CASE REPORT

Sodium valproate: cacosmia and dysgeusia as uncommon side effects

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ABSTRACT

Smell and taste disturbances are potential adverse reactions of many drugs used in Psychiatry, such as antidepressants, anti-Parkinson agents, lithium, minor and major tranquilizers. To our knowledge, only one clinical case regarding valproate and cacosmia has been reported so far. However, several anticonvulsants are reported to cause taste and smell disturbances, although the underlying etiology is currently unclear. Our patient developed cacosmia and dysgeusia when taking valproic acid, both effects quickly disappeared upon drug discontinuation. In this article we not only report this uncommon side effect, but we discuss the plausible mechanisms behind such an adverse reaction. Our case is to date the second similar case in the literature. The aim of the present article is to make clinicians informed about this very uncommon and unpleasant side effect.

KEYWORDS: bipolar; valproate; smell; cacosmia; dysgeusia

INTRODUCTION

Drug-induced chemosensory disorders are frequent in clinical practice. Many drugs, such as diuretics, antihypertensives, myorelaxants, antihistamines, antibiotics and psychotropic agents are related to smell and taste dysfunction [1-3]. In the case of our patient, the continuous unpleasant taste and smell were installed early after valproic acid administration and resolved quickly after treatment discontinuation. Sodium valproate is an antiepileptic: valproate is a negative ion, valproic acid is its conjugate acid. It is widely used in psychiatry to treat anxiety and bipolar spectrum diseases. Many adverse drug reactions have been reported in relation with valproate use, either as monotherapy or polytherapy. Genetic factors probably influence the likelihood of adverse effects. The side effects commonly reported are: nausea, vomiting, constipation, increased appetite and weight gain, dizziness, somnolence, and tremor. Severe, but uncommon adverse reactions include hepatotoxicity, pancreatitis, hyperammonemic encephalopathy and mitochondrial toxicity [4,5]. However, valproic acid is generally well tolerated and when adverse reactions are reported they are usually mild. Most adverse effects resolve with continued therapy or when the dose is decreased. Valproate serum levels must be routinely monitored to minimize side effects and guarantee a safe use [4,5]. Reversible taste and smell dysfunction associated with sodium valproate has been previously reported in only one case report [6]. However, many psychiatric prescriptions are known to lead to chemosensory disturbances. Lithium has been associated with taste alterations, probably due to an olfactory effect. Many tranquilizers and hypnotics can also cause taste disturbances. For example, zolpidem can produce taste alteration and parosmia [1]. Tryciclicic antidepressants and serotonin reuptake inhibitors can provoke taste loss and perversion. Fluoxetine is also associated with parosmia [1,2]. Many antiepileptics are reported to induce chemosensory abnormalities: phenytoin, carbamazepine, lamotrigine, topiramate and felbamate [7-11]. Symptoms vary greatly among patients: a loss of taste and smell has been recorded with topiramate administration, while both persistent salty taste with hypersalivation and bitter taste with hyposalivation have been described in patients taking lamotrigine [8,9]. Carbamazepine has been associated with bitter phantogeusia [10]. Moreover, antipsychotics have been associated with taste and smell dysfunction. Haloperidol, olanzapine and risperidone can determine dysgeusia [1]. Olfactory capacity may decrease in patients treated with neuroleptics. A decline in olfactory capacity appears correlated with the presence and gravity of extrapyramidal symptoms [12]. The aim of our work is to raise awareness on this possible side effect, to help clinicians achieve a rapid management of such an uncommon occurrence.

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CASE REPORT

The patient was a 69-year-old woman and was diagnosed with bipolar depression. She was initially treated with paroxetine 20 mg/day, alprazolam 0.75 mg/ day and pregabalin 150 mg/ day. Pregabalin was then suspended and the patient took only paroxetine and alprazolam.

After seven years of this therapy the patient experienced a sudden worsening and a diagnosis of depressive episode with mixed features was made. She was subsequently treated by adding to the previous therapy valproic acid. Valproic acid was started at the dosage of 300 mg/ day and after one week was increased to 600 mg/ day. Two days after, the patient began to complain about vague taste disturbances and persistent and very disturbing cacosmia. She also reported a mild dyspepsia. No other symptoms were referred and routine laboratory tests were normal. We quickly ruled out psychosis because neither the patient nor her family had ever reported delusions and hallucinations. The patient was also taking a statin for high cholesterol and bisoprolol for high blood pressure. However, she had been taking these drugs for about eight years when she suddenly complained about cacosmia and dysgeusia. Valproic acid dose was quickly reduced to 300 mg/day and the patient soon reported a partial amelioration. Nonetheless those symptoms were still intolerable for the patient, so we suspended the medication. After a few days, the patient reported a full recovery from cacosmia and dysgeusia. Due to the close temporal relation and the fast improvement of the symptoms when the medication was reduced and then discontinued, no further analysis and exams were performed.

DISCUSSION

Many antiepileptics are reported to induce taste and smell disturbances. In most cases, the underlying etiology remains unknown [3]. In most cases, it remains unclear whether taste disturbances are a consequence of olfactory effect, taste effect or both. With regards to valproate, it is possible to hypothesize some potential mechanisms. One article reported ageusia following the administration of intravenous phenytoin (750 mg). The patient also had a significant increase in liver enzymes, so the medication was discontinued and the ageusia disappeared [7]. It is interesting to note that valproate can also induce an increase in liver enzymes and liver disease is a known cause for smell disturbances, so it is feasible to hypothesize this effect on the liver as a mechanism of valproate-related smell disturbances [7]. Valproate is regularly present in saliva. The concentrations in saliva were roughly 1% of those found in plasma, which could account for taste dysfunction in some patients [13]. When absorption, excretion, and tissue distribution of radioactivity of sodium valproate were examined, a small amount was excreted in the exhaled air. This may result in smell disturbances [14]. Taste in the mouth is mediated by sodium channels receptors. Since valproate is well known for blocking sodium channels, it is conceivable that it also influences the taste receptors [1,15]. A similar mechanism has been proposed for amitriptyline-induced taste disturbances [1]. Drug-related dysgeusia has been associated to low zinc levels in various studies [3]. Antithyroid drugs such as thiamazole and carbimazole lower zinc level and are often associated with subtle taste disturbances. It has been reported that treatment with zinc resulted in restoring of normal taste capacity The patient had previously experienced some taste disturbances after taking carbimazole [3,16]. Taste alteration induced by of penicillamine treatment were corrected by zinc administration [17]. Valproate seems responsible for causing decreased zinc serum levels, both in animals and humans [18,19]. It is then possible to postulate that valproate may affect taste by interfering with zinc absorption and metabolism [3]. Many anticonvulsants, such as carbamazepine and oxcarbamazepine, can provoke SIADH (syndrome of inappropriate antidiuretic hormone secretion), thus inducing hyponatremia, especially in the elderly. Hyponatremia has been reported to trigger dysgeusia. Valproate-induced hyponatremia has been described. Thus, it may be an additional mechanism [1]. Taste disturbances are a very common oral side effect, they were reported in a third of subjects (33%) in a community-based sample [20]. It is advisable to achieve a rapid management of such an uncommon occurrence since the longer this side effect was left untreated the longer it took to have a full recovery, sometimes requiring a period of 6 to 9 months [10,11]. It should also be considered that in many cases patients become aware of smell dysfunction only when it becomes more severe [1]. The probability of developing such a side effect seems higher when polypharmacy is present and the concurrent use of many medications is currently the norm in elderly patients. In fact, older adults are more prone to develop taste disturbances [1,3,6].

CONCLUSIONS

Our patient developed cacosmia and taste abnormalities shortly after starting valproate treatment. To our knowledge only one similar case was reported in clinical practice. The strong temporal relation between the side effects and medication introduction and discontinuation are strongly suggestive. The existence of a relation between valproate and dysgeusia and cacosmia is supported by the presence of several possible mechanisms and other reports of similar adverse effects with many antiepileptics. This uncommon side effect of sodium valproate should be kept in mind by clinicians to achieve a prompt management of similar cases, especially when older populations are involved.

Conflict of interest

The authors declare that they have no competing interests.

Consent for publication

Written informed consent from the patient has been obtained and is available for review by Editor in chief of the journal.

REFERENCES

1. Doty RL, Shah M, Bromley SM. Drug-induced taste disorders. *Drug Saf*. 2008;31(3):199-215. PMID: 18302445. doi: 10.2165/00002018-200831030-00002.
2. Naik BS, Shetty N, Maben EV. Drug-induced taste disorders. *Eur J Intern Med*. 2010;21(3):240-243. PMID: 20493431. doi: 10.1016/j.ejim.2010.01.017.
3. Tomita H, Yoshikawa T. Drug-related taste disturbances. *Acta Otolaryngol Suppl*. 2002;(546):116-121. PMID: 12132608. doi: 10.1080/00016480260046490.
4. Kishi T, Ikuta T, Matsuda Y, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Mol Psychiatry*. 2022;27(2):1136-1144. PMID: 34642461; PMCID: PMC9054678. doi: 10.1038/s41380-021-01334-4.
5. Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem*. 2013;46(15):1323-1338. PMID: 23792104. doi: 10.1016/j.clinbiochem.2013.06.012.
6. Alvarez P, Papaseit E, Pérez V, et al. Reversible taste and smell dysfunction associated with sodium valproate and quetiapine in

bipolar depression: a case report. *Actas Esp Psiquiatr*. 2019;47(1): 33-36. PMID: 30724329.
7. Baumann CR, Ott PM, Siegel AM. Hypogeusia as an adverse reaction of phenytoin. *Br J Clin Pharmacol*. 2004;58(6):678-679. PMID: 15563368; PMCID: PMC1884645. doi: 10.1111/j.1365-2125.2004.02217.x.
8. Avoni P, Contin M, Riva R, et al. Dysgeusia in epileptic patients treated with lamotrigine: report of three cases. *Neurology*. 2001; 57(8):1521. PMID: 11673609. doi: 10.1212/WNL.57.8.1521.
9. Ghanizadeh A. Loss of taste and smell during treatment with topiramate. *Eat Weight Disord*. 2009;14(2-3):e137-e138. PMID: 19934627. doi: 10.1007/BF03327811.
10. Rollin H. Drug-related gustatory disorders. *Ann Otol Rhinol Laryngol*. 1978;87(1 Pt 1):37-42. PMID: 623418. doi: 10.1177/000348947808700108.
11. Sachdeo R, Kramer LD, Rosenberg A, et al. Felbamate monotherapy: controlled trial in patients with partial onset seizures. *Ann Neurol*. 1992;32(3):386-392. PMID: 1416808. doi: 10.1002/ana.410320313.
12. Thiermann F, Buchbauer G. Influence of drugs on smelling capacity. A review. *Flavour Fragr J*. 2017; 32:147–158. doi: 10.1002/ffj.3368.
13. Abbott FS, Burton R, Orr J, et al. Valproic acid analysis in saliva and serum using selected ion monitoring (electron ionization) of the tert.-butyldimethylsilyl derivatives. *J Chromatogr*. 1982;227(2):433-444. PMID: 6801067. doi: 10.1016/S0378-4347(00)80396-5.
14. Bertolino M, Acerbi D, Canali S, et al. 14C-NaVP and 14C-PEV repeated dose study in rat. Pharmacokinetic study in rats after repeated oral administrations of 14C-valproic acid sodium salt and 14C-valproic acid pivaloyl oxymethyl ester. *Eur J Drug Metab Pharmacokinet*. 1998;23(2):223-229. PMID: 9725486. doi: 10.1007/BF03189344.
15. Gao N, Lu M, Echeverri F, et al. Voltage-gated sodium channels in taste bud cells. *BMC Neurosci*. 2009;10:20. PMID: 19284629; PMCID: PMC2660338. doi: 10.1186/1471-2202-10-20.
16. Erikssen J, Seegaard E, Naess K. Letter: Side-effect of thiocarbamides. *Lancet*. 1975;1(7900):231-232. PMID: 47475. doi: 10.1016/S0140-6736(75)91417-8.
17. Henkin RI, Bradley DF. Hypogeusia corrected by Ni++ and Zn++. *Life Sci II*. 1970;9(12):701-709. PMID: 5478084. doi: 10.1016/0024-3205(70)90278-X.
18. Korkmazer N, Vurucu S, Demirkaya E, et al. Serum and liver tissue biotinidase enzyme activity in rats which were administrated to valproic acid. *Brain Dev*. 2006;28(8):515-520. PMID: 16682156. doi: 10.1016/j.braindev.2006.03.003.
19. Yilmaz Y, Tasdemir HA, Paksu MS. The influence of valproic acid treatment on hair and serum zinc levels and serum biotinidase activity. *Eur J Paediatr Neurol*. 2009;13(5):439-443. PMID: 18922714. doi: 10.1016/j.ejpn.2008.08.007.
20. Shinkai RS, Hatch JP, Schmidt CB, et al. Exposure to the oral side effects of medication in a community-based sample. *Spec Care Dentist*. 2006;26(3):116-120. PMID: 16774189. doi: 10.1111/j.1754-4505.2006.tb01434.x.