Metamizole Use by Latino Immigrants: A Common and Potentially Harmful Home Remedy

Joshua L. Bonkowsky, MD, PhD*; J. Kimble Frazer, MD, PhD*; Karen F. Buchi, MD†; and Carrie L. Byington, MD*‡§

ABSTRACT. A 4-year-old boy presented with fever, septic arthritis, and persistent neutropenia. Bone marrow biopsy revealed no evidence of neoplasia. Additional history disclosed that the patient had been given metamizole for pain before onset of his illness. Metamizole, a nonsteroidal antiinflammatory agent, is prohibited in the United States because of the risk of agranulocytosis but is widely used in Mexico and other countries. The increasing number of Latinos in the United States and the extensive cross-border transfer of medicines raise concerns that metamizole use and associated complications may become more frequent. After identification of the index patient, additional inquiry revealed that the patient’s mother was hospitalized previously for overwhelming sepsis associated with metamizole use. These cases prompted an investigation of metamizole use in an urban pediatric clinic, which revealed that 35% of Spanish-speaking Latino families had used metamizole; 25% of these families had purchased the medication in the United States. We conclude that metamizole use is common and may be underrecognized in immigrant Latino patients. Physicians in the United States, especially those who practice primary care, hematology/oncology, and infectious diseases, must be aware of the availability and use of metamizole in specific patient populations and its potential for harmful side effects. Pediatrics 2002;109(6). URL: http://www.pediatrics.org/cgi/content/full/109/6/e98; metamizole, neutropenia, home remedy.

ABBREVIATIONS. WBC, white blood cell; ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor.

Metamizole, or dipyrrone, is a pyrazolone nonsteroidal antiinflammatory agent.1 It has been associated with fatal agranulocytosis and was withdrawn from the US market by the US Food and Drug Administration in 1979.1 Metamizole is available without a prescription in Mexico and other countries and is used to treat fever and pain. It is marketed in Latin America under hundreds of brand names, including Neo-melubrina (Table 1). Despite the common use of metamizole in other countries and warnings issued in the United States to travelers regarding the risks of medications that contain pyrazolone analgesics,2 many US physicians remain unaware of these potentially harmful medications.

CASE REPORTS

A 4-year-old Latino boy presented to an urban public health clinic in Salt Lake City, Utah, for evaluation of limp and fever. His parents had given him Neo-melubrina (metamizole) for his symptoms. His medical history was unremarkable. The boy’s family history was remarkable for sepsis in the mother 5 months before the child’s illness. His social history was notable for recent emigration from Mexico.

Physical examination revealed a temperature of 39.5°C and active resistance to rotation of his left hip. Laboratory testing demonstrated a white blood cell count (WBC) of 3800/μL (19% band forms, 26% segmented neutrophils, 48% lymphocytes, 7% monocytes), absolute neutrophil count (ANC) of 1710, hemoglobin 12.3 g/dL, platelets 285 000/μL, Westergren erythrocyte sedimentation rate of 20 mm/h, and C-reactive protein of 1.7 mg/dL. Radiographs of the hips showed an effusion on the left, subsequently confirmed by ultrasonography. A bone scan was normal. Hip joint aspiration yielded cloudy fluid; Gram stain was negative. A bacterial culture of synovial fluid was obtained. The patient was admitted, and treatment with nafcillin and clindamycin was initiated.

The patient remained febrile to 40.4°C and the C-reactive protein increased to 4 mg/dL. The WBC decreased to 2800/μL with an ANC of 1190. Hematopathologic evaluation of the peripheral blood smear revealed neutropenia, lymphopenia, and a single myeloid blast. The synovial fluid culture yielded Enterobacter agglomerans. Antibiotic coverage was adjusted. Left hip arthroscopy and bone marrow biopsy were performed 2 days after admission.

The bone marrow demonstrated normocellular marrow and no evidence of myelodysplasia but revealed myeloblastosis consistent with a reactive process. The patient’s ANC decreased to 640. The patient received 2 doses of granulocyte colony-stimulating factor (G-CSF) with temporary improvement. A repeat bone marrow biopsy was performed 22 days after admission secondary to a persistently low ANC; no evidence of a neoproliferative process was seen. The patient completed a 28-day course of antibiotics. One month postdischarge, his WBC was 5500/μL with an ANC of 3410.

The patient’s 27-year-old mother was interviewed, and her medical records were reviewed. She reported 1 week of fever and abdominal pain 5 months before her child’s presentation for which she purchased Neo-melubrina and an antibiotic to treat her symptoms. Her symptoms worsened, and she was admitted to the hospital with a temperature of 40°C, disseminated intravascular coagulation, and shock. Computed tomography of the abdomen revealed acute cholecystitis. She required treatment in the intensive care unit, and she completed a 10-day course of antibiotics. During her hospitalization, her WBC counts ranged from 3000 to 4000/μL with an ANC of 1500 to 2000 and an absolute lymphocyte count of 700. The family purchased Neo-melubrina without a prescription from a Latin American market in Salt Lake City. No directions or warnings were included with the medication. Members of the clinic staff were able to purchase the same medication at the market.

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the time of the clinic visit but had no neutropenia. More diverse, physicians must become increasingly educated regarding the dangers of metamizole and asked the parents the survey questions. After the survey, parents were instructed to ask the parents the survey questions while obtaining the patient’s history. Questions were asked in the patient’s preferred language, and trained medical interpreters were available for physicians who were unable to speak Spanish. The children of surveyed parents ranged in age from 3 days to 14 years. All parents approached answered all of the survey questions. After the survey, parents were educated regarding the dangers of metamizole and given recommendations for safer alternatives.

There were 186 patient visits during the study period with 152 (82%) representing Spanish- or Portuguese-speaking families. A total of 113 parents were surveyed, representing 75% of the eligible patient visits during the 2-week period. Parents were from Mexico (88%) and 9 other countries: Argentina, Brazil, Chile, Ecuador, El Salvador, Honduras, Guatemala, Peru, and the United States. Forty parents (35%) had used metamizole; 35% of those had also given it to their children. Among metamizole users, 20% had the medication in their home and 25% had purchased metamizole in the United States. Parents from Mexico reported metamizole use more frequently than parents from other countries (39% vs 21%; \( P = .09 \)). One child was taking metamizole at the time of the clinic visit but had no neutropenia.

### DISCUSSION

As the population of the United States becomes more diverse, physicians must become increasingly aware of potentially harmful folk or home remedies used by different cultural groups. The medical literature has several examples of serious illness and even death caused by home remedies.3-5 The patients in this report had neutropenia or leukopenia and serious infection associated with metamizole use. Neutropenia can be the result of serious infection but would be expected to be short-lived, especially after the initiation of antibiotic therapy.6-7 The patients in this report both had abnormalities of neutrophils for weeks even on appropriate antibiotic therapy and the pediatric patient required G-CSF therapy, consistent with other reports of neutropenia associated with metamizole use.8 Because metamizole has been banned in the United States for more than 2 decades, most practicing physicians may be unfamiliar with the medication and its side effects.

Agranulocytosis and aplastic anemia are the leading causes of drug-induced death.9 An international study performed in the 1980s associated metamizole with agranulocytosis, although risk varied by country.10 A population-based study in the Netherlands described a 23-fold increased relative risk of agranulocytosis associated with metamizole use.11 Estimates regarding the frequency of agranulocytosis have varied from 1.1 in 1 million doses to 1 in 3000 doses.10,12 Worldwide, metamizole is associated with an estimated 7000 cases/y of agranulocytosis.13 Metamizole metabolites bind to neutrophil membranes, creating a novel antigen that induces antibody formation.14 The resultant immune response causes both peripheral and bone marrow cell lysis. Treatment is supportive and includes discontinuing the drug. G-CSF has been used with varying success.15,16 The mortality rate associated with metamizole-induced agranulocytosis ranges from 24% to 32%.17 Recovery may require up to 1 month.8 A genetic predisposition to metamizole-induced agranulocytosis has been described.18 Metamizole has been linked with other serious side effects, including anaphylaxis.1,19 When used during pregnancy, it has been associated with increased risk of Wilms’ tumor20 and infant leukemia.21 In the English-language literature, there are

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TABLE 1. Common Preparations That Contain Metamizole Manufactured in Mexico1,25

<table>
<thead>
<tr>
<th>Generic Description</th>
<th>Brand Name (Mexican Manufacturer)</th>
<th>Marketed Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metamizole or dipyrrone as a single agent</td>
<td>Commel (Sanofi Winthrop)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td>Metamizole or dipyrrone plus pargeverine hydrochloride</td>
<td>Bipasmin Compuesto (Promeco)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td>Metamizole or dipyrrone plus hyoscyamine butylbromide</td>
<td>Buscapina Compositum (Boehringer Ingelheim Sons)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td>Metamizole or dipyrrone plus vitamin B</td>
<td>Dolofort (Farcoral)</td>
<td>Pain and neuritis</td>
</tr>
</tbody>
</table>

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few recent reports on the risks of metamizolone and none describing pediatric patients.16,22-24 Metamizolone has been banned in the United States, Canada, Japan, and many European countries but continues to be sold in Latin America, Africa, and Asia.1 The Micromedex Drugdex lists more than 240 metamizolone preparations manufactured in 18 countries.1 Patients may refer to the medication as aspirin or “Mexican aspirin.”16,25

Our survey results were similar to recent results obtained in San Diego26 and indicate that at least 35% of Latino patients had used metamizolone and 20% of these had the medication in their home. A limitation of this survey is that parents were queried about metamizolone using only 4 of the hundreds of brand names. The survey may actually underestimate the frequency of metamizolone use in immigrant Latinos.

Patients who live in US-Mexican border communities may cross to Mexico to purchase medication.27-29 Salt Lake City, however, is more than 700 miles from the Mexican border, and 25% of metamizolone users indicated that they had purchased the drug in the United States. Markets that provide medication from other countries are common in immigrant communities.30 Recent immigrants may turn to these establishments for medical care.31 It is also possible that US-born Latinos and other groups may have access to metamizolone in these markets, but the survey did not address this issue.

In other communities, markets have been closed for illegally selling medications from Mexico.32,33 We have initiated a campaign in cooperation with the Mexican Consulate in Salt Lake City and the state health department to inform Latino families in Utah about metamizolone risks and to control its sale. Public service announcements in Spanish have been created for local radio and television. Our clinic staff has been educated about metamizolone, and present in all examination rooms are bilingual posters discouraging the use of Neo-melubrina and asking patients to talk to their doctor about the risks of metamizolone and safer ways to manage fever.

Metamizolone is widely available in other countries and is likely available in many areas of the United States. Health care providers must be aware of the dangers of metamizolone and inquire about its use in immigrant patients. Public health entities must be vigilant regarding the sale of illegal medications in their communities.

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