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).

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 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.

One month postdischarge, his WBC was 5500/μL with an ANC of 1500 to 2000 and an absolute lymphocyte count of 3410. 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 myeloblast. The WBC was 5500/μL with an ANC of 3410.

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Metamizole, or dipyrrone, is a pyrazolone nonsteroidal antiinflammatory agent. It has been associated with fatal agranulocytosis and was withdrawn from the US market by the US Food and Drug Administration in 1979. 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, many US physicians remain unaware of these potentially harmful medications.

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

Approval was obtained from the University of Utah Institutional Review Board. During the first 2 weeks of October 2001, all Spanish- or Portuguese-speaking parents of children who were evaluated in the clinic were asked 5 questions regarding metamizole by the child’s pediatrician, either a resident or a faculty physician. Questions included whether the adult had ever used Neo-melubrina, metamizole, dipyrone, or dipirona; whether the adult had ever given this medication to a child; whether the family had the medication in their home; whether they had purchased the medication in the United States; and their country of origin. A standard form was attached to their charts, and the clinic physicians 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% purchased metamizole in the United States. Parents from Mexico reported metamizole use more frequently than parents from other countries (99% 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’ tumor\(^20\) and infant leukemia.\(^21\) In the English-language literature, there are

### TABLE 1. Common Preparations That Contain Metamizole Manufactured in Mexico\(^1\),\(^25\)

<table>
<thead>
<tr>
<th>Generic Description</th>
<th>Brand Name (Mexican Manufacturer)</th>
<th>Marketed Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metamizole or dipyrone as a single agent</td>
<td>Conmel (Sanofi Winthrop)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Dalmasin (Columbia)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Fardolipin (Farcoral)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Magnol (Atlantis)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Neo-melubrina (Hoechst Marion Roussel)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Prodolina (Promeco)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td></td>
<td>Utudol (Dbas)</td>
<td>Pain or fever</td>
</tr>
<tr>
<td>Metamizole or dipyrone plus pargerverine hydrochloride</td>
<td>Bipasmin Compuesto (Promeco)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td>Metamizole or dipyrone plus hyoscine butylbromide</td>
<td>Buscapina Compositum (Boehringer Ingelheim Sons)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td></td>
<td>Busconet (Sons)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td></td>
<td>Busprina (Farcoral)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td></td>
<td>Colepren (Randall)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td></td>
<td>Retodol Compositum (Rimsa)</td>
<td>Relief of smooth muscle pain and spasm</td>
</tr>
<tr>
<td>Metamizole or dipyrone plus vitamin B</td>
<td>Dolonfort (Farcoral)</td>
<td>Pain and neuritis</td>
</tr>
<tr>
<td></td>
<td>Dolo-Tiaminol (Silanes)</td>
<td>Pain and neuritis</td>
</tr>
</tbody>
</table>
few recent reports on the risks of metamizole and none describing pediatric patients.\textsuperscript{16,22–24}

Metamizole has been banned in the United States, Canada, Japan, and many European countries but continues to be sold in Latin America, Africa, and Asia.\textsuperscript{1} The Micromedex Drugdex lists more than 240 metamizole preparations manufactured in 18 countries.\textsuperscript{1} Patients may refer to the medication as aspirin or “Mexican aspirin.”\textsuperscript{16,25}

Our survey results were similar to recent results obtained in San Diego\textsuperscript{26} and indicate that at least 35% of Latino patients had used metamizole and 20% of these had the medication in their home. A limitation of this survey is that parents were queried about metamizole using only 4 of the hundreds of brand names. The survey may actually underestimate the frequency of metamizole use in immigrant Latinos.

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

In other communities, markets have been closed for illegally selling medications from Mexico.\textsuperscript{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 metamizole 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 metamizole, and present in all service announcements in Spanish have been created warning: dipyrone in over-the-counter drugs.

REFERENCE

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