mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Perampanel-induced, new-onset food aversion in a 29-year-old female with medically refractory frontal lobe epilepsy

Marketa Marvanova, PharmD, PhD, BCGP, BCPP[1]

How to cite: Marvanova M. Perampanel-induced, new-onset food aversion in a 29-year-old female with medically refractory frontal lobe epilepsy. Ment Health Clin [Internet]. 2019;9(2):100-4. DOI: 10.9740/mhc.2019.03.100.

Abstract

Background: Perampanel is a selective, noncompetitive amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor antagonist indicated for management of partial-onset and primary generalized seizures in epilepsy patients aged ≥12 years.

Patient History: A 29-year-old, white female with significant history of medically refractory frontal lobe epilepsy, status post right frontal and temporal resections, was initiated on perampanel as an add-on therapy to phenytoin extended-release (330 mg/d) and clonazepam (2.5 mg/d). She previously failed several antiepileptic drugs because of inefficacy and/or intolerance. Perampanel was initiated at 2 mg/d and the dose was increased by 2 mg/d increments every 2 to 3 weeks. Following the first dose, nausea and drowsiness were reported but resolved the following day. Three days after titration to 6 mg/d, the patient developed complete food aversion and became more irritable and anxious while no seizure frequency improvement was noted. No change of sense of taste was reported. After reduction to 4 mg/d, adverse effects improved but did not completely resolve until 2 months following perampanel discontinuation.

Review of Literature: A PubMed search revealed no published literature or case reports of perampanel-induced food aversion or anorexia in a presence or absence of phenytoin and clonazepam.

Conclusion: In this report, a temporal relationship was observed between perampanel dose-increase and the development of food aversion. Return to baseline appetite and eating habits following perampanel discontinuation strongly suggest perampanel involvement. At this time, the exact mechanism(s) behind food aversion associated with perampanel is/are unknown.

Keywords: frontal lobe epilepsy, perampanel, food aversion, phenytoin, CYP3A4, AMPA receptor, medically refractory epilepsy

[1] (Corresponding author) Chair and Associate Professor, Department of Pharmacy Practice, School of Pharmacy, College of Health Professions, North Dakota State University, Fargo, North Dakota, marketa.marvanova@ndsu.edu, ORCID: https://orcid.org/0000-0003-4998-8921

Disclosures: M.M. serves as a clinical specialist consultant in neurology and psychiatry for Lexicomp, Wolters Kluwer.

Background

Perampanel (PER) is a selective, noncompetitive amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist; and is the first-in-class antiepileptic drug (AED) with this mechanism of action.[1,2] It is currently approved as a monotherapy for partial-onset seizures with or without secondary generalization, and as an add-on therapy for primary generalized seizures in patients with epilepsy aged ≥12 years.[1,3] It displays linear pharmacokinetics at clinically-relevant doses of 2 to 12 mg/d and is administered once daily at bedtime because of its long half-life (approximately 105 hours).[1] Perampanel is a primary substrate for liver cytochrome P450 (CYP) 3A4 isoenzymes and undergoes extensive liver metabolism via oxidation and subsequent glucuronidation to inactive metabolites.[1] It is, therefore, a target for drug interactions with medications with strong-inducing or inhibiting CYP3A4 effects.[1] Administration of phenytoin or

TABLE 1: Social history and home medication regimen, vital signs, and laboratory results at admission

Admission Information
Social history
Smoking: negative
Alcohol: negative
Illicit drug use: negative
Living situation: lives with her parents, who are her primary caregivers
Sexually active: negative
Home medications
Phenytoin ER, 30 mg in the morning and 300 mg in the evening
Clonazepam, 1 mg in the morning and 1.5 mg in the evening
Folic acid, 1 mg daily
Calcium carbonate, 500 mg daily
Cholecalciferol, 3000 IU daily
Vital signs
Blood pressure: 114/60 mm Hg
Heart rate: 76 bpm
Body mass index: 19.9 kg/m^2 (normal range: 18.5 to 24.9 kg/m^2)
Laboratory
Complete blood count: WNL
Comprehensive metabolic panel: WNL
Free phenytoin level: 2.1 mg/dL

ER = extended-release; WNL = within the normal limit.

carbamazepine, both strong inducers of CYP3A4, are reported to be associated with significantly decreased PER plasma concentrations, 50% and 67%, respectively.[1]

Initial PER dose is 2 mg/d when administered in the absence of a medication inducing its metabolism or 4 mg/d if administered with a strong CYP3A4 inducer. Based on therapeutic response and tolerance, the dose can be increased weekly by 2 mg/d to a maximum of 12 mg/d.[1] The most commonly-reported treatment-emergent adverse effects (AEs) of PER in adults were dizziness, somnolence, irritability, nervousness, vertigo, ataxia, headache, and nausea.[1,4-7] In agreement, PER use in 39 treatment-resistant patients with frontal lobe epilepsy as an add-on therapy to other 3 to 4 AEDs was associated with dizziness, somnolence, irritability, malaise, and headache.[8]

Despite nausea as a common AE, randomized, double-blind placebo-controlled Phase III registration studies[4-7,9,10] of PER in patients with refractory partial-onset seizures reported weight increase. Weight increase above 7% of baseline weight was reported in 11.6% to 19.2% of PER-treated adults versus 4.4% to 8.3% in placebo-treated groups. On average, PER-associated weight increase was 1.2 kg compared to 0.4 kg with placebo.[4-7,9] In addition, Youn et al[10] reported appetite and weight changes, reflecting either increase or decrease, however no report of food aversion.

In this report, I describe what I believe is the first report of PER-induced total food aversion in an individual with medically refractory epilepsy. Food aversion is characterized by alteration of eating or feeding behavior manifesting as select food intolerance, repulsion and avoidance associated with adverse physical reaction such as nausea and/or vomiting. It is a very diverse condition with different severity levels and can be associated with psychological or emotional state, environment or exposure to aversive stimulus, medications, or a physiological state such as pregnancy.[11-13]

Case Report

A 29-year-old, right-handed white female was admitted to the epilepsy monitoring unit for video electroencephalography monitoring and medication adjustment in a large urban academic medical center. Her medical history was significant for medically refractory frontal lobe epilepsy with complex focal seizures with or without secondary generalization status post partial right frontal (2001) and right temporal resection (2008). Medication adjustment was warranted because of frequent daily seizures including clusters of 2 to 3 seizures despite adherence to phenytoin and clonazepam (CLZ). A complete list of home medications, social history, and admission vital signs and labs, are included in Table 1. Several AEDs and a modified Atkin's diet were previously discontinued because of inefficacy and/or intolerance (Table 2).

Perampanel was added to her current home AED regimen of phenytoin and CLZ and, because of her prior history of paradoxical reactions, patient was initiated at 2 mg/d, a lower dose than recommended for an individual on concomitant strong CYP3A4 inducers.[1,14] She denied all commonly reported AEs following initial administration other than nausea and drowsiness which resolved the next day. Her electroencephalogram remained unchanged. The day after initiation of PER 2 mg/d, she was discharged with instructions to increase by 2 mg/d every 2 weeks up to 6 mg/d until follow-up with her epileptologist (sooner for AEs or increased seizure frequency). Previous home doses of phenytoin and CLZ were continued. Upon admission and discharge (hospital day 2) complete blood count and complete metabolic panel were unremarkable and free phenytoin level was unchanged (2.1 mg/dL).

She tolerated the initial PER dose titration well. Three days after the dose increase to 6 mg/d, she experienced

TABLE 2: Tolerability and efficacy of previous trials of pharmacologic and nonpharmacologic modalities

Treatment Modality	Adverse Event/Paradoxical Reaction	Efficacy
Pharmacologic		
Carbamazepine	Suicidal ideation and depression	
Lamotrigine	Increased anxiety	Lack of efficacy
Levetiracetam	Increased seizure frequency	
Phenobarbital	Status epilepticus	
Valproic acid and its derivatives	Increased anxiety	Lack of efficacy
Zonisamide	Increased anxiety	Lack of efficacy
Nonpharmacologic		
Modified Atkin's diet	Weight loss (22 lb)[a]	Lack of efficacy

[a]Modified Atkin's diet was discontinued 4 months prior to the trial with perampanel. With the diet, the patient experienced a 22-lb weight loss in the absence of decreased appetite or food aversion.

new-onset food aversion. Over the phone, the food aversion was described by her mother (primary caregiver) as the smell or sight of any food including fruits or vegetables resulting in nausea despite absence of any physical problem. No change in sense of taste was reported. This was a new presentation for her, not previously experienced. In addition, the patient became more irritable and anxious after the dose increase. No seizure frequency improvement was reported. The patient and her mother expressed interest in PER discontinuation. Two days after dose reduction to 4 mg/d, she was able to sit by the kitchen table during meal times but had some residual effect and was unable to eat a large amount of food, and this further improved when dose was decreased to 2 mg/d. When PER was discontinued, it took about 2 months before return to baseline appetite. During PER trial, the patient lost a total of 8.4 lb (body mass index = 18.5 kg/m^2). Body mass index increased to 19.3 kg/m^2 within approximately 2 months after PER discontinuation.

Literature Search

A PubMed search in May 2018 revealed no published case report or information on PER-induced food aversion or anorexia associated with monotherapy or combinational therapy with another AED in adults with epilepsy. Key words used were: perampanel, food aversion, decreased appetite, nausea, and anorexia.

Discussion

This report describes new-onset total food aversion 3 days after PER dose increase from 4 mg/d to 6 mg/d in a young adult female with medically refractory frontal lobe epilepsy, partial right frontal and temporal resections, and a variety of paradoxical AED reactions. The Naranjo total score was 6, estimating that this was a probable adverse drug reaction associated with PER. A temporal relationship was observed between PER dose of 6 mg/d and development of food aversion. Perampanel dose decrease was associated with improvement and PER discontinuation followed by washout period was associated with return to baseline appetite and eating, strongly suggesting PER-contribution.

As about 50% of PER plasma concentration would be decreased by concomitantly administered phenytoin due to CYP3A4 induction, it can be postulated that food aversion was induced by lower PER serum concentration that would correspond to an oral PER dose of 3 mg/d in an individual with PER monotherapy.[1] However, it is difficult to pinpoint association with specific PER serum level as the patient's pharmacogenomic profile was unknown (to identify CYP3A4 phenotype) and no PER serum levels were obtained.

Because of general lack of understanding of etiology, mechanisms, and involved neurocircuit(s) behind food aversion, at this time the precise mechanism(s) of observed total food aversion are unknown. However, as PER acts as a selective glutamate AMPA receptor antagonist and onset of food aversion was associated with PER dose increase, AMPA receptors involvement is suggested.[1] In support of this, the patient experienced increased anxiety and irritability following dose increase which are known PER AEs linked to AMPA-receptor antagonism.[1,2] AMPA receptors are widely expressed in the brain, and PER-antagonism is associated with antiepileptic activity due to antagonism in the cerebral cortex and hippocampus, while AEs are associated with receptor antagonism in similar or other brain regions.[1,2,15] Brain regions associated with feeding and aversive motivational control, such as the ventromedial prefrontal cortex, lateral hypothalamus, lateral habenula, and ventral tegmental, may play a role in food aversion.[16-22]

I cannot rule out pharmacodynamic interaction(s) between PER and phenytoin, however no food aversion was previously reported.[10,23,24] It is highly unlikely that aversion was caused by PER-induced pharmacokinetic changes of phenytoin or CLZ as PER at this dose is neither a potent inhibitor nor inducer of liver enzymes.[1] Clonazepam and PER are primarily eliminated via CYP3A4 metabolism, therefore, CLZ serum concentration could be increased due to competition for CYP3A4-iduced metabolism and thus possibly potentiate the anorectic effect of CLZ.[1] Without serum concentration data for CLZ, I cannot definitively rule this out; however, a recent study[25] demonstrated that PER administration had no significant impact on clonazepam clearance. As PER has a low hepatic extraction ratio (<0.3), and free phenytoin levels remained unchanged at PER doses of 2 mg/d and 4 mg/d (2.1 vs 2.0 mg/dL), I can rule out decreased PER albumin-binding due to phenytoin.[1,15]

It is possible that food aversion can be a complex interplay between PER and frontal lobe epilepsy, neurocircuitry changes due to partial frontal and temporal dissections, and pharmacogenomic differences in CYP3A4 and/or AMPA receptors. It can also be postulated that a 2-month delay in return to baseline appetite and eating habits after PER discontinuation could be due to its long half-life.

Conclusion

This patient experienced new-onset total food aversion 3 days after a PER dose increase to 6 mg/d. A temporal relationship was observed between dose-increase of PER and development of food aversion as well as between dose decrease and discontinuation of PER with return to normal appetite and eating habits. However, at this time, the exact mechanism(s) behind this is unknown.

References

1. Eisai Inc. FYCOMPA (perampanel) tablets, package insert [Internet]. Bethesda (MD): National Library of Medicine (US); c2018 [updated 2017 Jul; cited 2018 Jun 14]. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=71cf3309-e182-473c-8bob-280cabd0e122&type=display
2. Steinhoff BJ. Introduction: Perampanel–new mode of action and new option for patients with epilepsy. Epilepsia. 2014;55 Suppl 1:1-2. DOI: 10.1111/epi.12495. PubMed PMID: 24400689.
3. French JA, Krauss GL, Wechsler RT, Wang X-F, Diventura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. Neurology. 2015;85(11):950-7. DOI: 10.1212/WNL.0000000000001930. PubMed PMID: 26296511.
4. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79(6):589-96. DOI: 10.1212/WNL.0b013e3182635735. PubMed PMID: 22843280.
5. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54(1):117-25. DOI: 10.1111/j.1528-1167.2012.03638.x. PubMed PMID: 22905857.
6. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78(18):1408-15. DOI: 10.1212/WNL.0b013e318254473a. PubMed PMID: 22517103.
7. Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Clément J-F, et al. Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307. Epilepsia. 2014;55(7):1058-68. DOI: 10.1111/epi.12643. PubMed PMID: 24867391.
8. Cheng MY, Lim SN, Wu T. Perampanel as an adjunctive therapy in patients with frontal lobe epilepsy in Taiwan. J Neurol Sci [Internet]. 2017;381(Suppl):338-9. DOI: 10.1016/j.jns.2017.08.961.
9. Montouris G, Yang H, Williams B, Zhou S, Laurenza A, Fain R. Efficacy and safety of perampanel in patients with drug-resistant partial seizures after conversion from double-blind placebo to open-label perampanel. Epilepsy Res. 2015;114:131-40. DOI: 10.1016/j.eplepsyres.2015.04.011. PubMed PMID: 26088896.
10. Youn SE, Kim SH, Ko A, Lee SH, Lee YM, Kang H-C, et al. Adverse events during perampanel adjunctive therapy in intractable epilepsy. J Clin Neurol. 2018;14(3):296. DOI: 10.3988/jcn.2018.14.3.296. PubMed PMID: 29971974; PubMed Central PMCID: PMC6031997.
11. Logue AW. The psychology of eating and drinking. 4th ed. New York and London: Routledge; 2015.
12. Bowen DJ. Taste and food preference changes across the course of pregnancy. Appetite. 1992;19(3):233-42. DOI: 10.1016/0195-6663(92)90164-2.
13. Logue AW. Conditioned food aversion learning in humans. Ann N Y Acad Sci. 1985;443:316-29. DOI: 10.1111/j.1749-6632.1985.tb27082.x. PubMed PMID: 3860075.
14. Brodie MJ, Stephen LJ. Prospective audit with adjunctive perampanel: preliminary observations in focal epilepsy. Epilepsy Behav. 2016;54:100-3. DOI: 10.1016/j.yebeh.2015.11.002. PubMed PMID: 26700063.
15. Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. Epilepsia. 2015;56(1):12-27. DOI: 10.1111/epi.12865. PubMed PMID: 25495693.
16. Padulo C, Delli Pizzi S, Bonanni L, Edden RAE, Ferretti A, Marzoli D, et al. GABA levels in the ventromedial prefrontal cortex during the viewing of appetitive and disgusting food images. Neuroscience. 2016;333:114-22. DOI: 10.1016/j.neuroscience.2016.07.010. PubMed PMID: 27436536; PubMed Central PMCID: PMC5523136.
17. Stamatakis AM, Van Swieten M, Basiri ML, Blair GA, Kantak P, Stuber GD. Lateral hypothalamic area glutamatergic neurons and their projections to the lateral habenula regulate feeding and reward. J Neurosci. 2016;36(2):302-11. DOI: 10.1523/JNEUROSCI.1202-15.2016. PubMed PMID: 26758824; PubMed Central PMCID: PMC4710762.
18. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 2010;68(5):815-34. DOI: 10.1016/j.neuron.2010.11.022. PubMed PMID: 21144997; PubMed Central PMCID: PMC3032992.
19. Yasoshima Y, Morimoto T, Yamamoto T. Different disruptive effects on the acquisition and expression of conditioned taste aversion by blockades of amygdalar ionotropic and metabotropic glutamatergic receptor subtypes in rats. Brain Res. 2000;869(1-2):15-24. DOI: 10.1016/S0006-8993(00)02397-0. PubMed PMID: 10865054.

20. Hettes SR, Gonzaga WJ, Heyming TW, Nguyen JK, Perez S, Stanley BG. Stimulation of lateral hypothalamic AMPA receptors may induce feeding in rats. Brain Res. 2010;1346:112-20. DOI: 10.1016/j.brainres.2010.05.008. PubMed PMID: 20580634.
21. Echo JA, Lamonte N, Christian G, Znamensky V, Ackerman TF, Bodnar RJ. Excitatory amino acid receptor subtype agonists induce feeding in the nucleus accumbens shell in rats: opioid antagonist actions and interactions with μ-opioid agonists. Brain Res. 2001;921(1-2):86-97. DOI: 10.1016/S0006-8993(01)03094-3. PubMed PMID: 11720714.
22. Stratford TR, Swanson CJ, Kelley A. Specific changes in food intake elicited by blockade or activation of glutamate receptors in the nucleus accumbens shell. Behav Brain Res. 1998;93(1-2): 43-50. DOI: 10.1016/S0166-4328(97)00140-X. PubMed PMID: 9659985.
23. Chiang H-I, Lim S-N, Hsieh H-Y, Cheng M-Y, Chang C-W, Johnny Tseng W-E, et al. Preliminary Asian experience of using perampanel in clinical practice. Biomed J. 2017;40(6):347-54. DOI: 10.1016/j.bj.2017.09.003. PubMed PMID: 29433838; PubMed Central PMCID: PMC6138609.
24. Gidal BE, Ferry J, Majid O, Hussein Z. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures. Epilepsia. 2013;54(8):1490-7. DOI: 10.1111/epi.12240. PubMed PMID: 23772853.
25. Majid O, Laurenza A, Ferry J, Hussein Z. Impact of perampanel on pharmacokinetics of concomitant antiepileptics in patients with partial-onset seizures: pooled analysis of clinical trials. Br J Clin Pharmacol. 2016;82(2):422-30. DOI: 10.1111/bcp.12951. PubMed PMID: 27038098; PubMed Central PMCID: PMC4972158.