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1. Radecki RP, Spiegel RJ. Adventures with andexanet alfa in efficacy, effectiveness, and one-armed studies: May 2019 *Annals of Emergency Medicine Journal Club*. *Ann Emerg Med*. 2019;73:545-547.
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In reply:



We appreciate the responses to our Journal Club¹ article by Drs. Milling and Connolly, and by Dr. Pallin. Publications in this section of *Annals* are intended to be succinct and broadly educational; it is not always possible to delve into the nuances and details of a topic. In response to Drs. Milling and Connolly's concerns, we regret any personal offense members of the study team may have felt by our mention of the ethical considerations of single-arm studies. Our point was that in this rapidly shifting field, equipoise should be assessed not only at trial inception but also continuously as new and alternative treatments emerge.²

Dr. Pallin's thoughtful comments highlight the challenges of drug development, Food and Drug Administration oversight, and the implications for the comparative clinical trial design. We, too, agree that postpublication peer review is necessary to help protect patients.

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1. Radecki RP, Spiegel RJ. Adventures with andexanet alfa in efficacy, effectiveness, and one-armed studies: May 2019 *Annals of Emergency Medicine Journal Club*. *Ann Emerg Med*. 2019;73:545-547.
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Inhalational Methanol Intoxication: Emerging Issues in the Netherlands Resulting From Illegal Drug Production



To the Editor:

Inhalational methanol intoxications are rare. However, since 2018, the Dutch Poisons Information Center has been increasingly contacted for information requests and treatment advice concerning patients who developed severe symptoms caused by methanol inhalation while working in an illegal drug-manufacturing laboratory. In this communication, we report 3 cases.

A 28-year-old man arrived home with general complaints after "a night out." The next morning, he was found unresponsive and transported to a hospital. On arrival, he presented with coma (Glasgow Coma Scale [GCS] score 3), apnea, hypertension (blood pressure 166/78 mm Hg), tachycardia (pulse rate 129 beats/min), and fixed dilated pupils. Laboratory examination showed metabolic acidosis (pH 6.31; lactate level 21.7 mmol/L) with high anion gap (46.9 mmol/L) and osmolal gap (108 mmol/L). Approximately 8 hours later, 2 relatives (men aged 26 and 20 years) arrived at the hospital. They both felt ill, but were fully conscious (GCS scores 14 and 15). Laboratory results showed metabolic acidosis (pH 7.1 and 7.2) with an increased anion gap (39.6 and 22 mmol/L) and osmolal gap (54 and 41 mmol/L). One of the patients admitted working in an ecstasy (methylecstasy) laboratory for greater than 40 consecutive hours more than 24 hours before admission. Considering the differential diagnosis of a metabolic acidosis with high anion and osmolal gap,

accompanied by the history of working in a drug laboratory, a toxic methanol exposure was suspected.

Treatment of all patients was extensive and consisted of hemodialysis, continuous venovenous hemofiltration, or both, combined with administration of sodium bicarbonate, ethanol, fomepizole, and folinic acid. The first patient never regained consciousness and progressive multiorgan failure developed. Computed tomographic scans showed massive cerebral edema, and given the extremely poor prognosis, supportive care was terminated after 4 days. The other 2 patients fully recovered within 4 days.

Methanol is used as a solvent in producing synthetic drugs such as methyleendioxyamfetamine. The production process involves mixing, heating, and extracting the desired compound with a solvent. A change in production facilities might have caused these intoxications. In the past, clandestine laboratories were predominantly found in abandoned places. Nowadays, drug-producing facilities have been positioned within residential areas.^{1,2} Doors and windows are often taped shut or otherwise sealed to prevent fumes from alerting neighbors or passersby from noticing operations of the clandestine laboratory. This prevents effective ventilation and exposes workers to chemical fumes, including methanol. The latent period between exposure and first symptoms may add to prolonged exposure and severity of subsequent intoxication.

Methanol exposure should be considered when patients appear with severe metabolic acidosis with high anion and osmolal gap. Considering the illegality of the drug laboratory, patients tend to hold back information about the nature of their symptoms, causing delay in lifesaving treatment. Swift antidotal treatment (fomepizole or ethanol), concomitant hemodialysis, and folinic acid are necessary.³⁻⁵

Toxicologists should be aware of this infrequent but potentially increasing route of exposure to methanol in order to reach a swift diagnosis and provide proper treatment. Delay of adequate treatment might result in severe morbidity or even death. Severe inhalational methanol exposure was uncommon in the Netherlands, but has been increasingly noticed.

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