Dipyrone, Great Killer or Innocent as Any Drug: Two Case Reports Presenting Rare and Life-Threatening Adverse Effects of Dipyrone

Dipiron Büyük Katil ya da Her İlaç Kadar Masum: Dipironun Nadir ve Yaşamsal Risk Oluşturan Yan Etkilerinin Gözlendiği İki Olgu

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ABSTRACT Dipyrone is a potent analgesic and antipyretic drug that has been used clinically for more than 80 years. In some parts of the world, it has been banned because of its association with agranulocytosis. We reported two different cases, presenting with rare but life-threatening adverse effects of dipyrone. First case was a 63-year-old woman that presented to the emergency department with fever. She had developed neutropenia after taking a 500 mg oral dipyrone tablet and following further evaluation was diagnosed with dipyrone-induced agranulocytosis. Second case was a 70-year-old man who presented to the emergency department with diffuse erythematous skin rash after dipyrone injection and was diagnosed with toxic epidermal necrolysis associated with dipyrone. The balance between the benefit and harm is particularly important. Nevertheless, agranulocytosis is not the only life-threatening risk with dipyrone use and limiting the discussion of risks of dipyrone to agranulocytosis leads to an underestimation of the dangers of the drug.

Key Words: Dipyrone; adverse effects; agranulocytosis; epidermal necrolysis, toxic

ÖZET Dipiron, 80 yıldır kullanılan güçlü bir analjezik ve antipiretiktir. Dünyanın bazı bölgelerinde agranülositoz riski nedeniyle bu ilacın kullanımı yasaklanmıştır. Bu makalede, dipirona bağlı nadir fakat ölümcül olabilen yan etkiler ortaya çıkan iki olgu sunulmuştur. Birinci olgu ateş nedeniyle ağızdan 500 mg dipiron tablet kullandıktan sonra acil servise nötropeni ile başvuran 63 yaşında bir kadındır. İkinci olgu, dipiron enjeksiyonundan sonra acil servise difüz eritematöz döküntülerle başvuran ve toksik epidermal nekroliz tanısı alan 70 yaşında bir erkektir. Bir ilaç için fayda-zarar dengesi çok önemlidir. Dipiron kullanımına bağlı hayatı tehdit eden tek yan etki agranülositoz değildir ve tartışmaları sadece bununla sınırlamak, potansiyel diğer tehlikelerin dikkatten kaçmasına yol açabilir.

Anahtar Kelimeler: Dipiron; istenmeyen etkiler; agranülositoz; epidermal nekrolizis, toksik

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Dipyrone (metamizole) is an antipyretic analgesic that was introduced into clinical practice in 1922. The drug is indicated for severe pain conditions, especially those associated with smooth muscle spasm or colic affecting the gastrointestinal, biliary or urinary tracts. Moreover, it is useful for the treatment of cancer pain and migraine as well as fever refractory to other treatments.[1]

Dipyrone is a pro-drug that undergoes non-enzymatic hydrolysis in the stomach to form 4-methylamino-antipyrine (4-MAA). This active metabolite is rapidly and almost completely absorbed. Nausea, vomiting, gastric irrita-

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tion, xerostomia, tiredness, skin rashes and eruptions, and hypotension after IV administration are the main adverse effects.[2] The most common side effect is rash, but toxic epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome and anaphylactic shock have also been reported.[3] Agranulocytosis is an infrequent but unpredictable and potentially fatal adverse effect of dipyrone.

Dipyrone is available in oral, rectal, and injectable forms. Because of the risk of agranulocytosis, it has been banned or been withdrawn from the market in most industrialized countries, although the drug is still available in some countries in Europe including Germany, France and Spain. In many countries such as UK, it has never been licensed. It is still widely used in many parts of the world, including the Far East, Africa and Latin and South America.[4] It is available without prescription in places such as Brazil, Israel, Mexico, Russia and Turkey. In Turkey, dipyrone is available in oral tablet, drop and syrup, rectal suppository and injectable forms and almost all forms are cheap in price. Two different cases presenting with rare but life-threatening adverse effects of dipyrone were reported in this paper.

CASE REPORTS

CASE 1

A 63-year-old woman presented to the emergency department with fever. She had fever, chills and sore throat for two days. Her fever was 39°C and she had taken a 500 mg oral dipyrone tablet. The day after, she had presented to the city hospital because of her complaints. The complete blood count run in the city hospital revealed agranulocytosis and she was referred to the university hospital for further evaluation about the cause of this febrile neutropenia. On admission her vital signs were as follows: blood pressure 134/84 mm Hg, pulse rate 117 beats/min, respiratory rate 16 breaths/min, body temperature 38.9°C, and oxygen saturation (SpO_2) detected by pulse oxymeter was 96% on room air. Her physical examination was normal except for the hyperemic view of the pharynx. The leukocyte count was 800 cells/mm^3 with 9.1% neutrophils. The platelet and erythrocyte counts and other laboratory findings including liver enzymes, creatinine, glucose, and electrolytes were within normal limits. She was admitted to the hospital for further evaluation. All other tests including immunoglobulin, complement factors, Antinuclear Antibody Test (ANA), Anti-Neutrophilic Cytosplasmic Antibodies (ANCA) levels were normal. Bone marrow findings did not reveal any other abnormality such as leukemia. Her fever dropped on the seventh day of the hospitalization and neutropenia improved on the tenth day. She was discharged from the hospital after 14 days without any ongoing problems. She was diagnosed with dipyrone-induced neutropenia.

CASE 2

A 70-year-old man presented to the emergency department with diffuse erythematous skin rash. Two years ago, he had had a stroke, which he had survived with minimal morbidity. Three days before he presented to the university hospital emergency department, he had been admitted to the state hospital neurology clinic for evaluation. His complaint was headache and he was suspected to have a new stroke attack. Any neurologic deficit different from the past findings was not detected in the examination. In the neurology clinic, he was given an intramuscular dipyrone injection for his headache. He received a second injection the following morning and in the afternoon on the same day, he developed macular eruptions in the axillary and groin areas. The eruptions spread rapidly to all body areas and erosions developed. He was referred to our university hospital for further evaluation and treatment. At presentation his vital signs were as follows: blood pressure 126/74 mm Hg, pulse rate 89 beats/min, respiratory rate 16 breaths/min, body temperature 36.1°C, and oxygen saturation (SpO_2) detected by pulse oxymeter was 95% on room air. Diffuse erythematous maculopapular lesions and skin erosions were detected in the physical examination. Nikolsky sign-epidermal separation induced by gentle lateral pressure on the skin surface was positive. Erosions were also present in the oral and genital mucosal areas. He was admitted to the hospital with toxic epidermal necrolysis associated with dipyrone. In addition to wide spectrum antibiotics (Meropenem IV), antipyretics, supportive fluid therapy and prednisolone 80 mg/day was initiated. His

body temparature was normal in the emergency department but he had fever during hospitalization. After 5 days, the skin lesions recovered and steroid treatment was stopped. He was discharged from the hospital with his formal medications he was using for hypertension and previous stroke.

DISCUSSION

Dipyrone is widely used in some parts of the world as an analgesic, in other regions it has been banned because of its controversial association with agranulocytosis. Nonchemotherapy drug-induced agranulocytosis is a rare adverse reaction characterized by a decrease in peripheral neutrophil count to less than $0.5x10^9$ cells/L due to immunologic or cytotoxic mechanisms.[5] Idiosyncratic drug-induced agranulocytosis is a rare disease. The incidence increases with age, as only 10% of cases are reported in children and young adults, and more than half of the episodes occur in people over 60 years of age.[6] Both cases we presented were older than 60 years of age.

The criteria used to assess causality were neutrophil count $<0.5\times10^9$/L±presence of fever and/or any sign of infection and the onset of agranulocytosis during treatment or within 7 days in the case of previous intake of the same drug and complete recovery with more than 1.5×10^9/L neutrophils in blood cell count, 1 month after drug interruption.[6] The median duration of drug exposure before onset of acute agranulocytosis ranges from 19 to 60 days in different drugs; for dipyrone, the median drug exposure is only 2 days and the time between the onset of acute agranulocytosis and normalization of neutrophil count is 10 days.[5] These time intervals were similar in our patients.

Dipyrone clearly causes agranulocytosis, but there is insufficient useful information to quantify the risk adequately. Furthermore, there are true geographical differences in risk, which may also depend on genetic and/or environmental local cofactors. In a case control study, the multivariate rate ratio estimate for dipyrone was higher in Ulm, West Berlin and Barcelona and lower in Israel and Budapest.[7] More recent reports from different countries confirm this geographic heterogeneity.

Hedenmalm and Spigset described Swedish cases of agranulocytosis when it was a prescription-only medicine.[4] They estimated an incidence of 1 case per 1431 prescriptions on eight cases resulting from 10 892 outpatient prescriptions between 1995 and 1999. If this high incidence was reflected in populations in which dipyrone is commonly used, as in Spain or Brazil, many individuals would succumb to agranulocytosis every year. However, Ibanez et al from Spain reported that agranulocytosis attributable to dipyrone was rare.[8] Moreover, the conclusion of the LATIN study was that drug-induced agranulocytosis did not seem to be a major public health problem in the study regions.[9]

Underreporting is one explanation for low reported event-rates in countries with high use of dipyrone, but cannot alone clarify discrepancy. Dipyrone-induced agranulocytosis is a hypersensitivity reaction. Therefore, once a patient has become sensitized to the drug, the severity of the reaction should be unrelated to the dose taken. However, it is possible that higher doses or longer exposure periods are more likely to induce sensitization. Seven of eight Swedish cases had total treatment duration of 13 days or more and the exposed cases in the Spanish study tended to take dipyrone for longer periods and at seemingly higher doses. This suggests that the dose of dipyrone and the duration of its use may be risk factors for the development of agranulocytosis. However, in our case the patient took only one tablet and developed agranulocytosis on the second day.

Absolute risks are important in order to determine the harm. For assessing the risk of agranulocytosis with dipyrone, absolute risks have not been determined in high-quality systematic reviews. The only way to settle the argument should be to run larger studies in countries that are heavy users of dipyrone.

Nevertheless, agranulocytosis is not the only life-threatening risk with dipyrone use and limiting the discussion of risks of dipyrone to agranulocytosis leads to an underestimation of the dangers of the drug. After reporting serious hypotension with dipyrone in one per 3000 patients in 1983, the hospital-based monitoring system in Bremen reported other

serious immune reactions to dipyrone, such as anaphylaxis, asthma, serum sickness, hypersensitivity vasculitis, alveolitis, pneumonitis, hepatitis, or haemolytic- uraemic syndrome about four times more often than agranulocytosis in 1999. Since it takes about 2 weeks to trigger immune reactions in patients new to the drug, short-term studies miss the drug's dangerous effects.[10] Besides, there are case reports about severe anaphylactic reactions caused by dipyrone in the literature.[11-13]

Dipyrone is also the analgesic that most frequently causes hypersensitivity reactions. The most common reactions are IgE-mediated reactions and idiosyncratic reactions, although non-immediate reactions have also been described, including severe cutaneous reactions, such as Stevens–Johnson syndrome or necrotic epidermolysis and other delayed reactions such as fixed drug eruption and contact dermatitis.[14]

Toxic epidermal necrolysis (TEN) is a rare, potentially life-threatening medical emergency characterized by widespread epidermal sloughing of the skin accompanied by mucous membrane involvement. In the majority of the cases, there is a history of recent drug ingestion. Antibiotics, non-steroidal anti-inflammatory drugs, analgesics, and anticonvulsant medications are the most common drugs. Reported mortality varies from 30 to 50%, and the primary cause of death is infection and multi-system organ failure.[15]

Despite continued research efforts and an enhanced understanding of the likely mechanisms involved, no specific treatment has demonstrated significant improvement to reduce effectively the associated morbidity and mortality. Supportive management remains the mainstay of the treatment for TEN. This involves skilled clinical assessment with early identification of the culprit drug and immediate withdrawal. Close fluid and electrolyte monitoring in an intensive care setting is optimal. Antibiotics should also be considered in the event of infection.[16]

Corticosteroids have been used as a treatment modality for over 30 years. Despite laboratory evidence of potential success, the use of corticosteroids in the treatment of TEN remains controversial. In most published articles, intravenous steroids are reported not to alter the course of the illness and in fact may prove harmful by possibly increasing the risk of infection, prolonging wound healing and promoting gastrointestinal bleeding. Plasmapheresis has been reported to be effective. Despite case series supporting the use of intravenous immunoglobulin, other groups have demonstrated no improvement in outcome.[15] Our second patient received low dose steroids and supportive care and recovered in 5 days without further problems.

To use or not to use dipyrone is very controversial and a great debate is going on. Dipyrone supporters think that the drug is offering good analgesic efficacy with a favorable safety profile. They believe that there is strong negative emotion in spite of weak rationale especially about dipyrone induced agranulocytosis, and suppose some rumors about the ban of the drug. The balance between the benefit and harm is particularly important for developing countries where dipyrone may be the first-line analgesic, and where other drugs may not be readily available.

CONCLUSION

Agranulocytosis is not the only life-threatening risk with dipyrone use as in our second case. Immune reactions such as anaphylaxis and TEN are quite serious problems and this fact impedes the underestimation of the dangers of the drug.

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