocitose causada pela clozapina é baixa e, por isso, o uso deste fármaco é seguro, desde que haja um acompanhamento rigoroso do paciente.

**Palavras-chave:** agranulocitose, dipirona, clozapina

***Abstract***

*Agranulocytosis is a type of blood dyscrasia, characterized by low levels of total granulocytes in peripheral blood, which can be caused by several drugs, from over-the-counter drugs, such as dipyrone, to controlled substances, such as clozapine. As it is available and without a medical prescription, self-medication with dipyrone is common in all age groups. Clozapine, on the other hand, is a second-generation antipsychotic used to treat schizophrenia in patient's refractory to other drugs. The use of any of the drugs is associated with agranulocytosis, a serious and potentially lethal side effect. Therefore, this study aims to discuss the epidemiological data and the mechanisms by which these drugs can induce the occurrence of agranulocytosis. For the preparation of this review, scientific articles were used, written in English and Portuguese, found using the descriptors "agranulocytosis; dipyrone; clozapine" or "agranulocytosis; dipyrone; clozapine", in the Pubmed, Scielo and Google Scholar databases. Studies show that there are reports of cases of agranulocytosis associated with dipyrone, however, in general, with low incidence. Regarding clozapine, this drug remains the first choice in the pharmacological treatment of refractory schizophrenia and, in addition, studies show that the incidence of agranulocytosis caused by clozapine is low and, therefore, the use of this drug is safe if there is strict monitoring of the patient.*

***Keywords:*** *agranulocytosis; dipirone; clozapine.*

## 1 Introduction

Agranulocytosis is an acute blood dyscrasia characterized by a decrease in the total number of granulocytes circulating in peripheral blood, mainly neutrophils (RIBEIRO et al., 2011; SOUZA et al., 2013). Due to the crucial role of these immune cells in protecting against infectious agents, agranulocytosis dramatically increases the risk of infections (RIBEIRO et al., 2011). The use of a wide variety of medications, including anticonvulsants, antipsychotics, and anti-inflammatory drugs, is associated with the occurrence of blood dyscrasias (ANDERSOHN; KONZEN; GARBE, 2007). The causes of iatrogenic dyscrasias are still incompletely understood, but associated risk factors include ethnicity, age, immune reaction and idiosyncratic causes (LIMA et al., 2019). Among the drugs associated with this complication, clozapine and dipyrone are of particular importance, due to the extent of their use.

Clozapine is an atypical second-generation antipsychotic medication, widely used in the treatment of schizophrenia, as it is notably effective in critically ill patients and resistant to other typical and atypical antipsychotics, in addition to having a low incidence of adverse effects when compared to other antipsychotic drugs (OLIVEIRA, 2000). Despite its effectiveness, clozapine can rarely induce agranulocytosis, usually in the initial phase of treatment, and this complication can be fatal if the use of the drug is not interrupted (FALCÃO et al., 2018; FERREIRA et al., 2013). The concomitant use of other drugs associated with blood dyscrasias is contraindicated because it has a synergistic action in the production of side effects (FERREIRA et al., 2013).

Dipyrone is a widely used drug in Brazil and worldwide, whose sale takes place with no prescription in 80% of cases (DANIELI and LEAL, 2003). Dipyrone is rapidly absorbed through different routes of administration and, despite being a weak non-steroidal anti-inflammatory drug (NSAID), dipyrone is a potent analgesic and antipyretic, indicated for pathologies such as headache; neuralgia and rheumatic pain; pain involving smooth muscle fibers (eg, renal colic); postoperative and other origins, in addition to fevers in conditions with contraindication to the use of acetylsalicylic acid (ASA) (VALE, 2006). The use of dipyrone can depress the bone marrow and induce agranulocytosis and aplastic anemia, which justifies its prohibition in several countries, such as the USA and the United Kingdom. Some authors, however, emphasize the safety of its use, especially compared to ASA, including in pregnant women, infants, and children (DANIELI and LEAL, 2003; MIOTI and CASTRO, 2017; VALE, 2006). Dipyrone is the active substance or one of the substances in several drugs marketed in South America, South Africa, the Middle East and some European countries. Several studies have been carried out to assess its safety. The extensive International Study of Agranulocytosis and Aplastic Anemia (1986) observed a risk of 1.1 cases per million users, with no association with aplastic anemia (Boston Study). The risk increases with the duration of treatment and disappears ten days after the last dose administered (IBÁÑEZ et al., 2005).

## 2 Agranulocytosis

Leukocytes (“white blood cells”) are cells that are components of the immune system. They play a crucial role for the defense of the organism against pathogenic organisms and for tissue regeneration (CRUVINEL et al., 2010). Circulating leukocytes are classified according to cell morphology into two groups of main cells: granulocytes (neutrophils, eosinophils and basophils) and agranulocytes (monocytes and lymphocytes). Agranulocytosis is a severe reduction in the amount of circulating granulocytes, usually observed by reducing the count of neutrophils (neutropenia), which constitute about 90% of circulating granulocytes (ANDERSOHN; KONZEN; GARBE, 2007; RIBEIRO et al., 2011). The reference value for adults is around 4,000 neutrophils/μL, with considerable variation between sexes and ethnicities (KARAZAWA and JAMRA, 1989; RIBEIRO et al., 2011). Neutrophils are constantly renewed by myelopoiesis in the bone marrow, with a short half-life of 6 hours to 10 hours (FERREIRA et al., 2013 Therefore, neutropenia can occur due to the decrease in the production or anomalous production of neutrophils by the bone marrow or by the increase in peripheral destruction (RIBEIRO et al., 2011).

The diagnosis of agranulocytosis is made by blood count due to the finding of a marked reduction in the number of neutrophils (severe neutropenia), with less than 500 neutrophils/μL of blood volume (MARIQUITO et al., 2019; RIBEIRO et al., 2011). Granulocytes are essential cells of innate immunity; thus, agranulocytosis dramatically increases susceptibility to bacterial infections. The main clinical symptoms, due to associated infections, are fever, chills, headache, throat ulcers, gastrointestinal tract and other mucous

membranes. The immediate suspension of medication is indicated in case of suspected agranulocytosis (VALE, 2006). Mortality in drug-induced agranulocytosis is 5% to 10% in western countries (FERREIRA et al., 2013).

**3 Dipyrone**

Dipyrone (or metamizole) is an antipyretic, analgesic, and antispasmodic with some anti-inflammatory effects, indicated for pathologies such as headache, neuralgia and rheumatic pain, renal colic, postoperative pain and other sources (KNAPPMANN and MELO, 2010; HAMERSCHLAK, 2005). It is one of the most consumed drugs in Brazil, where about 125 dipyrone-based products are available, associated with other substances in 71 of these preparations, and more than 80% of sales occur without a prescription (DANIELI and LEAL, 2003).

After oral administration, dipyrone is rapidly and fully hydrolyzed to 4 N methylaminoantipyrine (MAA), its main active metabolite, which is then rapidly absorbed, with 85% bioavailability. The main active metabolite is subsequently metabolized to 4 N-formyl aminoantipyrine (final metabolite), with an elimination half-life of 2.6 h to 3.5 h (LEVY; ZYLBER-KATZ; ROSENKRANZ, 1995).

Worldwide, the use of dipyrone is controversial, mainly due to reports of agranulocytosis related to its use. For this reason, its use and commercialization are prohibited in several countries, including USA, United Kingdom, Australia and Norway (LUCCHETTI et al., 2010). Several dipyrone-like drugs, such as aminopyrine and antipyrine, were associated with agranulocytosis in the 1930s in the USA. Dipyrone came to be observed with suspicion and, possibly, associated with a high incidence (about 1: 300) of agranulocytosis (DISCOMBE, 1952). Despite the severe methodological limitations and the considerable overestimation of the incidence of agranulocytosis caused by dipyrone in the work of Discombe (VALE, 2006), dipyrone was withdrawn from the market in countries like the USA, Australia and Sweden based on this study (PIRES and OLIVEIRA, 2015; VALE, 2006).

Indeed, dipyrone is the drug most often related to agranulocytosis caused by drugs, but later studies have shown a relatively low incidence. This determination tends to underestimate the incidence of agranulocytosis, since only severe cases, which require medical attention, are reported (LUCCHETTI et al., 2010).

In 1986, results of the Boston study (THE INTERNATIONAL AGRANULOCYTOSIS AND APLASTIC ANEMIA STUDY, 1986), carried out in seven countries (Germany, Bulgaria, Spain, Hungary, Israel, Italy, and Sweden) were published from 1980 to 1984, with the participation more than 22.2 million people. The absolute risk for agranulocytosis among dipyrone users in European Western European countries was estimated at 1.1 in 1 million. In Hungary and Israel, there was no risk.

Ibáñez et al., 2005 point out that, although the use of dipyrone is the fourth most common cause of agranulocytosis, the effect is quite rare. The authors estimated an absolute risk of 0.56 (0.4-0.8) cases in a million, like the Boston study. Compared to other NSAIDs, the use of dipyrone is associated with a higher incidence of agranulocytosis, but this does not prevent the mortality associated with its use (25 in 100 million) being lower than that of acetylsalicylic acid (185 in 100 million) and diclofenac (592 in 100 million) and comparable to that of paracetamol (20 in 100 million) (VALE, 2006). In Brazil, where the use of dipyrone is widespread, the Latin Study (HAMERSCHLAK et al., 2005) found a total incidence of agranulocytosis of only 0.5 cases per 1 million inhabitants, indirectly reiterating the relative safety of the drug.

The mechanism by which dipyrone produces agranulocytosis is not completely understood, although it is known for aminopyrine. Aminopyrine induces the formation of antibodies that lead to the destruction of mature circulating neutrophils and, presumably, also precursors in the bone marrow (JOHNSTON; UETRECHT, 2015). Given the similarity of dipyrone, it is assumed that it acts by the same immune mechanism.

**4 Clozapine**

Clozapine is an atypical second generation antipsychotic, used in the treatment of positive and negative symptoms of schizophrenia since 1958 (SILVA et al., 2017). Schizophrenia is a complex and chronic syndrome, characterized by symptoms such as hallucinations and distortions of thinking and perception (positive symptoms), apathy, social withdrawal and emotional dullness (negative symptoms), with a prevalence of about 1% of the world population (SILVA et al., 2016). Antipsychotic drugs are used in the pharmacological treatment of schizophrenia symptoms, in all their stages, being crucial for the reduction of hospitalization time and patient autonomy

(VICTORINO, 2018). Antipsychotics are classified as typical or atypical, the latter being more effective in controlling symptoms, especially negative ones, and cause less extrapyramidal motor side effects and hyperprolactinemia (OLIVEIRA, 2000).

Clozapine, like other atypical antipsychotics, is an antagonist of dopaminergic and serotonergic receptors, which probably explains its advantages over typical dopaminergic antipsychotics (FALCÃO et al., 2018). Clozapine is especially effective in critically ill patients or in about 30% of schizophrenic patients who do not respond adequately to treatment with other antipsychotics (refractory or treatment-resistant schizophrenia). It also has a lower incidence of side effects than other antipsychotics (SILVA et al., 2017). Despite these advantages, the report of the association of its use with severe agranulocytosis in Finland in 1975 led to the suspension of its use and commercialization in several countries (PONS ET AL, 2012); in countries where it is used, the prescription is reserved for patients with refractory schizophrenia (FALCÃO et al., 2018).

The mechanisms of clozapine-induced agranulocytosis and, less frequently, other antipsychotics, include direct toxic effects on the bone marrow, the formation of antibodies against hematopoietic precursors or the destruction of peripheral cells. Mortality reaches 5% to 10% in western countries (FERREIRA et al., 2013). The causes that trigger the toxic mechanisms of agranulocytosis are not completely known, but suggested risk factors include ethnicity, age, immune reaction and idiosyncratic causes (PONS et al., 2012).

In a hematological monitoring of schizophrenic patients treated with clozapine, between 2010 and 2012, one case of neutropenia and one case of thrombocytopenia were observed among the 22 patients; in both cases, interruption of treatment was not necessary. No case of agranulocytosis was observed (SILVA et al., 2017).

In a 5-year study of 231 patients at Barcelona clinical Hospital, seven participants had neutropenia, but there were no cases of agranulocytosis. In the following two years, the same follow-up was carried out, observing a case of neutropenia in 120 patients, without any case of agranulocytosis (PONS et al., 2012).

Nery-Fernandes et al. (2006) report that a patient with refractory schizophrenia was observed at the hospital of the Federal University of Bahia to start treatment with clozapine. The patient, then patient, was voluntarily absent from follow-up, but maintained the use of clozapine and weekly blood counts. Upon return, a drop in neutrophil counts was observed, below the recommended level for discontinuing treatment, but without any clinical repercussions and with spontaneous resolution after three months. The suspension of treatment, indicated with leukocytes below 3,000/mm³ or neutrophils below 1,500/mm³, allows ample safety in the use of clozapine, but may deprive patients refractory to treatment capable of adapting to the initial neutropenia of the clinical benefits of clozapine (NERY-FERNANDES et al., 2006).

Strict hematological monitoring is indicated while using clozapine. The blood count with platelet count should be performed weekly, during the first 18 weeks of treatment, and monthly thereafter (BRASIL, 2013). This protocol has been successful in reducing worldwide rates of agranulocytosis and consequent fatalities (SILVA et al., 2017)

**5 Conclusion and final remarks**

It is well known that the use of dipyrone can induce agranulocytosis and blood dyscrasias and that, due to these symptoms, its use and commercialization has been restricted in several countries. Reports of cases of agranulocytosis associated with dipyrone are frequent in the literature, however, in general, with low incidence. Based on the various studies cited, it is reasonable to conclude that dipyrone-induced agranulocytosis does not constitute a major health problem in Brazil, possibly due to genetic differences between populations in different countries (MARIQUITO et al., 2019) and its relative effectiveness indicate against prohibiting its use. This fact does not, however, detract from the relevance of additional epidemiological studies on the issue, especially in places or populations where the consumption of dipyrone is excessive, to investigate the possibility of interactions with other drugs, ensure its use and ensure full information of patients, since its use is widespread and commonly without medical prescription. Clozapine remains the drug of choice in refractory schizophrenia. In general, studies show that the incidence of agranulocytosis is low and the use is safe, provided the patient is followed and monitored intensively.

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