May 2021

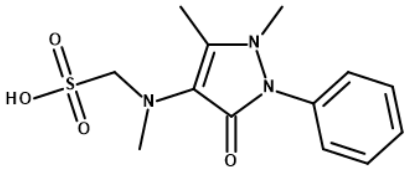
Dipyrone (Metamizole): A Toxic Adulterant Found in Illicit Street Drugs.

PUBLIC HEALTH ALERT

Substance abuse treatment providers, clinicians, outreach workers, and public health clinics should be aware of the following information. Dipyrone is an adulterant that has been identified in seized drug material also containing cocaine, fentanyl and/or heroin. Dipyrone is considered to be a relatively safe drug when used under medical supervision, however, chronic unsupervised use may lead to development of agranulocytosis and other hematologic disorders. Studies have shown that with repeated administration tolerance to the antinociceptive effects of dipyrone develops. In a study at Fredric Rieders Family Foundation (FRFF) supported by the Colombo Plan and JMJ Technologies on the presence of toxic adulterants in seized drugs (n=2,000), dipyrone was found in 5.3% percent of the exhibits. Colombo Plan and Argentine Provincial Police drug testing detected dipyrone in seized cocaine samples in Argentina.

Background: Dipyrone is a non-opioid analgesic with antipyretic activity, which was developed by the German company Hoechst AG in 1920 with mass production starting in 1922. It is a pro-drug, which is rapidly metabolized after oral administration to active pyrazolone compounds. Dipyrone is also know under different generic names such as metamizole, noramidopyrine, and others. Dipyrone was sold as an over-the-counter (OTC) analgesic until the 1970s, at which time it was banned in several countries, including the United States, several European nations, Japan, and Australia following reports of users developing agranulocytosis, occasionally resulting in death. The safety of the drug is still controversial, resulting in varying levels of restriction and regulation worldwide. Dipyrone is still available, however, by prescription and OTC in many countries in Europe, South America, and Asia.

Dipyrone



Recommendations for Clinicians

- Be aware that illicit drugs may contain toxic adulterants that can complicate the clinical presentation.
- Be aware that routine hospital drug tests will not disclose the presence of dipyrone, which requires a special test.

Adverse Effects of Dipyrone

- Most common are gastrointestinal effects:
  - Nausea
  - Vomiting
  - Abdominal pain
  - Diarrhea
- Headaches
- Dizziness
- Renal dysfunctions
- Hypersensitivity skin reactions (rash, urticaria or erythema)
- Less commonly agranulocytosis, aplastic anemia, and anaphylaxis

Recommendations for MEs & Coroners

- Conduct testing for dipyrone in suspected stimulant or opioid-related fatalities where agranulocytosis is noted.

Recommendations for Forensic and Clinical Laboratories

- Include dipyrone in the scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including dipyrone.
- Be aware of analytical challenges associated with the confirmation of dipyrone by traditional mass spectrometry techniques.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners and coroners.

Health Impacts: Coadministration of dipyrone and morphine has been found to potentiate antinociceptive effects. Concomitant use of dipyrone and illicit drugs can enhance the toxicity of the illicit drug. In a study using rats, coadministration of dipyrone and morphine in acute treatment resulted in almost tripling the C_{max} of morphine. Additionally, multiple doses of coadministration produced accumulation of morphine in the plasma, which may be explained by inhibition of enzymatic morphine metabolism. Tolerance to antinociceptive effects was also found to be attenuated with the coadministration of dipyrone and morphine. One study found that naloxone was unable to reverse the effect of dipyrone alone or in combination with morphine. Another study found that a dose of naloxone that is effective to block morphine is only partially effective in blocking the supra-additive effects of morphine plus metamizole. To almost abolish the potentiated effect produced by this combination, it is necessary to administer higher naloxone dose. Dipyrone has shown some hepatoxic potential, however, the risk of development of hepatic disorders is low. Deterioration of renal function is a side effect and cases of renal failure have been reported. Agranulocytosis is the most concerning effect.

People with substance abuse disorder may be more vulnerable to COVID-19 due to the drug's effects on the immune system. The problem is further exacerbated by the addition of adulterants like dipyrone that results in a decrease of white blood cells that lower immunity and increase susceptibility to such infections.

Analytical challenges in the confirmation of dipyrone as an adulterant in illicit samples have been noted. Dipyrone is susceptible to thermal degradation and/hydrolytic decomposition, forming decomposition products, 4-methyl aminoantipyrine and aminopyrine, also known drugs, complicating interpretation. Electrospray ionization mass spectrometry in positive mode or NMR are recommended techniques for the confirmation of intact dipyrone.

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Dipyrone (Metamizole) – Diagnosis and Treatment

Adverse Effects

Physical

Nausea	Rash/urticaria
Vomiting	Diaphoresis
Diarrhea	Toxic epidermal necrolysis (TEN)
Abdominal pain	Bronchospasm
Dry Mouth	Deterioration of renal function
Headache	Agranulocytosis/neutropenia
Dizziness	
Drowsiness	

Provider Response to Adverse Effects

Physical

IV fluids and electrolyte replacement
Treat bronchospasm with inhaled beta agonists
Treat rash/urticarial with oral antihistamines, if severe
Monitor CBC/differential daily
Monitor serum creatinine/BUN daily
Consider broad spectrum antibiotic therapy in patients with fever and agranulocytosis

Further Treatment Needed?

In most cases, further treatment is not required. Conditions such as TEN or agranulocytosis are potentially deadly and require highly specialized care in a hospital setting.

References and Related Articles:

Andrade S, Bartels DB, Lange R, Sandford BS, Gurwitz J (2016) "Safety of metamizole: A systematic review of the literature." Journal of Clinical Pharmacy and Therapeutics. 41(5): 459-477. doi: 10.1111/jcpt.12422.

Domínguez-Ramírez AM, Cortés-Arroyo AR, Hurtado y de le Peña M, Medina López JR, López-Muñzo FJ. (October 2010) "Effect of metamizole on morphine pharmacokinetics and pharmacodynamics after acute and subchronic administration in arthritic rats." European Journal of Pharmacology. 645 (1-3): 94-101. doi: 10.1016/j.ejphar.2010.07.019.

Hernández-Delgadillo GP, Cruz SL (September 2006) "Endogenous opioids are involved in morphine and dipyrone analgesic potentiation in the tail flick test in rats." European Journal of Pharmacology. 28;546(1-3) 54-59. doi: 10.1016/j.ejphar.2006.07.027.

Isaacs RCA, Harper, MM, Miller EC (August 2016) "Analytical challenges in the confirmative identification of dipyrone as an adulterant in illicit drug samples." Forensic Science International. 270: 185-192. doi: 10.1016/j.forsciint.2016.08.023.

Jaseicka A, Maślanka T, Jaroszewski JJ (2014). "Pharmacological characteristics of metamizole." Polish Journal of Veterinary Sciences. 17 (1): 207-214. doi: 10.2478/pjvs-2014-0030.

Kötter T, da Costa BR, Fässler M, Blozik E, Linde K, Jüni P, et. al. (2015) "Metamizole-Associated Adverse Events: A Systematic Review and Meta-Analysis." PLoS ONE. 10(4): e0122918. doi:10.1371/journal.pone.0122918.

Nikolova I, Tencheva J, Voinikov J, Petkova V, Benbasat N, Danchev, N et. al. (2012) "Metamizole: A Review Profile of a well-known 'forgotten' drug. Part I: Pharmaceutical and Nonclinical Profile." Biotechnology and Equipment. 26(6): 3329-3337. doi: 10.5504/BBEQ.2012.0089.

Nikolova I, Petkova V, Tencheva J, Benbasat N, Voinikov, Danchev N (2013) "Metamizole: A Review Profile of a well-known 'forgotten' drug. Part II: Clinical Profile." Biotechnology and Equipment. 27(2): 3605-3619. doi: 10.5504/BBEQ.2012.0135.

Taylor J, Mellström B, Fernaud I, Naranjo IF (June 1998) "Metamizol potentiates morphine effects on visceral pain and evoked c-Fos immunoreactivity in spinal cord." European Journal of Pharmacology. 12;351(1) 39-47. doi: 10.1016/s0014-2999(98)00298-2.

Acknowledgements: This report was prepared by Amanda L.A. Mohr, MS; Thom Browne, MA; Lewis Nelson MD, and Barry K. Logan, PhD. Funding for this document was received by the Fredric Rieders Family Foundation from the Colombo Plan via U.S. Department of State/INL under 2019-RG-061 and 2017-RG-61, and other Colombo Plan funding sources.

The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on dipyrone is available by contacting mandi.mohr@frfroundation.org.