Journal of Pharmacovigilance and Drug Research

April-June 2024
JPADR, 2024; 5(2): 20-24
DOI: 10.53411/jpadr.2024.5.2.5



Journal home page: www.jpadr.com

CASE REPORT

Levetiracetam Induced Acute Pancreatitis– An ADR Case Report

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ARTICLE INFO

Received 04 December 2023;
Revised 22 January 2024;
Accepted 25 February 2024.

Keywords:
Levetiracetam, Acute Pancreatitis, Pharmacovigilance, Adverse Drug Reaction.

ABSTRACT

Introduction: Acute pancreatitis is an acute inflammation of the pancreas due to premature activation of pancreatic pro-enzymes, resulting in various degrees of damage. There are various causes of acute pancreatitis, including alcohol poisoning, infections, etc. One of the rarer known causes of acute pancreatitis is an adverse drug reaction due to the anti-epileptic drug levetiracetam.
Case report: A 35-year-old male patient presented to the casualty with complaints of sudden-onset pain in the abdomen that was progressive in intensity, nausea, and vomiting for 1 day. He has been an alcoholic for over 20 years. He has had a similar history—on and off since 3 years—and has been on Tab. Levetiracetam (500mg) for epilepsy for two years. Initial examination revealed a soft abdomen with tenderness in the epigastric region. In this patient, investigations revealed serum amylase of 542 IU/L (the normal reference range is 28–100 IU/L). Raised more than 5 times the normal reference range, and abdominal pain was consistent with pancreatitis.
Conclusion: In this article, we discussed various possible causes of acute pancreatitis, with a special focus on levetiracetam induced acute pancreatitis. Further studies are required to understand the etiological factors, epidemiological factors, and outcome of treatment.

An official publication of the Global Pharmacovigilance Society.

Introduction

Acute pancreatitis is an acute inflammation of the pancreas due to premature activation of pancreatic pro-enzymes, resulting in various degrees of damage. (Pawłowska-Kamieniak et al., 2021). There are various causes of acute pancreatitis, including alcohol poisoning, infections, etc. One of the rarer known causes of acute pancreatitis is an adverse drug reaction due to the anti-epileptic drug levetiracetam (SmPC of Keppra 500 mg film-coated tablets).

Levetiracetam is an anti-epileptic drug that was approved by the FDA in 1999, and its use in India was approved in 2005. It is currently the drug of choice for partial seizures for patients over the age of 4 years. Rare cases of levetiracetam causing acute pancreatitis have been recorded in previous literature (Pawłowska-Kamieniak et al., 2021).

An adverse drug reaction (ADR) is any undesirable or unintended consequence of drug administration. Our institute is a registered centre for ADR monitoring with

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Available online 1 June 2024

the National Coordination Centre-Indian Pharmacopoeia Commission (NCC-IPC), Government of India, and is always on the lookout for adverse drug reactions caused by various drugs that are used in our tertiary care centre. In this manner, many individual cases have been identified and studied. Individual case studies (ICS) represent a relevant, timely, and important study design that allows us to dwell into finer details and helps in advancing medical scientific knowledge, as every case is different and adds to our understanding of the aetiology, pathogenesis, natural history, and treatment of the disease. The objective of this article is to present a case of acute pancreatitis that is suspected to be due to Levetiracetam, its investigations, and its management.

Case Report

A 35-year-old male patient presented to the casualty with complaints of sudden-onset pain in the abdomen that was progressive in intensity, nausea, and vomiting for 1 day. He has been an alcoholic for over 20 years. He has had a similar history on and off since 3 years and has been on Tab. Levetiracetam (500mg) for epilepsy for three years. He has no other co-morbidities like diabetes, hypertension, or asthma and is not a case of tuberculosis.

Initial examination revealed a soft abdomen with tenderness in the epigastric region. The cardiovascular system, respiratory system, and central nervous system examinations were found to be normal.

The evaluation of the pancreas is done according to the Revised Atlanta Classification (Banks et al., 2013), diagnosis is made if at least 2 out of 3 criteria are met:

- A lipase or amylase level is three times the upper limit;
- abdominal pain is consistent with pancreatitis;
- abdominal imaging is consistent with acute pancreatitis.

In this patient, investigations revealed serum amylase of 542 IU/L (the normal reference range is 28–100 IU/L). Raised more than 5 times the normal reference range, and abdominal pain was consistent with pancreatitis. The third criteria could not be properly assessed since the pancreas was obscured due to the presence of gas in the abdomen. Two out of three criteria were met, and hence, a provisional diagnosis of acute pancreatitis was made. However Contrast-enhanced CT scans of the abdomen and magnetic resonance imaging (MRI) of the abdomen are the best imaging modalities for visualisation of pancreatic pathology. The classic features, such as the presence of focal or diffuse enhancement of the pancreas, indicate acute pancreatitis (Chatila et al., 2019). This test was not conducted on this patient.

He was then given the following treatment: Stop Levetiracetam medication; IV fluids; 10 mL normal saline, ringer lactate, or dextrose normal saline at the rate of 100 mL per hour; injection of Tramadol IV in 100 mL normal saline; injection of Pantoprazole 40 mg and nil per Oral until further investigation.

The results of the investigations that were performed while the patient was admitted to our tertiary centre are given in Table 1

Table 1. Investigation results of the Patient

Parameter	Result	Normal Reference Range
Haemoglobin (Hb)	22.7 g/dL	13-17 g/dl (Male)
		12-15 g/dl (Female)
Packed Cell Volume (PCV)	67.1%	45-52 % (Male)
		37-48 % (Female)
RBC Count	7.58 million/cu mm	4.7-6.1million/cu mm (Male)
		4.2-5.4 million/cu mm (Female)
Mean Corpuscular Volume (MCV)	88.5 fl	80-100 fl
Mean Corpuscular Haemoglobin (MCH)	30 pg	27-32 pg
Mean Corpuscular Haemoglobin Concentration (MCHC)	33.9 gm/dL	32-35 gm/dL
Red cell Distribution Width (RDW)	16.5%	11.5-14.5%
Total WBC Count	13350 cells/cu mm	4000-11000 cells/cu mm
Differential Count		
Neutrophils	82%	40-70%
Lymphocytes	9%	20-45%
Eosinophils	1%	1-6%
Monocytes	8%	2-10%
Basophils	0%	0-1%
Platelet count	1.88 lakhs/cu mm	1.5-4.5 lakhs/cu mm
Ultrasonography	Liver: Mild increased echo texture	
	Pancreas: Obscured	
	Spleen: Mild enlargement seen. Size13.9 cm. Normal echo texture.	
	Impression: Mild splenomegaly and Grade I fatty liver.	
Chest X-ray and KUB view	No abnormality noted.	
CT of Abdomen and Pelvis	Not done	

The patient recovered after medical management, as mentioned above. The patient was discharged with the advice to consume a soft diet orally and revisit for follow-up after one week. The patient was also referred to Neurologist for consultation to change the anti-epileptic drug from Levetiracetam to other drugs like Pregabalin

Discussion

Jones MR et al., (2015) reported that acute pancreatitis is reported among 230,000 hospitalised patients in the United States alone per year. Drug-induced pancreatitis is reported in 1–2% of these patients. Other researchers reported that drug-induced pancreatitis can account for up to 4.8% of all cases. The common drugs that are known to cause pancreatitis are 6-mercaptopurine, sulfonamides, diuretics, didanosine, pentamidine, tetracycline, azathioprine, ACE inhibitors, statins, oral contraceptives, hormone replacement therapy, diuretics, antiretroviral therapy, valproic acid, and oral hypoglycemic agents. (Chatila et al., 2019 ; Jones et al., 2015; Balani et al., 2008).

As per the Summary of Product Characteristics (SmPC), levetiracetam pancreatitis is a rare (≥1/10,000 to <1/1,000) ADR. Other common side effects of this drug include anxiety, change in personality, chills, cough, deep or fast breathing with dizziness, etc. (SmPC of Keppra 500 mg film-coated tablets). The prognosis of pancreatitis induced by levetiracetam is generally good with low mortality (Karahan et al., 2023). The overall mortality rate in severe pancreatitis is around 5% to 17%, and in mild pancreatitis, it is around 1.5. (Chatila et al., 2019).

The main pathophysiological event that starts the process that leads to acute pancreatitis is the premature activation of the enzyme trypsinogen to trypsin within the acinar cell instead of the duct lumen. There are various aetiologies for this premature activation of trypsinogen: The drugs may cause ATP depletion and increase the intra-acinar calcium concentration, which stimulates the activation of the enzyme; Hypercalcemia due to steroids, cancer, certain infections, and trauma (Jones et al., 2015); While alcohol itself (the second most common toxin) may play a role in causing pancreatitis, it should be remembered that it takes over five years of heavy alcohol use to induce alcohol-related pancreatitis (Gapp et al., 2023). Other causes of pancreatitis include smoking, hyperlipidemia, scorpion venom, and retrograde cholangiopancreatography using endoscopy (Jones et al., 2015).

The causality assessment was done using the WHO-UMC causality assessment scale (WHO) and found to be possibly related to the levetiracetam drug. Alcohol consumption for more than 20 years may also be the other possible cause of pancreatitis in the current case under discussion. This is supported by mild hepatitis with a grade I fatty liver. Exposure to Lievetiracetam in a chronic alcoholic could have accelerated the development of pancreatitis in this case.

Other laboratory abnormalities were related to haematological parameters and splenomegaly, as given in Table No. 01. In contrast to these findings, levetiracetam is known to cause leukopenia, eosinophilia, and rarely pancytopenia. In addition, rare cases of serum enzyme elevations and rare cases of clinically apparent liver injury are also reported. (Kumar et al., 2023). The reasons for the contrasting results could be explained by Systemic Inflammatory Response (SIRS) following pancreatitits.

The patient recovered symptomatically after conservative treatment. Currently, no specific antidote or specific therapeutic agent for drug-induced acute pancreatitis or to prevent its complications is available. The only treatment protocols currently available are intravenous fluid resuscitation, enteral nutrition, and analgesics (Szatmary et al., 2022). In addition, withdrawal and replacement of the causative agent with an alternate available treatment for the underlying condition can be considered. In cases where serious ADRs to Levitiracetam have been seen, the drug can be replaced with Pregabalin. (Azar et al., 2014).

Even though there has been a lot of research that has identified the pathophysiological background of acute pancreatitis, no specific antidotes have been identified (Garami et al., 2023). This is believed to be due to unidentifiable or undruggable therapeutic targets. The potential molecular targets for treatment include management for impaired autophagy, mitochondrial dysfunction, excessive intracellular calcium overload, premature trypsin activation, impaired unfolded protein response, lipotoxicity, and calcineurin activation (Abu-El-Haija et al., 2018). Studies exist for each of these molecular targets. Recently, the role of Bradykinin 2 in the progression of acute pancreatitis has been identified, and studies have shown that pharmacological blockage of type 2 Bradykinin helps to alleviate the characteristic cellular changes that happen in acute pancreatitis (Garami et al., 2023). Another novel study showed the role of Protease A Disintegrin and Metalloproteinase 17 (ADAM 17) in mediating the inflammatory response, and now pharmacological agents for the blockade of ADAM17 need to be researched (Saad et al., 2022). Another important finding from these studies suggested that smaller groups do better; smaller study groups with more personalised criteria have shown better results; this highlights the importance of precision medicine / personalised medicine in the treatment of acute pancreatitis (Garami et al., 2023).

Conclusion

In this article, we discussed various possible causes of acute pancreatitis, with a special focus on drug-induced acute pancreatitis. Levetiracetam is rarely known to cause acute pancreatitis. The treating physician needs to watch for acute pancreatitis if the patient has additional etiological factors known to enhance the development of pancreatitis. The patient must be made aware of the signs of acute pancreatitis and instructed to report to the doctor immediately if such symptoms are encountered. All patients who are admitted with acute pancreatitis must be counselled on the cessation of alcohol and also informed of the high mortality rate in severe pancreatitis. Further studies are required to understand the etiological factors, epidemiological factors, and outcomes of treatment in acute drug-induced pancreatitis.

Acknowledgement

We acknowledge support extended by staff and management of Department of Pharmacology and General Surgery, CDSIMER, Devarakaggalahalli, Ramanagara District, Karnataka.

Funding

No funding received for this project.

Conflict of Interest

None

References

Abu-El-Haija, M., Gukovskaya, A. S., Andersen, D. K., Gardner, T. B., Hegyi, P., Pandol, S. J., Papachristou, G. I., Saluja, A. K., Singh, V. K., Uc, A., & Wu, B. U. (2018). Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis: Summary of the Working Group on Drug Development and Trials in Acute Pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas, 47(10), 1185–1192.

Azar, N. J., & Aune, P. (2014). Acute pancreatitis and elevated liver transaminases after rapid titration of oral levetiracetam. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 21(6), 1053–1054.

Balani, A. R., & Grendell, J. H. (2008). Drug-induced pancreatitis : incidence, management and prevention. Drug safety, 31(10), 823–837.

Banks, P. A., Bollen, T. L., Dervenis, C., Gooszen, H. G., Johnson, C. D., Sarr, M. G., Tsiotos, G. G., Vege, S. S., & Acute Pancreatitis Classification Working Group (2013). Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut, 62(1), 102–111.

Chatila, A. T., Bilal, M., & Guturu, P. (2019). Evaluation and management of acute pancreatitis. World journal of clinical cases, 7(9), 1006–1020.

Gapp, J., Tariq, A., Chandra, S. (2023). Acute Pancreatitis. [Updated 2023 Feb 9]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Retrieved from-https://www.ncbi.nlm.nih.gov/books/NBK482468/

Garami, A., & Hegyi, P. (2023). Precision Medicine in Pancreatitis: The Future of Acute Pancreatitis Care. Function (Oxford, England), 4(3), zqad015. .

Jones, M. R., Hall, O. M., Kaye, A. M., & Kaye, A. D. (2015). Drug-induced acute pancreatitis: a review. Ochsner journal, 15(1), 45–51.

Karahan, H. T., Tanoglu, A., Senoymak, M.C., Yeniçeri, M., Bas, S., Karahan, E., Atakan, B. (2023). Levetirasetam induced acute pancreatitis : an uncommon case report. Intercontinental Journal of Internal Medicine. 1(3), 71-72.

Kumar A, Maini K, Kadian R. Levetiracetam. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK499890/

Pawłowska-Kamieniak, A., Krawiec, P., & Pac-Kożuchowska, E. (2021). Acute Pancreatitis as a Complication of Antiepileptic Treatment: Case Series and Review of the Literature. Pediatric reports, 13(1), 98–103.

Saad, M. I., Weng, T., Lundy, J., Gearing, L. J., West, A. C., Harpur, C. M., Alanazi, M., Hodges, C., Croagh, D., Kumar, B., Sagi, I., Rose-John, S., & Jenkins, B. J. (2022). Blockade of the protease ADAM17 ameliorates experimental pancreatitis. Proceedings of the National Academy of Sciences of the United States of America, 119(42), e2213744119.

Summary of Product Characteristics (SmPC) of Levetiracetam (Keppra 500 mg film-coated tablets) Available at: https://www.medicines.org.uk/emc/product/2293/smpc/print Accessed on 16/Sep/2023.

Szatmary, P., Grammatikopoulos, T., Cai, W., Huang, W., Mukherjee, R., Halloran, C., Beyer, G., & Sutton, R. (2022). Acute Pancreatitis: Diagnosis and Treatment. Drugs, 82(12), 1251–1276.

WHO. The use of the WHO–UMC system for standardised case causality assessment. Retrieved from https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf. Accessed on 30/Aug/2023.