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CASE REPORT

Dipyrone-related granulocytopenia. Case report

Granulocitopenia por dipirona: reporte de caso

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Abstract

Introduction: Dipyrone has been positioned in several countries as one of the first over-the-counter options for pain management. Its possible adverse effects are known worldwide; among them, agranulocytosis is the most lethal, with a mortality of approximately 10% and an associated risk of 1 per 1,000,000 patients.

Clinical findings, interventions, and outcomes: A case of a patient who, after 23 days of using dipyrone for pain management, developed a progressive drop in leukocyte count. Other potential causes of the event were ruled out. After dipyrone discontinuation, leukocyte counts returned to their normal values.

Conclusion: The probable diagnosis of granulocytopenia as a dipyrone-related adverse drug reaction was established. Although rare, dipyrone-related granulocytopenia, may occur in patients who use this medication for long periods.

Resumen

Introducción: La dipirona se ha posicionado en varios países como una de las primeras opciones de venta libre al público para el manejo del dolor. Sus posibles efectos adversos son conocidos a nivel mundial; entre ellos, la agranulocitosis es la más letal con una mortalidad aproximada del 10% y un riesgo asociado de 1 por cada 1.000.000 pacientes.

Hallazgos clínicos, intervención y resultados: Se presenta un caso de una paciente que luego de recibir 23 días seguidos dipirona para el manejo del dolor presentó disminución progresiva de los leucocitos documentados en el hemograma. Se descartaron otras posibles causas de dicho evento. Luego de suspender la administración de la dipirona los leucocitos volvieron a sus valores normales.

Conclusión: Se estableció la sospecha de diagnóstico probable de granulocitopenia como reacción adversa medicamentosa por dipirona. La granulocitopenia por dipirona aunque poco frecuente, se puede presentar en pacientes que la reciben por largos periodos de tiempo.

Introduction

Dipyrone (metamizol) is a drug with analgesic effects used for the treatment of acute post-operative pain, oncologic pain, cramp-like pain, and migraine.[1–3] It was widely used before the 1970s, until an association was started to be found between its use and serious adverse reactions such as agranulocytosis,[4,5] defined as a drop in granulocyte count to less than 0.5×10^9/L; although infrequent, the associated mortality was 10%, due to the predisposition to develop pneumonia, sepsis, toxic epidermal necrolysis,

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and necrotizing fasciitis,[6–9] prompting the Federal Food and Drug Administration (FDA) to ban it in the United States in 1977.[10] Since then, more than 30 countries to date have banned its general use.

Several factors that could contribute to the onset of agranulocytosis, have been proposed, but no direct relationship has been established for any of them so far. The most important include extended use (>14 days), female gender, age (over 60 years), concomitant use of methotrexate, and immune and metabolic susceptibility.[11] The following is a case description that illustrates this effect.

Patient information

A 59-year-old woman with a history of arterial hypertension, unspecified depressive disorder and a surgical history of cystocele repair in 2010. The pharmacological history included hydrochlorothiazide, losartan, verapamil, acetyl salicylic acid, and fluoxetine.

Clinical findings

The patient was taken to the emergency service on October 17, 2016 after a traffic accident as a passenger on a motorcycle. She presented with evidence of exposed tibial fracture, bilateral periorbital ecchymosis suggesting skull base fracture, hypotension, and amnesia about the episode. Medical management was initiated with dipyrone 2 g intravenously (iv) every 6 hours, cefazolin 1 g iv every 6 hours, and gentamicin 160 mg iv every 24 hours.

On the same day, the patient was assessed by the general surgeon and taken to closed thoracostomy due to left pneumothorax. Orthopaedic surgery for open reduction of the tibial fracture was performed during the same surgical stage. Dipyrione 1 g iv was continued every 6 hours during the postoperative period, together with tramadol 100 mg every 8 hours only in case of intense pain, ranitidine 50 mg iv every 12 hours, enoxaparin 40 mg SQ daily, and the same antibiotic management. The only notorious finding in the initial complete blood count (CBC) was severe anemia (hemoglobin 6.6 mg/dL). This result prompted transfusion of 2 units of red blood cells.

On October 19, 2016 the dipyrone dose was increased to 2 g iv every 6 hours, while the rest of the medications were continued with no change. On October 21, 2016 left tibia and fibula plating was performed. The follow-up CBC showed slight improvement of the anaemia (hemoglobin 7 mg/dL). Thoracostomy was removed on October 21, 2016 the clinical course continued uneventfully and management continued unchanged. Serial follow-up blood tests remained within normal limits. On October 26, 2016, the patient was assessed by the maxillofacial surgeon who performed orbital floor reconstruction; 1 unit of packed red blood cells was transfused during the procedure. Thoracentesis was scheduled because of a reported left pleural effusion found on computed axial tomography of the chest, quantified at 471 mL on chest ultrasound. However, drainage was postponed due to suspected cellulitis in the left hemithorax, which in the end was found to be only skin irritation caused by the adhesive tape. The orthopaedic surgeon and the maxillofacial surgeon discharged the patient. The clinical course continued while waiting for the thoracentesis procedure. A new chest ultrasound scan performed on November 7, 2016 showed persistent left pleural effusion, which prompted new follow-up tests before the procedure, including CBC done on November 8, 2017 which showed leukopenia, neutropenia, and lymphopenia (Table 1), and creatinine and blood urea nitrogen within normal limits.

Table 1. Complete blood count testing of a female patient admitted with multiple fractures during the time of dipyrone use and after its discontinuation

Parameter/Dates	17/10/16	18/10/16	20/10/16	22/10/16	24/10/16	27/10/16	03/11/16	08/11/16	09/11/16	11/11/16
Leukocytes	23,470	9260	8070	9620	8100	11,210	5710	2900	1920	5150
Neutrophils	17,500	7200	5350	6440	4910	7490	2650	1190	850	1950
Lymphocytes	3920	1180	1780	1720	1920	2230	1510	830	560	1.920
Hemoglobin	9.5	6.6	8.6	7	6.7	8.4	9.9	10.4	10.8	12.4
Hematocrit	29.5	20	25.9	21	21.7	27.5	33	33.6	34.2	39.2
MCV	93	89.7	90.2	93.1	95.2	95.2	97.9	95.5	92.4	92.7
RDW	12.6	13	13.9	14.7	15.4	15.8	16.6	15.6	15.2	14.9
Platelets	274,000	188,000	188,000	240,000	281,000	418,000	671,000	413,000	343,000	321,000

MCV = medium corpuscular volume, RDW = red cell distribution width.
Source: Authors.

Therapeutic intervention

Thoracentesis performed on November 9, 2016 retrieved 180 mL of serous material which was sent for analysis, and was found to be a serous exudate with no signs of infection. However, due to the CBC findings, the internal medicine physician decided to discontinue dipyrone after 23 days of administration. The follow-up CBC showed worsening of white blood cell counts.

Follow-up and results

Stringent follow-up continues with CBC results showing improvements in the parameters mentioned previously (see Table 1).

Diagnosis evaluation

After applying the algorithm by Naranjo et al, the diagnosis is probable leukopenia related to the use of dipyrone. The patient was discharged and asked to come back in 1 month with a follow-up CBC. The radiological course of the pleural effusion was satisfactory and the general surgeon decided to discharge the patient and order outpatient follow-up.

Time line

Table 1 shows the results of all the complete blood count tests taken during the time the patient remained in the hospital.

Discussion

Dipyrone is a pyrazolone derivative with analgesic, antipyretic, and antispasmodic effects, but with little anti-inflammatory effect.[1,7] It is used in the management of postoperative pain, cramp-like pain, cancer pain, and migraine; although its use is very controversial in many countries because of the risk of agranulocytosis, it is still sold over the counter in other countries.[12]

Its antipyretic effect is believed to be due to a reduction in blood levels of prostaglandin E_2 followed by an antipyretic effect on the EP3 located on anterior hypothalamic thermoregulatory neurons.

Associated adverse effects include nausea, vomiting,[1] hypotension, cardiogenic shock,[13,14] exanthemata, urticaria,[5] interstitial nephritis, acute renal failure,[15] anaphylaxis,[16] and Stevens–Johnson syndrome,[17] pancytopenia, and agranulocytosis,[1,6,18] these latter 2 being the conditions that have limited its widespread use. Regarding agranulocytosis, several explanations have been proposed: one of the theories suggests a toxic effect on peripheral blood caused by aminopyrine where drug-dependent anti-neutrophil antibodies are formed which then induce the formation of immune complexes with the drug, leading to neutrophil cell lysis.[19] However, lysis of these leukocytes may also occur in the bone marrow given that one of the metabolites of dipyrone is capable of interacting with lysine chains in the cell, and triggering an immune response. Another theory proposes that neutrophils produce reactive oxygen species capable of oxidizing some drugs into reactive products which act as haptens, inducing antibody formation.[7,20] Another immune mechanism suggests a reduced in vitro growth of myeloid progenitor cells, multipotent primitive progenitor cells and erythroid progenitor caused by dipyrone in an in vitro culture of bone marrow and CD34+ cells.[21]

On the other hand, several factors have been proposed as contributors to the onset of agranulocytosis, including exposure to high doses, prolonged treatment (>14 days), female gender, age over 65 years, drug interactions, and genetic predisposition.[1,11] However, no direct relationship has been established with dipyrone-induced agranulocytosis for any of them.[11,22]

We present the case of a 59-year-old female in a multiple-trauma context, managed with dipyrone for 23 days, and who developed granulocytopenia from no other apparent cause. No temporal association could be found between the other medications she received and this same type of adverse event. When the drug was discontinued, the follow-up complete blood count showed evidence of increased leukocytes. The patient did not have an underlying infectious process and was discharged with no additional complication. In accordance with the protocols and recommendations required in these types of events, the algorithm by Naranjo et al[23] was applied in an attempt to establish a causality association. The result was a score of 7, consistent with a probable adverse drug reaction.

Although this reaction is infrequent in our setting, physicians and staff caring for patients with pain for prolonged periods should bear in mind the risk of using dipyrone for more than 14 days, as well as its associations with a drop in white blood cell counts and, consequently, immunosuppression and increased probability of infection.

Patient perspective

The patient only expressed her gratitude for the care received and because she was able to walk again.

Ethical disclosures

Protection of human and animal subjects. The case report was prepared with the informed consent of the family, in accordance with Resolution No. 8430 of 1993 of the Colombian Ministry of Health, guaranteeing patient information confidentiality pursuant to the principles of the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the and 2 witnesses. This document work in the power of the correspondence author.

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Conflicts of interest

The authors report no conflicts of interest.

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