Case Report

Acute agranulocytosis after prolonged high-dose usage of intravenous dipyrone – a different mechanism of dipyrone toxicity?

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Summary. Two seriously injured trauma patients presenting with intense and progressive neutropenia are described. Bone marrow examination in both cases showed virtually absent granulopoiesis but normal erythropoiesis and megakaryopoiesis, allowing the diagnosis of acute agranulocytosis. Discontinuation of only one drug (dipyrone) with no further treatment was required for normalization of blood parameters. The association of dipyrone with neutropenia is still debatable. The recent medical literature on dipyrone generation of agranulocytosis is reviewed.

Key words: Agranulocytosis – Dipyrone – Neutropenia – Side effect

Introduction

Development of neutropenia in critically ill patients usually reflects an increase in peripheral consumption caused by gram-negative bacterial infections. Appropriate care of the primary disease results, in general, in normalization of leukocyte counts. There are, however, situations in which abrupt a decrease in neutrophil numbers indicates a functional bone marrow failure. Acute agranulocytosis is an often fatal disease manifested by virtual absence of granulocytes in the blood, associated with specific marrow granulocytic hypoplasia [12]. The extremely uncommon condition incidence of this was recently determined to be approximately seven per million per year [13]. In this report we describe two seriously injured trauma patients who developed severe selective granulocytopenia after several days of intensive care. Both patients were receiving prescription high-dose intravenous dipyrone.

Case reports

Case 1. An 18-year-old Korean man was transferred to our intensive care unit (ICU) 6 h after being involved in a car accident. He arrived intubated and artificially ventilated. On admission the patient was found to be in deep coma and to have decerebrate posturing on painful stimulation. His pupils were moderately dilated, presenting prompt reactions to light. A CT scan showed discrete brain swelling. The patient was then submitted to intracranial pressure monitoring and was mechanically hyperventilated while receiving intravenous phenobarbital for sedation.

Antibiotic therapy administered initially as prophylaxis and then for a chest infection consisted of cephalothin from day 1 to day 4, cefotaxime and metronidazole from day 5 to day 13, and pefloxacin from day 14 to day 17.

Sixteen days after admission a gradual decrease in the patient’s leukocyte count was noted (Fig. 1). Platelet and reticulocyte values were 300000/mm² and 1.6% respectively. Bone marrow aspiration performed on day 17 revealed an absolute absence of granulocytic...
elements, with no abnormalities in other hematopoietic series (Fig. 2a). At this time, besides antibiotics and phenobarbital, the patient was receiving only ranitidine and dipyrone. Because of several hypertonic reactions, inevitably followed by several febrile episodes, the latter was being administered intravenously, in an average daily dosage of 2–5 g. On day 17 dipyrone was substituted by acetaminophen and the antibiotics were changed to ceftazidime and amikacin. Phenobarbital and ranitidine were maintained. The patient recovered well from his granulocytopenia (Fig. 1) and on day 27 was discharged from the ICU to the infirmary, extubated and reacting to verbal suggestions.

Case 2. A 25-year-old Caucasian man was transferred to our ICU because of multiple trauma including a serious head injury. He arrived mechanically hyperventilating and in a hemodynamically stable condition. At admission the patient was found to be in deep coma (Glasgow coma scale 4), and to have decerebrate posturing on stimulation and a third nerve palsy. A diffuse brain swelling with multiple small brain hemmorhages was demonstrated by CT scan. The patient was immediately put under sedation with phenobarbital and intravenous mannitol was initiated, while intracranial pressure was monitored.

Antibiotic administrations were as follows: cephalothin from day 1 to day 4, cefoxitin and amikacin from day 5 to day 17, and ciprofloxacin from day 18 to day 21. The only other drugs used here were ranitidine and dipyrone. In this case, dipyrone was also being given at a high intravenous dosage (4 g/day in average) because of very frequent and intense febrile episodes.

On day 21 after admission a very severe and progressive neutropenia was diagnosed, complicated by an instability in the patient’s hemodynamic parameters (Fig. 1). Introduction of dobutamine was required, and antibiotics was changed to imipenen, vancomycin, and amikacin. A bone marrow aspirate showed granulopoiesis to be almost absent, with very few forms seen beyond the promyelocyte stage. Erythropoiesis and megakaryopoiesis were normal (Fig. 2b). Administration of dipyrone was interrupted on the same day and fever was controlled by acetaminophen. Ranitidine was maintained. The patient’s leukocyte counts were again normal on day 28 after admission. On day 43 the patient was transferred to a rehabilitation hospital in stable hemodynamic and neurologic condition.

Discussion

Blood dyscrasias such as agranulocytosis, aplastic anemia, hemolytic anemia, and thrombocytopenia feature prominently as adverse drug reactions [2]. Among these diseases, agranulocytosis has received special attention because, along with aplastic anemia, it constitutes the leading cause of drug-induced death [9]. The drugs most commonly associated with a risk of agranulocytosis are metamizole (dipyrone), the sulfonamides and the thyrerostatics [2]. Data on dipyrone generation of neutropenia are still debatable, however.

The first case of agranulocytosis associated with dipyrone was reported in 1935 [reviewed in 6]. At this time, aminopyrine, a compound chemically similar to dipyrone and also used as an analgesic and antipyretic, had already been implicated in more than 85% of all agranulocytosis cases reported in the medical literature [8]. By the middle of this century, both drugs had virtually disappeared from the therapeutic scene in the United States. In 1986, the International Agranulocytosis and Aplastic Anemia Study Group published a population-based control study, conducted in Europe and Israel, relating these two diseases with analgesic consumption. Dipyrone was associated with an increased risk of agranulocytosis in West Germany and Spain but not in Israel and Hungary [7]. A recent communication from the Bulgarian Medical Academy revealed that in spite of dipyrone being the most commonly used analgesic, and despite its being prescribed substantially more often in Bulgaria than elsewhere in Europe, agranulocytosis has remained a rare disease there [14].

Three different mechanisms may lead to drug-induced blood dyscrasias: immunologic reactions, drug toxicity, and congenital metabolic defects have been described in this context [3]. There is strong evidence that agranulocytosis due to dipyrone is allergic or immunologic in origin [1, 5]. This immunologic mechanism is not completely...