

Stomatitis Associated With Olanzapine and Sodium Valproate Combination Treatment

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Abstract

The purpose of this article is to draw attention towards possibility of drug reaction while starting a combination of sodium valproate and olanzapine for the treatment of acute mania. We describe four cases (three with bipolar disorder, current episode manic, one schizoaffective disorder, bipolar type), who developed stomatitis and pharyngitis within first week while on sodium valproate and olanzapine combination. In three out of four cases the symptoms resolved after withdrawing olanzapine and instituting symptomatic treatment (German J Psychiatry 2005; 8, 27–28).

Keywords: Olanzapine, sodium valproate, stomatitis, interaction

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Introduction

Bipolar disorder affects approximately 1 % of the population. Several drugs like lithium, antipsychotics, antiepileptics and benzodiazepines have been used to control acute manic symptoms. Both divalproex (Bowden et al., 1994) and olanzapine (Tohen et al., 1999; Tohen et al., 2000) have demonstrated acute antimanic efficacy in placebo-controlled, parallel-group trials. Sodium valproate and olanzapine combination is frequently being used in treatment of acute manic episodes. Although rare, stomatitis has been described previously with sodium valproate (Russo, 1981; Ryan et al., 2002) and olanzapine (Abdollahi and Radfar, 2003) therapy, in addition to other types of oral drug reactions. Pathogenesis of drug reactions could be related to either immunologic or non-immunologic mechanism. Most adverse reactions to drugs are mediated by immune system are drug allergies.

Case reports

We describe four cases (3 with bipolar disorder, currently manic episode, 1 schizoaffective disorder, bipolar type), who developed stomatitis and pharyngitis within first week

while on sodium valproate and olanzapine combination. All the cases had detailed oral examination and were referred to otolaryngology department for opinion. This is the first report of such unusual adverse effect of such combination therapy.

Case 1: Mr. A, a 32 year old married male, diagnosed as having bipolar affective disorder, current episode mania with psychotic features, and was prescribed tab divalproex 1000 mg/day, tab olanzapine 15 mg/day and tab lorazepam 2 mg/day. On the fourth day he developed reddish discoloration of buccal cavity, tongue, oropharynx; difficulty in swallowing and speaking. Olanzapine was withdrawn and cap amoxicillin and cloxacillin 500 mg tid, multivitamin capsules and H₂O₂ mouthwash was advised. No improvement was observed after 15 days after which patient was lost at follow up.

Case 2: Mr. B, a 38 year old married male, having diagnosed bipolar affective disorder, current episode mania with psychotic features, was prescribed tab divalproex 1500 mg/day, tab olanzapine 15 mg/day and tab lorazepam 2 mg/day. He developed reddish discoloration of buccal cavity, tongue, oropharynx; difficulty in swallowing, chewing and speaking; soreness and thickening of tongue on 3rd day of starting treatment. Olanzapine was withdrawn and he was prescribed tab co-amoxiclav 625 mg tid and tab nimesulide 100 mg bid, following which there was complete disappearance of symptoms after 7 days.

Case 3: Ms. C, an 18 year old unmarried female, who developed first episode mania was prescribed tab divalproex 1000 mg/day and tab olanzapine 10 mg/day. On third day she developed reddish discoloration of tongue, palate, oropharynx; difficulty in swallowing, chewing and speaking. Olanzapine was withdrawn on third day and substituted with risperidone, divalproex was replaced with lithium on fifth day, betadine mouthwash was advised along with local glycerine application. There was complete disappearance of all symptoms after 5 days.

Case 4: Mrs. D, a 45 year old married female, diagnosed as having schizoaffective disorder, bipolar type was prescribed tab divalproex 1000 mg/day, tab olanzapine 15 mg/day. She developed reddish discoloration of tongue and palate; difficulty in swallowing, chewing and speaking; thickening sensation of tongue on third day of treatment. Olanzapine was withdrawn and there was complete disappearance of all symptoms after 3 days.

Discussion

All of the cases developed symptoms after 3-4 days after starting divalproex and olanzapine combination. In 3 cases the symptoms subsided completely after withdrawing olanzapine and symptomatic treatment. Readministration of the offending drug helps to establish the etiology. In our cases rechallenge was not possible as the reactions were severe and patients did not give consent for it.

Ryan et al. (2002) reported a case of severe stomatitis in a 5-year-old child with pediatric epilepsy 18 months after institution of divalproex sodium, and cessation of the medication was associated with resolution of the stomatitis over 2 weeks.

Russo (1981) had reported 2 cases of late onset of stomatitis which resolved after 3 days of discontinuation of sodium valproate. One patient developed erythematous tongue within 1 month of valproic acid therapy initiation, and the second patient developed vesicular lesions over tongue and gingival after 3 months of divalproex sodium therapy. One of them was rechallenged and stomatitis recurred.

Apthous stomatitis, glossitis and oral ulceration have been described with olanzapine (Abdollahi and Radfar, 2003). In apthous stomatitis lesions appear as small, painful, discrete or grouped papules, vesicles which may ulcerate. They appear predominantly over labial or buccal mucosa, and heal without scarring in 10-14 days. Glossitis is inflamma-

tion of tongue which is characterized by swelling, redness and intense pain. Sodium valproate has the potential to cause gingival hyperplasia (Abdollahi and Radfar, 2003). The growth starts as painless, beadlike enlargement of interdental papilla and extends to the facial and lingual gingival margin. Later it usually becomes generalized throughout the mouth but is more severe in the maxillary and mandibular anterior region.

The etiology of medication-induced stomatitis is unclear. It can be caused by direct mucosal contact with medication (contact stomatitis), but this seems unlikely as patients gave no history of keeping the medications for a long time in mouth. The reaction could be a systemic allergic reaction of the combination therapy. No significant pharmacokinetic interaction has been reported between sodium valproate and olanzapine.

The diagnosis of drug reaction requires high index of suspicion and careful history taking. Most of the drug reactions occur during the first 1-2 weeks of starting treatment, and reactions seen after 2 weeks are less likely to be due to medication use. Unusual drug reaction as described seen within first week of starting combination therapy with olanzapine and valproate warrants monitoring of patients for such adverse event. Early withdrawal of the offending drugs would enhance treatment compliance.

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