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Case Report

Excipient lung disease in a patient taking the benzodiazepine derivative etizolam: A case report ^{☆,☆☆}

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ARTICLE INFO

Article history:

Received 4 January 2022

Accepted 15 January 2022

ABSTRACT

Excipient Lung Disease is an inflammatory response to the intravenous administration of oral formulations of drugs and their excipients (additives). Previously described offenders include opioids and Ritalin, whose excipients, when crushed and administered intravenously, lead to inflammation and are demonstrated by centrilobular nodules and ground-glass formations on Chest Computed Tomography. In this case report, we demonstrate Chest CT findings of excipient lung disease in a patient using etizolam, a benzodiazepine derivative commonly used as an anxiolytic in Japan. Of note, the patient acquired etizolam for purchase through online retailers without prescription, which is becoming more common occurrence and offers the additional risk of unknown formulations.

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Introduction

An estimated 7.5 million people aged 12 or older are affected by substance use disorder (SUD) related to illicit drugs [1]. Of the 7.5 million, benzodiazepines and related tranquilizer misuse is seen in an estimated 1.7 million, with current population prevalence of benzodiazepine use disorder cited at up to 2.2% [2]. Etizolam, an analog of benzodiazepines within the

thienodiazepine class, differs slightly in chemical structure to its benzodiazepine counterparts but remains an agonist to the GABA receptor with overlapping anxiolytic and central nervous system depression properties [3–5]. Etizolam is commonly prescribed as an anxiolytic in Japan and was thought to be of low abuse potential, but more recently has demonstrated misuse due to its sedative and skeletal muscle relaxant properties [4, 6]. Because of this, etizolam remains an illegal substance without FDA approval in the United States(US);

[☆] Key Points: 1. Excipient Lung Disease is a sequelae of drug misuse and has specific findings of gravity dependent ground glass opacities in a primarily centrilobular distribution on Chest CT. 2. Opioids and Ritalin are most commonly implicated in ELD, but any oral formulation with causative excipients could lead to this inflammatory response when ingested intravenously. 3. The ability of patients to acquire drugs of misuse and abuse with unknown excipient formulations could lead to increased incidence or novel presentations of ELD.

^{☆☆} Competing Interests: The authors deny any personal, monetary, professional or other influences that would interfere with the objectivity of this submission.

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<https://doi.org/10.1016/j.radcr.2022.01.035>

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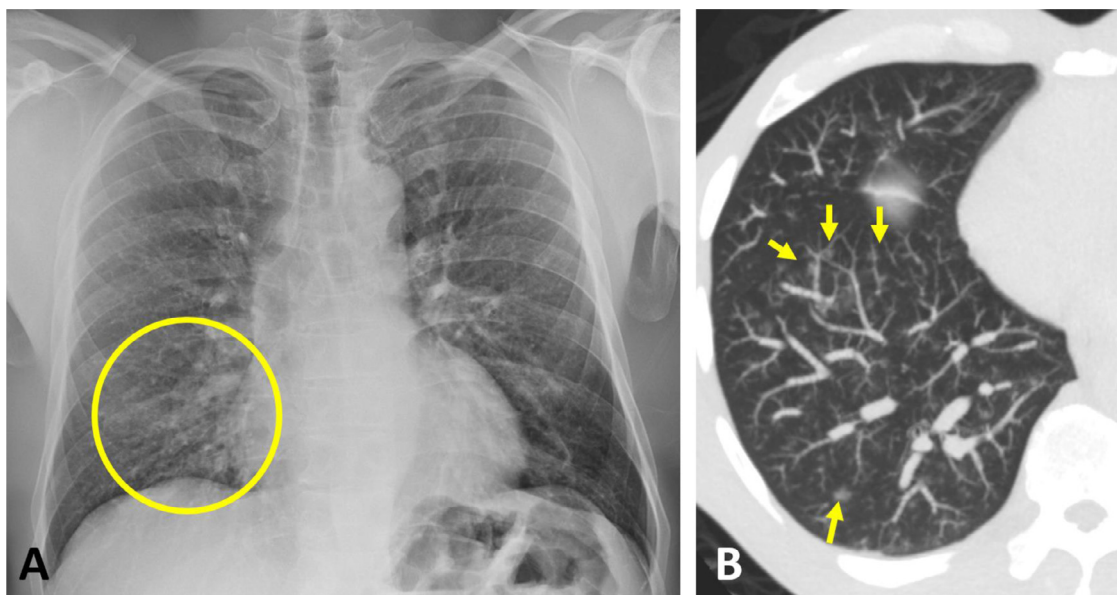


Fig. 1 – Chest x-ray (A) and lung bases on CT Abdomen and/or Pelvis (B) during emergency department evaluation for trauma and suspected drug use. The chest x-ray reveals patchy and nodular opacities at the right lung base. CT demonstrates scattered centrilobular and tree-in-bud ground glass nodules most pronounced in the right lung base. These findings were considered to be related to aspiration in the setting of trauma or pneumonia. A 3 month follow-up CT was recommended.

however, within the US, etizolam is commonly implicated as a drug available for online purchase labeled as a “research chemical,” leading to misuse [7, 8]. Like benzodiazepines users, etizolam users are susceptible to altered mental status, withdrawal seizures, and respiratory depression if taken in excess [9].

While not included in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for misuse, intravenous (IV) injection of crushed oral formulations of pharmaceuticals is a dangerous form of drug use with clinical significance. Clinicians often consider risks including skin and soft tissue infection, bacteremia, and endocarditis in these patients; however, an additional concern occurs when oral formulations of the drugs, and more specifically, their additive fillers (excipients), are self-administered intravenously, resulting in excipient lung disease (ELD). ELD is caused by excipient particles lodging within the pulmonary vasculature, which results in a granulomatous reaction and subsequent lung nodule formation [10, 11]. This reaction has common findings on CT, often demonstrated by centrilobular nodules and ground-glass formations [11–14]. Common ELD offenders include opioids and Ritalin (colloquially known as “Ritalin Lung”), [15] with excipients including talc (hydrated magnesium silicate), microcrystalline cellulose, and starch within their oral formulations [10, 16, 17]. Etizolam is often shipped to the purchaser in powdered or oral formulations, both of which can be implicated in IV drug use when crushed and placed into a solution and therefore not immune to ELD [7]. In this case report, we demonstrate the radiographic findings of excipient lung disease in a chest CT for a patient with benzodiazepine dependence who obtains the benzodiazepine analog etizolam through an online retailer.

Case Report

This patient is a 42-year-old male with a past medical history notable for distant polysubstance use including crack-cocaine, opioids, and IV heroin use. He is noted to have ongoing benzodiazepine use disorder complicated by recurrent withdrawal seizures. He currently purchases the benzodiazepine analog etizolam through an online website, in addition to carisoprodol (Soma), a muscle relaxant. He initially presented to the emergency department (ED) secondary to an unwitnessed fall, was found to have polytrauma with multiple abrasions, ecchymoses and scrapes on his head, face, chest, abdomen and flank and back. The patient endorsed multiple drug use in the setting of the fall, including etizolam and carisoprodol. In the ED, his vitals were unremarkable, a complete blood count was notable for leukocytosis to 17.4. His complete metabolic panel demonstrated a sodium of 122, potassium 5.4, creatinine 1.74 (baseline 1.3, high muscle mass). His creatine kinase was elevated to 42,900. Urine Drug Screen was positive for benzodiazepines.

Initial trauma imaging workup included a chest x-ray (Fig. 1A) which demonstrated patchy and nodule opacities at the right lung base. Additional CT brain and face was normal except for overlying soft tissue hematomas of the scalp and cheeks. The patient was noted to have frank blood in urine. Due to trauma, overlying abdominal and flank ecchymoses, and blood in urine, the patient received a CT Abdomen and Pelvis to rule out structural kidney injury in addition to suspected rhabdomyolysis. No acute renal pathology was noted, however, there were scattered centrilobular and tree-in-bud ground-glass nodules in the right greater than left lung bases

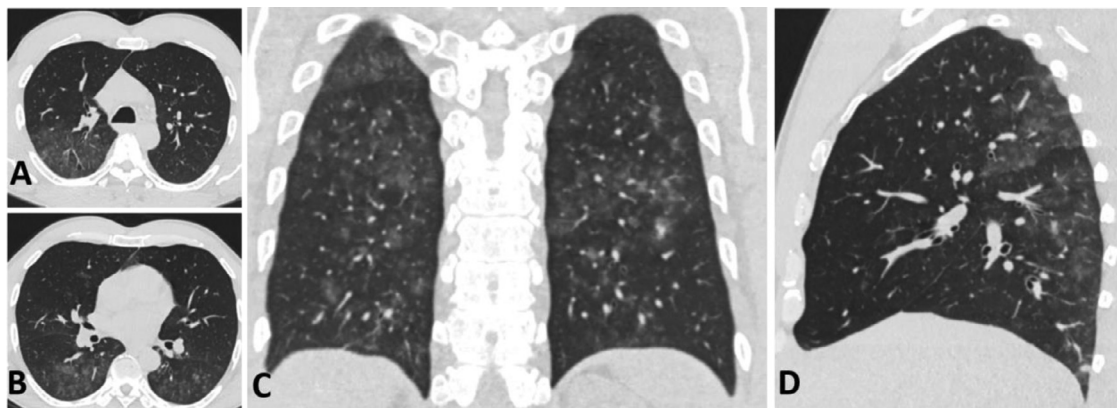


Fig. 2 – Axial (A and B), coronal (C), and sagittal (D) CT chest reconstruction demonstrating extensive gravity dependent ground glass opacities in a primarily centrilobular distribution. Given this appearance, particularly the striking gravity dependence, excipient lung disease was suggested.

considered to be likely of infectious or inflammatory origin (Fig. 1B). A dedicated follow-up CT chest was recommended in 3 months.

A follow-up non-contrast CT Chest was completed nearly 5 months later with no interval trauma or other pulmonary symptoms. This study revealed increased right greater than left gravity dependent ground-glass opacities in a primarily centrilobular distribution (Fig. 2A-D). The central airways were clear.

Discussion

Excipient lung disease is infrequently considered in the clinical setting of substance use disorder due to non-specific clinical symptomatology and relatively non-specific findings on imaging. In this young patient presenting with trauma and elevated white blood cell count, the initial incidental note of ground glass opacities in the lower lungs were non-specific findings with a differential which primarily included infection or aspiration. Given the persistence and imaging appearance of these findings on the dedicated follow-up CT chest 5 months later, ELD was strongly suggested in this patient with a known history of benzodiazepine use disorder and recurrent positive UDS for benzodiazepines [11–14]. One additional consideration in this patient is the route of ingestion. The patient had a significant medical history of IV drug-use, however there was no documented injection sites or endorsement of IV use of the benzodiazepine during the current presentation by the ordering physician. Reports of similar findings on CT have been demonstrated in other routes of street drug abuse, including snorting [18–20] and inhalation [21] although not specifically in benzodiazepine use. Of additional interest in this patient, etizolam was acquired over the internet, which is becoming more commonplace and offers the additional risk of unknown formulations. One could extrapolate that as access to these medications continues to expand, this diagnosis may become more prevalent in the coming years [8, 9, 22, 23]. Because of this, it remains important for the consulted

radiologist to remain vigilant to the imaging findings of ELD, especially given the non-specific clinical symptomatology and stigma behind drug-use that limits acknowledgement of use by the patient to the clinician.

Patient Consent statement

The patient signed a universal consent form allowing for inclusion in research activities. Care was given to minimize personal health information within this case report.

REFERENCES

- [1] Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (2017).
- [2] Votaw VR, Geyer R, Riesellbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. *Drug Alcohol Depend* 2019;200:95–114. doi:10.1016/j.drugalcdep.2019.02.033.
- [3] Pariente F, Caddeo S, Ecarri U. Etizolam in the treatment of generalized anxiety disorder associated with depressive symptoms. *Curr Med Res Opin* 1989;11(9):543–9. doi:10.1185/03007998909112670.
- [4] Nakamae T, Shinozuka T, Sasaki C, et al. Case report: Etizolam and its major metabolites in two unnatural death cases. *Forensic Sci Int* 2008;182(1-3):e1–6. doi:10.1016/j.forsciint.2008.08.012.
- [5] Casacchia M, Bolino F, Ecarri U. Etizolam in the treatment of generalized anxiety disorder: a double-blind study versus placebo. *Curr Med Res Opin* 1990;12(4):215–23. doi:10.1185/03007999009111650.
- [6] Kolbe V, Rentsch D, Boy D, Schmidt B, Kegler R, Buttner A. The adulterated XANAX pill: a fatal intoxication with etizolam and caffeine. *Int J Legal Med* 2020;134(5):1727–31. doi:10.1007/s00414-020-02352-7.
- [7] Etizolam 1 (2020).
- [8] Nielsen S, McAuley A. Etizolam: A rapid review on pharmacology, non-medical use and harms. *Drug Alcohol Rev* 2020;39(4):330–6. doi:10.1111/dar.13052.

- [9] O'Connell CW, Sadler CA, Tolia VM, Ly BT, Saitman AM, Fitzgerald RL. Overdose of etizolam: the abuse and rise of a benzodiazepine analog. *Ann Emerg Med* 2015;65(4):465–6. doi:[10.1016/j.annemergmed.2014.12.019](https://doi.org/10.1016/j.annemergmed.2014.12.019).
- [10] Diaz-Ruiz MJ, Gallardo X, Castaner E, Mata JM, Catala J, Ferreres JC. Cellulose granulomatosis of the lungs. *Eur Radiol* 1999;9(6):1203–4. doi:[10.1007/s003300050817](https://doi.org/10.1007/s003300050817).
- [11] Bendeck SE, Leung AN, Berry GJ, Daniel D, Ruoss SJ. Cellulose granulomatosis presenting as centrilobular nodules: CT and histologic findings. *AJR Am J Roentgenol* 2001;177(5):1151–3. doi:[10.2214/ajr.177.5.1771151](https://doi.org/10.2214/ajr.177.5.1771151).
- [12] Ward S, Heyneman LE, Reittner P, Kazerooni EA, Godwin JD, Muller NL. Talcosis associated with IV abuse of oral medications: CT findings. *AJR Am J Roentgenol* 2000;174(3):789–93. doi:[10.2214/ajr.174.3.1740789](https://doi.org/10.2214/ajr.174.3.1740789).
- [13] Marchiori E, Lourenco S, Gasparetto TD, Zanetti G, Mano CM, Nobre LF. Pulmonary talcosis: imaging findings. *Lung* 2010;188(2):165–71. doi:[10.1007/s00408-010-9230-y](https://doi.org/10.1007/s00408-010-9230-y).
- [14] Giuliano V, Velez-Rivera C, Carlone D. Cellulose granulomatosis of the lungs: CT findings. *AJR Am J Roentgenol* 1994;163(1):220–1. doi:[10.2214/ajr.163.1.8010226](https://doi.org/10.2214/ajr.163.1.8010226).
- [15] Stern EJ, Frank MS, Schmutz JF, Glenn RW, Schmidt RA, Godwin JD. Panlobular pulmonary emphysema caused by i.v. injection of methylphenidate (Ritalin): findings on chest radiographs and CT scans. *AJR Am J Roentgenol* 1994;162(3):555–60. doi:[10.2214/ajr.162.3.8109495](https://doi.org/10.2214/ajr.162.3.8109495).
- [16] Lamb D, Roberts G. Starch and talc emboli in drug addicts' lungs. *J Clin Pathol* 1972;25(10):876–81. doi:[10.1136/jcp.25.10.876](https://doi.org/10.1136/jcp.25.10.876).
- [17] Fields TA, McCall SJ, Reams BD, Roggli VL, Palmer SM, Howell DN. Pulmonary embolization of microcrystalline cellulose in a lung transplant recipient. *J Heart Lung Transplant* 2005;24(5):624–7. doi:[10.1016/j.healun.2004.01.023](https://doi.org/10.1016/j.healun.2004.01.023).
- [18] Pathak LK, Vijayaraghavan V. Hydrocodone snorting leading to hypersensitivity pneumonitis. *Proc (Bayl Univ Med Cent)* 2016;29(3):288–9. doi:[10.1080/08998280.2016.11929438](https://doi.org/10.1080/08998280.2016.11929438).
- [19] Khurana S, Chhoda A, Sahay S, Pathania P. Pulmonary foreign body granulomatosis in a chronic user of powder cocaine. *J Bras Pneumol* 2017;43(4):320–1. doi:[10.1590/S1806-37562015000000269](https://doi.org/10.1590/S1806-37562015000000269).
- [20] Karne S, D'Ambrosio C, Einarsson O, O'Connor PG. Hypersensitivity pneumonitis induced by intranasal heroin use. *Am J Med* 1999;107(4):392–5. doi:[10.1016/s0002-9343\(99\)00244-2](https://doi.org/10.1016/s0002-9343(99)00244-2).
- [21] McCarroll KA, Roszler MH. Lung disorders due to drug abuse. *J Thorac Imaging* 1991;6(1):30–5. doi:[10.1097/00005382-199101000-00006](https://doi.org/10.1097/00005382-199101000-00006).
- [22] Raine C, Webb DJ, Maxwell SR. The availability of prescription-only analgesics purchased from the internet in the UK. *Br J Clin Pharmacol* 2009;67(2):250–4. doi:[10.1111/j.1365-2125.2008.03343.x](https://doi.org/10.1111/j.1365-2125.2008.03343.x).
- [23] Mazer M, DeRoos F, Shofer F, Hollander J, McCusker C, Peacock N, et al. Medications from the web: use of online pharmacies by emergency department patients. *J Emerg Med* 2012;42(2):227–32. doi:[10.1016/j.jemermed.2010.05.035](https://doi.org/10.1016/j.jemermed.2010.05.035).