March 2023

Phenylbutazone: A Toxic Adulterant Found in Illicit Street Drugs

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The Center for Forensic Science Research & Education

Toxic Adulterant Alert

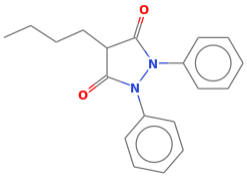
Substance abuse treatment providers, clinicians, outreach workers, public safety and public health agencies should be aware of the following information. Phenylbutazone ("Bute", Phenylcare®) has been identified as an adulterant in illicit drug material. In a review of case data from NMS Labs from 2016-2021, 116 seized drug samples from Pennsylvania were identified as containing phenylbutazone. This represents a small percentage of total samples analyzed during the time frame. Xylazine, which is now a national concern, first emerged in the northeast (principally Pennsylvania) before spreading across the United States. As phenylbutazone has been gaining prominence in Pennsylvania over a five-year period, the possibility exists that it too can spread nationwide. This adulterant was most frequently observed in samples containing heroin, fentanyl and/or fentanyl derivatives. In addition to illicit drug samples, there have been reports in the literature of adulteration of herbal medicines and supplements with phenylbutazone and self-medication with phenylbutazone prescribed by veterinarians. The serious adverse effects of phenylbutazone can include gastrointestinal bleeding, liver and kidney damage, and blood disorders.

Table 1. Phenylbutazone Positivity in Seized Drug Cases in PA 2016-2021

Year	No. of Positive Phenylbutazone Samples	Most Common Additional Findings
2016	15	Heroin, Fentanyl, Caffeine
2017	23	Heroin, Fentanyl, Xylazine, Additional Adulterants
2018	4	Heroin, Fentanyl, Xylazine, Additional Adulterants
2019	18	Heroin, Fentanyl, Xylazine, Additional Adulterants
2020	37	Heroin, Fentanyl, Acetylfentanyl, Xylazine, Additional Adulterants
2021	19	Heroin, Fentanyl, para-Fluorofentanyl, Valeryl Fentanyl, Cocaine, Tramadol, Xylazine, Additional Adulterants

Background: Phenylbutazone is a nonsteroidal anti-inflammatory drug (NSAID) introduced in the 1950s that has analgesic and anti-inflammatory properties. It inhibits the enzyme cyclooxygenase (COX), preventing prostaglandin creation. Phenylbutazone is highly absorbed when taken orally. It is highly bound to protein in plasma and has a low volume of distribution. Its half-life is widely variable but averages 70 hours. It is metabolized to oxyphenbutazone, 3'-hydroxyphenylbutazone, dihydroxyphenylbutazone, and glucuronides. Oxyphenbutazone is an active metabolite. Phenylbutazone was prescribed to treat arthritis, gout, and ankylosing spondylitis. Quickly after its introduction, side-effects were noted in patients using phenylbutazone both short and long term. **Phenylbutazone was largely discontinued from human use after reports of deaths caused by the medication.** It continues to be used in veterinary medicine, specifically for treating lameness, pain, and inflammation in horses.

Phenylbutazone



Recommendations for Clinicians

- Be aware that illicit drugs (mostly heroin or fentanyl) may contain **phenylbutazone** which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with **phenylbutazone** toxicity.
- Be aware that most hospital-based clinical laboratories do not offer **phenylbutazone** toxicology testing.

Frequent Indicators of Toxicity

- Rash
- Blurred Vision
- Nausea/Vomiting/ Diarrhea
- Edema
- Stomach pain
- GI bleeding
- Aplastic anemia
- Agranulocytosis
- Low blood pressure
- Confusion
- Incoordination
- Coma
- Convulsions
- Kidney failure
- Liver failure

Recommendations for MEs & Coroners

- If NSAID poisoning is suspected, conduct toxicology testing for **phenylbutazone** in opioid-related fatalities.

Recommendations for Forensic and Clinical Laboratories

- Consider including **phenylbutazone** in the routine scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **phenylbutazone**
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners and coroners.

Health Impacts:

Phenylbutazone has been identified in illicit opioid drug samples. Adverse effects of phenylbutazone included rash, blurred vision, tinnitus, dizziness, headache, and edema. Gastrointestinal symptoms can include nausea, vomiting and diarrhea, stomach/abdominal pain, ulcers, and bleeding. Phenylbutazone overdose can also cause hepatitis, kidney failure, and congestive heart failure. Serious blood disorders like agranulocytosis, leukopenia, thrombocytopenia, and aplastic anemia have also occurred and, in some cases, led to death at therapeutic doses. Toxic effects are more frequently seen when daily doses are greater than 600 mg or serum concentrations are greater than 100 mg/L, but have been noted at lower levels.

Treatment of phenylbutazone toxicity is generally supportive care, similar to poisonings involving other NSAIDs. Supportive care can include maintaining an airway, correcting metabolic imbalances, and fluid resuscitation. There are mixed reports on the use of dialysis and hemoperfusion to treat phenylbutazone toxicity, as it is highly protein bound and elimination will be minimal. If phenylbutazone exposure occurs through a mechanism other than intravenous opioid use, such as ingestion of adulterated herbal supplements or diversion of veterinary medicine, gastric lavage and activated charcoal may be useful.

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Acknowledgements: This report was prepared by Sarah A. Shuda, M.S., Amanda L.A. Mohr, M.S., Thom Browne, and Barry K. Logan, Ph.D. 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 phenylbutazone is available by contacting mandi.mohr@cfsre.org.