

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

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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 dipyrone, is a pyrazolone nonsteroidal antiinflammatory agent.¹ It has been associated with fatal agranulocytosis and was withdrawn from the US market by the US Food and Drug Administration in 1979.¹ Metamizole is available without a prescription in Mexico and other countries and is used to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/ μ L (19% band forms, 26% segmented neutrophils, 48% lymphocytes, 7% monocytes), absolute neutrophil count (ANC) of 1710, hemoglobin 12.3 g/dL, platelets 285 000/ μ L, 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/ μ L 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 arthrotomy 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/ μ L 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/ μ L 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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TABLE 1. Common Preparations That Contain Metamizole Manufactured in Mexico^{1,25}

Generic Description	Brand Name (Mexican Manufacturer)	Marketed Indication
Metamizole or dipyrone as a single agent	Conmel (Sanofi Winthrop) Dalmasin (Columbia) Fardolipin (Farcoral) Magnol (Atlantis) Neo-melubrina (Hoechst Marion Roussel) Prodolina (Promeco) Utidos (Diba)	Pain or fever
Metamizole or dipyrone plus pargeverine hydrochloride	Bipasmin Compuesto (Promeco)	Relief of smooth muscle pain and spasm
Metamizole or dipyrone plus hyoscine butylbromide	Buscapina Compositum (Boehringer Ingelheim Sons) Busconet (Sons) Busprina (Farcoral) Colepren (Randall) Retodol Compositum (Rimsa)	Relief of smooth muscle pain and spasm
Metamizole or dipyrone plus vitamin B	Dolnefort (Farcoral) Dolo-Tiaminol (Silanes)	Pain and neuritis

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% 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

few recent reports on the risks of metamizole and none describing pediatric patients.^{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.¹ The Micromedex Drugdex lists more than 240 metamizole 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 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-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 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.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 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.^{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 examination rooms are bilingual posters discouraging the use of Neo-melubrina and asking patients to talk to their doctor about the risks of metamizole and safer ways to manage fever.

Metamizole 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 metamizole and inquire about its use in immigrant patients. Public health entities must be vigilant regarding the sale of illegal medications in their communities.

REFERENCES

1. Bozzini L, Bunch C. *Dipyrone. Micromedex (R) Health Care Series*. Greenwood Village, CO: Micromedex, Inc; 2000
2. Travelers' warning: dipyrone in over-the-counter drugs. *Med Lett Drugs Ther*. 1974;16:64
3. Bakerink JA, Gospe SM Jr, Dimand RJ, Eldridge MW. Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. *Pediatrics*. 1996;98:944–947
4. Bose A, Vashistha K, O'Loughlin BJ. Azarcon por empacho—another cause of lead toxicity. *Pediatrics*. 1983;72:106–108
5. Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc*. 2002;77:12–16
6. Long S. Laboratory manifestations of infectious diseases. In: Long S, Pickering L, Prober C, eds. *Principles and Practice of Pediatric Infectious Diseases*. New York, NY: Churchill Livingstone; 1997:1559
7. Watts R. Neutropenia. In: Lee G, Foerster J, Lukens J, Paraskevas F, Greer J, Rodgers G, eds. *Winthrope Clinical Hematology*. 10th ed. Salt Lake City, UT: University of Utah; 1999:1864–1865
8. Heit W. Pyrazolone drugs and agranulocytosis. *Agents Actions Suppl*. 1986;19:283–289
9. Laporte JR, Carne X. Blood dyscrasias and the relative safety of non-narcotic analgesics. *Lancet*. 1987;1:809
10. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. *JAMA*. 1986;256:1749–1757
11. van der Klauw MM, Goudsmit R, Halie MR, et al. A population-based case-cohort study of drug-associated agranulocytosis. *Arch Intern Med*. 1999;159:369–374
12. Bottiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *Br Med J*. 1973;3:339–343
13. Kiatboonsri P, Richter J. Dipyrone trials in Thailand. *Lancet*. 1989;2:107
14. Hargis JB, La Russa VF, Redmond J, Kessler SW, Wright DG. Agranulocytosis associated with “Mexican aspirin” (dipyrone): evidence for an autoimmune mechanism affecting multipotential hematopoietic progenitors. *Am J Hematol*. 1989;31:213–215
15. Delannoy A, Geheon M. Colony-stimulating factor and drug-induced agranulocytosis. *Ann Intern Med*. 1989;110:942–943
16. Dorr VJ, Cook J. Agranulocytosis and near fatal sepsis due to “Mexican aspirin” (dipyrone). *South Med J*. 1996;89:612–614
17. Heit WF. Hematologic effects of antipyretic analgesics. Drug-induced agranulocytosis. *Am J Med*. 1983;75:65–69
18. Vlahov V, Bacracheva N, Tontcheva D, et al. Genetic factors and risk of agranulocytosis from metamizol. *Pharmacogenetics*. 1996;6:67–72
19. Kiatboonsri P, Richter J. Unethical trials of dipyrone in Thailand. *Lancet*. 1988;2:1491
20. Sharpe CR, Franco EL. Use of dipyrone during pregnancy and risk of Wilms' tumor. Brazilian Wilms' Tumor Study Group. *Epidemiology*. 1996;7:533–535
21. Alexander FE, Patheal SL, Biondi A, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res*. 2001;61:2542–2546
22. Cihan A, Menten BB, Sucak G, Karamercan A, Naznedar R, Ferahkose Z. Fournier's gangrene after hemorrhoidectomy: association with drug-induced agranulocytosis. Report of a case. *Dis Colon Rectum*. 1999;42:1644–1648
23. Daphan CE, Abbasoglu O, Agalar F, Yagmurduur MC. Neutropenic enterocolitis due to dipyrone use. *Aust N Z J Surg*. 1999;69:680–681
24. Ohishi M, Oobu K, Miyanosita Y, Yamaguchi K. Acute gingival necrosis caused by drug-induced agranulocytosis. *Oral Surg Oral Med Oral Pathol*. 1988;66:194–196
25. Lomeli A. Metamizol o dipirona, un analgesico de altisimo riesgo que deberia ser retirado del mercado. *Farmacos*; 1999. Available at: lanic.utexas.edu/project/farmacos/999com04.htm
26. Taylor L, Abarca S, Henry B, Friedman L. Use of Neo-melubrina, a banned antipyretic drug, in San Diego, California: a survey of patients and providers. *West J Med*. 2001;175:159–163
27. Macias EP, Morales LS. Crossing the border for health care. *J Health Care Poor Underserved*. 2001;12:77–87
28. Stoneham L. The southern exodus. Is seeking health care south of the border a healthy practice? *Tex Med*. 2000;96:48–52
29. Tabet SR, Wiese WH. Medications obtained in Mexico by patients in southern New Mexico. *South Med J*. 1990;83:271–273
30. Webb C. Immigrants flocking to “underground” health providers. *Salt Lake Tribune*. 1999;August 15:A22
31. Ruiz-Beltran M, Kamau JK. The socio-economic and cultural impediments to well-being along the US-Mexico border. *J Community Health*. 2001;26:123–132
32. Moreland J. Escondido doctor pleads guilty to federal smuggling charges. *North County Times* (San Diego). August 17, 2000. Available at: www.nctimes.com/news/081700/fff.html
33. Mrozek T. Crackdown on illegal pharmacies used by immigrants results in charges against 17 who dispensed medicine: authorities seize over \$8 million worth of drugs. United States Attorney Central District of California; 2000. Available at: www.usdoj.gov/usao/cac/pr/pr2000/217.htm