Archives of Psychiatry and Psychotherapy, 2019; 3: 57–60

DOI: 10.12740/APP/105690

Psychosis with lacosamide: a case report

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Summary

An association between epilepsy and psychosis has been demonstrated in various reviews, and it has been estimated that psychosis in the form of schizophrenia affects between 3% and 7% of all epileptic patients. Lacosamide an anti-epileptic was synthesised and used for treatment of epilepsy as well as neuropathic pain. Psychosis is not included as a common adverse effect of the drug. The mechanism by which psychosis is associated with lacosamide is not yet known and is not known to modulate serotonin or dopamine systems. Literature review shows only a few cases reported with similar presentations. We present here a case of a 38 year old male; with Lacosamide induced psychosis.

psychosis, epilepsy, lacosamide

INTRODUCTION

An association between epilepsy and psychosis has been demonstrated in various reviews, and it has been estimated that psychosis in the form of schizophrenia affects between 3% and 7% of all patients with epilepsy [1,-4], recent studies in temporal lobe epilepsy have been found to be as high as 10-19% [5]. This is higher as compared to 1% risk for the same in the general population.

Several mechanisms for this are clearly elucidated in literature are temporal lobe seizures, inter ictal and post ictal psychosis and structural brain lesions such as hematoma [6,7]. Psychotropic adverse effects of medication constitute another mechanism connecting epilepsy and psychosis[8]. Such diagnosis are possible with difficulty, and by exclusion of other causes.

Lacosamide (SPM 927, formerly harkoseride), the R-enantiomer of 2-acetamido-N-benzyl-3-methoxypropionamide, is a new chemical entity – an antiepileptic drug, being developed as an oral formulation [9]. Without affecting fast inactivation, lacosamide appears to selectively enhance sodium channel slow inactivation, which may help normalize activation thresholds and decrease pathophysiological neuronal activity, thus controlling neuronal hyper excitability [10]. We present here a case of a 38 year old male with Lacosamide induced psychosis. Though rare, there are few reports of similar presentation [11-13]. Patient anonymity has been preserved.

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Case History

Mr. SU, 38 years male was admitted at our hospital involuntarily by authorities via an order for observation and treatment. He was found unattended and alone, and hence brought by the police. At presentation he was poorly groomed, preoccupied and partially co-operative for interview. During first week of admission no major behavioral disturbances were noted. Attempts to trace family were unsuccessful due to inad-

equate details from the patient. Patient continued to be an inpatient during the course of his treatment.

After about a week of indoor stay patient developed tonic clonic seizure episodes and continued to have it at a frequency of once every week. His routine blood reports showed anemia (Hb 9.8mg/dl). His liver function tests and renal function was normal. Hypoglycemia and electrolyte disturbances were ruled out for the cause of seizure each time. Computerized tomography (CT) scan of the brain showed presence of bilateral basal ganglia calcification. His electroencephalography (EEG) following the convulsion during 2nd week showed focal epileptiform discharges. The area involved was bilateral frontal, central and anterior temporal regions, with secondarily spike and wave generalized involvement. Patient was started on Tab.Clobazam 10mg at night for the seizures. On Tab. Clobazam patient had 2 seizures within the first week of starting the drug. Patient was started on Tab. Sodium Valproate at 1gm loading dose as per body weight (50kg). He was treated with Tab. Sodium Valproate 1000mg and Tab. Clobazam 10mg. Patient remained seizure free for next 4 weeks. Serum valproate monitoring services were not available at our hospital for the serum levels. At this point he developed sedation, confusion, drowsiness and flaps, suggestive of valproate toxicity and it had to be discontinued. Patient was shifted to Tab. Phenytoin Sodium 300mg; in divided dosages with Tab. Clobazam 10mg. Patient seizure control was poor on phenytoin. He also displayed unsteady gait and ataxia, indicating poor tolerability. He had been taking Tab. Phenytoin for 5 weeks and had 3 seizure episodes. Hence Tab. Carbamazepine 200mg was started three times and increased to 800mg/day over a week. The Phenytoin was tapered and stopped. On these dosages too, the seizures were not adequately controlled. As there was prior evidence of seizure control with sodium valproate patient was re-tried on the same agent. Tab. Sodium Valproate was gradually up titrated over 3 weeks to 800mg/day. However response to oral valproate was not as robust this time around and he had 2 episodes of convulsions on this dose. Tab. Clobazam was increased to 15mg. Patient developed slurring and sedation by the 3rd week on Valproate rechallenge. Patient's serum ammonia was found to be elevated (96 Mmol/L) and valproate was discontinued. Due to poor tolerability to valproate and phenytoin and, inadequate seizure control on carbamazepine, patient was started oral levetiracetam.

Tab. Levetiracetam was started at 1000 mg, and built to 2000mg by 2 weeks, with clobazam 15mg. On this regimen patient continued to have intermittent seizures (2 episodes in 3 weeks) and clobazam was increased to 20mg. Despite adequate dose of both drugs patient continued to have seizures and therefore oral lacosamide was added to the regimen. It was initiated at 50mg twice a day and subsequently, increased to 100mg twice a day after 1 week. The levetiracetam was tapered and stopped during this time as patient had not shown good seizure response to the drug and hence it was being cross-titrated under liaison with a Neurologist with Tab. Lacosamide 100mg dose. Patient stabilized and was seizure free over next 2 weeks. On starting dose, within a week behavior changes were noted. Patient was irritable and and developed delusion of persecution. He would claim that nursing staff and other caretakers were plotting against him by poisoning him through the food. He would also claim that other patients were trying to assault him. Such behavior was not noted since his admission to the hospital. We tried to do an EEG to rule out a small possibility complex partial seizure as a cause for the behavior disturbance; however patient was uncooperative for the same. For control of psychotic symptoms Tab.Risperidone 1mg HS was introduced. With anti-psychotic medication his behavior improved. Patient did not have further seizure episodes on Tab. Lacosamide 200mg with Tab. Clobazam 20mg. In view of past poor tolerability and risk benefit ratio of adequate seizure control and control of psychotic symptoms, the above regimen, including risperidone has been continued for the last 4 months.

DISCUSSION

We considered a number of explanations for the above presentation. There exists a strong relationship between adequate control of seizure in refractory patients and development of psycho-

sis – epileptic psychosis following forced normalisation.[15] The features of forced normalization include presence of new behavioural disturbances, one-week absence of seizures, similar previous episodes and occurrence of such events on changes in antiepileptic pharmacotherapy [16-18]. In our difficult case scenario, the patient had been adequately controlled on Sodium Valproate 1000mg and Clobazam 10mg for a period of 4 weeks without symptoms of psychosis and therefore epileptic psychosis following forced normalisation was not considered. We tried for an EEG study to confirm regarding the same but due to agitation and behavioural problems this was not possible. Similarly peri-ictal psychosis [15] is another consideration for the above presentation. It usually consists of consists of features of a brief psychotic episode in patients having – complex partial seizures, bilateral interictal discharges, and frequent discharges involving the left amygdala. In our case patient had generalized tonic clonic seizure type of episodes throughout the duration of stay without any behavioural problems.

Other agent was Levetiracetam which is known to cause psychosis in a subset of patients [20-22]. These cases show onset of psychosis staring within a week of institution of therapy and rarely after long term treatment [23]. It has a short half-life of 8-10 hours [19], In our case patient had been on Levetiracetam 2000mg for almost a period of 2 weeks, with no symptoms of psychosis. Considering the pharmacokinetics and temporal relationship of Levetiracetam use in our patient, it is unlikely to be the causal factor. In addition Clobazam [24] is not known to cause or exacerbate psychosis.

CONCLUSION

Lacosamide selectively enhances sodium channel slow inactivation, which is its purported anti-epileptic mechanism. The mechanism by which psychosis is associated with lacosamide is not yet known and is not known to modulate serotonin or dopamine systems. Psychosis is not included as a common adverse effect of Lacosamide. [25-27] Considering the Bradford Hill criteria[28] our case report fulfils the temporality and analogy construct. Also as per the Naranjo Nomogram Scale for adverse drug reactions [29] the score is 3 indicating a 'possible' adverse drug reaction. The detailed clinical presentations of similar cases have been elucidated in the following table. (Table 1)

Table 1. Clinical presentations of similar cases

No.	Author	Clinical characteristics	EEG characteristics	Psychosis features
1.	Abou Khaled K et al.[11]	Epilepsy with different seizures types: simple partial seizures with dysphasia, seizures, generalized tonico-clonic seizures, and very disabling nocturnal seizures with confusion	Diffuse background slowing, with bilateral fronto-temporal independent sharp waves during wakefulness and nearly continuous poly – spikes and waves during sleep. A background consisting of reactive and symmetrical alpha rhythm was only seen intermittently in short fragments.	Aggressiveness, strange behaviour, visual hallucinations. He would be talking to himself or to an imaginary friend with various gestures (movements of throwing an invisible ball, digging or tapping) in addition to inappropriate laughter and paranoid delusions towards his mother and neighbors.
2.	Pinkhasov A. et al.[12]	Exacerbation of generalized tonic-clonic seizure disorder	no seizure activity was evident on electroencephalogram (EEG)	Severely agitated with paranoid delusion toward the nurse.
3.	Chatzistefanidis D. et al.[13]	Deterioration of his partial-onset seizures and secondary generalized tonic-clonic seizures	Alpha background rhythm of 9 to 11 Hz over the posterior regions and runs of generalized theta waves, with centrally localized higher amplitude, without hemisphere predominance.	Persecutory delusions of being watched by cameras, and ideas of reference (patient believed that television programs and other patients were referred to him), aggressiveness, self-harming and hostile behaviour and irritability

In above case our patient developed paranoid psychosis after initiation of Lacosamide which subsided with use of anti-psychotics. We suggest it being Lacosamide associated psychosis. Considering clinical scenarios, we recommend that emergence of abnormal behaviour symptoms in a patient started on Lacosamide needs careful review and a watchful observation for probability for induced psychotic phenomenon.

Disclosure statement

- Conflicts of Interests: Nil
- Acknowledgement: Nil
- Financial support/grant: Nil

REFERENCES

1. Clancy MJ., Clarke MC, Connor DJ, Cannon M, Cotter DR. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. BMC Psychiatry 2014;14:75.
2. Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007;48(12):2336-2344.
3. Toone BK. The psychoses of epilepsy. Journal of Neurology, Neurosurgery & Psychiatry 2000;69:1-3.
4. Rai D, Kerr MP, McManus S, et al. Epilepsy and psychiatric comorbidity: a nationally representative population-based study. Epilepsia 2012;53:1095–103.
5. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. ActaNeurol Scand. 2004;110(4):207–220.
6. Keshavan MS, Kaneko Y. Secondary psychoses: an update. World Psychiatry 2013;12:4–15.
7. Kanemoto K, Tadokoro Y, Oshima T. Psychotic illness in patients with epilepsy. Ther Adv Neurol Disord 2012;5:321-334.
8. Naha, Sowjanya et al. "A Young Woman with Seizures and Psychosis." BMJ Case Reports 2014. PMC. Web. 5 July 2018.
9. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI). Epilepsy Research 2002;51:31–71.
10. Errington AC, Coyne L, Stohr T, Selve N, Lees G. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology 2006;50:1016–1029.
11. Abou Khaled K, Khoury J, Macaron G, Richa S. Forced normalization and psychosis following use of lacosamide. Seizure. 2016;41:96-99.
12. Pinkhasov A, Lam T, Hayes D, Friedman M, Singh D, Cohen H. Lacosamide Induced Psychosis: Case Report, Review of Differential Diagnosis and Relevant Pharmacokinetics. Clin Neuropharmacol. 2015;38(5):198-200.
13. Chatzistefanidis D, Karvouni E, Kyritsis AP, Markoula S. First case of lacosamide-induced psychosis. Clin Neuropharmacol. 2013;36(1):27-8.
14. González MC, Gil Villar MP, Calvo MD, Corbalán ST, Martínez L, et al. Epileptic peri-ictal psychosis – a reversible cause of psychosis. Neurologia 2013;28(2):81-87.
15. Benjamin J. Sadock, Virginia A. Sadock. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. Philadelphia: Lippincott Williams & Wilkins, 2009.
16. Loganathan, MA, Enja M, Lippmann S. Forced Normalization: Epilepsy and Psychosis Interaction. Innovations in Clinical Neuroscience 2015;12(5-6):38–41.
17. Kanner AM, Palac S. Neuropsychiatric complications of epilepsy. Curr Neurol Neurosci Rep. 2002;2(4):365–372.
18. Krishnamoorthy ES, Trimble MR, Sander JW, Kanner AM. Forced normalization at the interface between epilepsy and psychiatry. Epilepsy Behav 2002;3(4):303–308.
19. U.S. Food and Drug Administration. Keppra (Levetiracetam) c. 2009 [updated 2016 April; cited 2018 Feb 01]. Available from: ttps://www.accessdata.fda.gov/ drugsatfda_docs/ label/2009/021035s078s080,021505s021s024lbl.pdf
20. Kumar N, Swaroop HS, Chakraborty A, Chandran S. Levetiracetam induced acute reversible psychosis in a patient with uncontrolled seizures. Indian J Pharmacol 2014;46(5):560.
21. Chen Z, Lusicic A, O'Brien TJ, Velakoulis D, Adams SJ, Kwan P. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. Brain 2016;139(10):2668-2678.
22. Zaki SA, Gupta S. Levetiracetam-induced acute psychosis in a child. Indian J Pharmacol 2014;46(3):341-342.
23. Bayerlein K, Frieling H, Beyer B, Kornhuber J, Bleich S. Drug induced psychosis after long-term treatment with levetiracetam. Can J Psychiatry 2004;49:868.
24. Food and Drug Administration. Onfi (Clobazam). [Home page on the Internet] c. 2016 [updated 2016 December; cited 2018 Feb 01]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/ label/ 2016/203993s005lbl.pdf
25. Food and Drug Administration. Vimpat (lacosamide). [Home page on the Internet] c. 2009 [updated 2009 November; cited 2018 Feb 01]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/ label/ 2009/ 022253s004, 022254s001lbl.pdf
26. Ben-Menachem E, Biton V, Jatuzis D, et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 2007;48(7):1308–1317.
27. Halasz P, Kälviäinen R, Mazurkiewicz-Beldzińska M, et al. Adjunctive lacosamide for partial onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia 2009;50(3):443–453.
28. Hill, A. B. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine 1965; 58(5),295–300.
29. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. Am J Hosp Pharm. 1986;43(7):1709-1714.