Reversible taste and smell dysfunction associated with sodium valproate and quetiapine in bipolar depression: a case report

Pilar Alvarez, PhD[1,2]
Esther Papaseit, PhD[3,4]
Víctor Pérez, PhD[1,2,4,5]
Antoni Bulbena, PhD[1,2,4]
Magí Farré, PhD[3,4]

[1]Hospital del Mar, Departamento de Psiquiatría. Barcelona, España
[2]IMIM (Institut Hospital del Mar d'Investigacions Mèdiques). Barcelona, España
[3]Hospital Universitari Germans Trias i Pujol-IGTP, Unidad de Farmacología Clínica. Badalona, España
[4]Universidad Autonóma de Barcelona (UAB). Barcelona, España
[5]CIBERSAM

Correspondence:
Pilar Álvarez
Hospital del Mar
Paseo Marítimo de la Barceloneta 25-29,
08003 Barcelona (Spain)
Tel.: 652443247
Fax: 93 2483254
E-mail: 94854@parcdesalutmar.cat

Dear Editor,

Drugs are the second most common cause of taste disturbances[1]. The most involved psychotropic drugs are antidepressants, anticonvulsants and lithium[2-7].

Valproate (2-propylpentanoate, valproic acid) is a broad-spectrum antiepileptic drug, mainly used in neurology in the treatment of generalized or partial epilepsies[8] and in the prophylaxis of migraine[9], and in psychiatry, especially in the maintenance treatment of bipolar disorder[10].

The most frequent adverse effects associated with valproate include gastrointestinal symptoms (nausea, vomiting, asthenia, abdominal pain and dyspepsia), somnolence, sedation, dizziness, tremor and rash[11,12]. These effects are usually mild, more common with higher doses and often resolve with continued treatment or after a reduction in dose.

Taste disorders have been described in less than 1% of patients treated with delayed-release divalproex sodium in controlled studies in bipolar disorder, manic episode[13], with a higher incidence than placebo. However, the review of the literature has not shown any case described in the usual clinical practice in patients with bipolar disorder.

Valproate tablets absorption starts immediately after administration with a half-life elimination of 8-20 hours. The protein binding level is dose-dependent (80-90%) and its metabolism is largely hepatic via glucoronide conjugation and mitochondrial ÿ-oxidation. Excretion of valproate or its metabolites into saliva can alter the chemical composition or flow rate of saliva and generate an unpleasant taste[14]. Moreover, it is probably excreted in expired air[15], which could contribute to the smell dysfunction.

Quetiapine, a dibenxothiazepine atypical antipsychotic, was originally approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia and, more recently, has been indicated for the acute treatment of manic episodes, both in monotherapy and in combination with lithium or divalproex sodium. Taste disorders are described as an infrequent adverse reaction in controlled clinical trials, ranging from 1/100 to 1/1000 patients treated with quetiapine[16]. Furthermore, dysgeusia is included among the adverse reactions occurring in 1% or more of the patients treated with quetiapine (doses of 300 and 600 mg/day) for bipolar depression during up to 8 weeks[16]. A wide revision of the scientific literature on smell and taste dysfunction among patients treated with valproate sodium and/or quetiapine has not shown similar reports in clinical practice.

Case report

We present the case of a 47-year-old male patient admitted to the acute psychiatric unit due to bipolar depression.

Diagnosed with bipolar disorder at age 27, he had required eleven previous admissions for manic episodes with psychotic symptoms (delusional ideas) and Day Hospital care for depression. Former treatments included quetiapine, lithium (levels in therapeutic range before most admissions) and electroconvulsive therapy (ECT). No other medical or psychiatric disordes were recorded and there was no active use of illicit drugs.

The patient was rehospitalized nine days after discharge from a moderate manic episode. Treatment at admission was quetiapine 500 mg/day and lithium carbonate 1000 mg/day. The family told of a sudden worsening characterized by memory deficits, repetitive movements, behavioural disturbances, insomnia and incoherent speech.

On examination he was alert and oriented, noncooperative, with mild psychomotor agitation and lack of eye contact. He presented low mood, sparse speech, short answers and periods of mutism that prevented an adequate psychopathological examination and expressed catastrophic delusional ideas.

Vital signs and physical examination were normal. Routine laboratory test, thyroid-stimulating hormone and T4 function and a 12-lead electrocardiogram were also normal. Serum lithium level was 0.24 mmol/l (therapeutic range 0.4-1.0 mmol/l). Urine toxicologic screening for common drugs of abuse was negative.

The patient was hospitalized with a suspected diagnosis of bipolar depression with psychotic symtoms. Given the severity and the previous good response to ECT, ECT was started in association with quetiapine tablets (maximum dose: 1100 mg/day). ECT was stopped after 12 sessions because informed consent was withdrawn by the patient after parcial symptomatic remission was achieved (full remission of the behavioural disturbances, psychomotor retardation and psychotic symptoms). As low mood, apathy, isolation and negative cognitions persisted, quetiapine dosage was progressively decreased to 300 mg/day. Given the high recurrence rate in spite of therapeutic lithium levels before most of the episodes, valproate sodium was started, being both a first-line option for maintenance treatment of bipolar disorder[10] and effective and well tolerated in bipolar depression[17].

Fourteen days after starting valproate and two days after increasing the dose (from 700 to 1000 mg/day) the patient complained of a continuous bad taste and smell, compatible with dysgeusia and cacosmia, that reminded him of the taste of valproate pills. The only concomitant treatment was quetiapine 300 mg/day.

A thorough head and neck examination ruled out any obstruction or inflammation. No other symptoms or signs were present. Plasma level for valproate was 64 µg/ml (therapeutic range 50 to 100 µg/ml). Lithium had been stopped 44 days before and plasma concentration levels were undetectable. Three days after the symptoms started, valproic dosage was reduced to 500 mg/day due to side-effect intolerance. Three days later, a marked improvement in taste and smell dysfunction was achieved, with full remission two days afterwards. Because of the quick symptomatic remission, complementary explorations like psychophysical test for odour/taste threshold or identification were not performed.

A drug-induced disorder was suspected given the absence of hallucinations in previous decompensations, the appearance of taste and smell dysfunction after symptomatic improvement and after the remission of the psychotic symptoms that were present at admission and, especially, given the close temporal relationship between the occurrence of dysgeusia and cacosmia and the increase in the dose of valproate and their remission after the reduction of the dose of valproate.

The Naranjo algorithm[18] was used to determine the causality relationship between the adverse effects and valproate treatment. A score of 6 was obtained, pointing to a probable adverse drug reaction.

To our knowledge, this is the first case-report describing taste and smell dysfunction associated to valproate and quetiapine treatment. The patient was treated with a fixed dose of quetiapine before starting treatment with valproate, which suggests a probable adverse reaction to valproate. We consider that the narrow therapeutic range of valproate, its hepatic metabolism, salivary excretion, oral administration and the close temporal relationship justify the causality relationship between this drug and the observed adverse effects.

In conclusion, taste and smell dysfunction induced by valproate (even within therapeutic serum levels) should be considered in light of this case-report. Concomitant treatment with drugs potentially involved in sense dysfunction (quetiapine in this case) may be a risk factor for experiencing taste and smell disturbances as a side effects of valproate. These side effects seem to be dose-dependent and may respond to a reduction in dose, drug discontinuation or switching to another drug. Clinicians should take into account valproate-induced taste and smell dysfunction as they could interfere with well-being, quality of life and treatment compliance.

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Intravenous perfusion of tiapride in a case of treatment-resistant delirium

Cecilia Calero-Mora[1]
Paloma Cano-Ruiz[2]
Alicia Gómez-Peinado[1]

[1]Facultativo especialista en Psiquiatría. Hospital General de Villarrobledo
[2]Facultativo especialista en Psiquiatría. Hospital General de Almansa

Correspondence:
Cecilia Calero Mora
E-mail: cecilya87@gmail.com

Dear Editor,

Delirium is an organic mental syndrome characterized by brain dysfunction and disorganized neuronal activity. It is usually related to alterations in perception, the state of consciousness, and disorganization of thought; it can be divided into: (a) hyperactive, when the predominant clinical sign is agitation, hyperactivity and excessive response or alert to external stimuli; (b) hypoactive, if there is a predominance of lack of response to stimuli; (c) mixed, when there is an alternation between agitation and lethargy[1]. The pathology appears due to a mixture of both predisposing and precipitating factors, including intracranial alterations such as tumor lesions, injuries caused by trauma, stroke, abscess, vasculitis, encephalopathy, embolism or acute demyelination. Between 3 and 48% of patients with delirium present intracranial pathology in imaging tests[2].

Delirium has been associated with an increase in mechanical ventilation time and hospital stay, with greater cognitive damage and higher mortality rates[3], so an optimized and individualized treatment would benefit their recovery and could reduce the sequelae and complications.

Presentation of the case

We present the case of a 33-year-old man admitted to the intensive care unit (ICU) with a diagnosis of multiple trauma after suffering a traffic accident. He is initially intubated and sedated by propofol and remifentanil. During his stay in the ICU, the electroencephalogram showed an epileptic status with bilateral expression and suggestive of anterior focal origin, which ceases subsequently at the beginning of treatment with levetiracetam and pheitonia; after that, sedoanalgesia was modified by midazolam and fentanyl. In subsequent electroencephalograms, no epileptogenic activity was observed, but there were signs of diffuse encephalopathy. In an initially cranial CT scan, a right and bifrontal posterior subgaleal hematoma with minimal blood content in the occipital horns of both lateral ventricles was observed, but without signs of fracture or involvement of the brain parenchyma.

After ten days in ICU, sedation starts to be withdrawn, appearing an agitation/hyperactive delirium with very poor pharmacological control. Suspecting that the bad evolution of the agitation was caused by a diffuse axonal lesion, a cranial magnetic resonance was done, discarding this pathology, but finding that there was a left frontal cortical retraction that associates adjacent subdural hydroma and remnants of chronic bleeding in medial areas of the right temporal and interventricular lobes (Figure 1).

In ICU, they try to control the agitation through multiple pharmacological treatments such as benzodiazepines (diazepam, chloracepate), antipsychotics both typical and

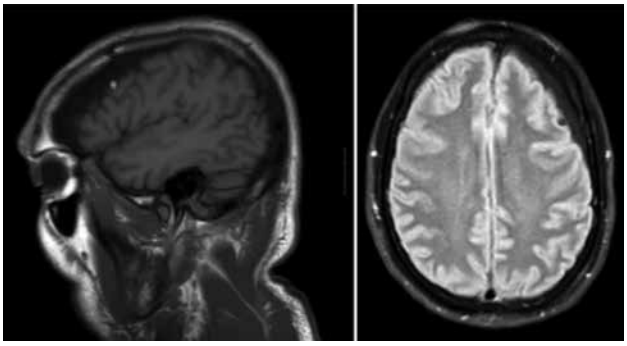

Figure 1 — *MRI images showing a left frontal cortical retraction, associated with adjacent subdural hydroma*

atypical (haloperidol, levomepromazine, risperidone, tiapride) and others (dexmedetomidine, clonidine), requiring mechanical containment in order to prevent injury, and responding only with sedation.

Due to the handling difficulties that the patient presented, they decided to request an assessment from the Psychiatric Interconsultation Service. After collecting information from the relatives, the patient had no history of disease, neither at somatic or psychiatric level, and there was no family medical history either. In the psychopathological exploration, the patient is conscious but without clear response to stimuli or connection with the environment. Although the patient impresses of occasional gaze fixation, he presents agitation with a predominance of continuous movements of doubtful purpose, which fluctuate throughout the day. At the time when we went to assess the patient, the scheduled treatment consisted of: intravenous tiapride 100 mg/6 hours, risperidone 2 mg/12 hours by nasogastric tube (SNG), sertraline 50 mg/24 hours for SNG and diazepam 5mg if needed also by SNG. We decided to start a continuous infusion of tiapride 600 mg in 500 mL of physiological serum at 21 mL/hour, with the addition, if required, of 2.5mg of intravenous haloperidol every 6 or 8 hours. We removed the rest of the medication, except propofol, which we indicated should only be administered during the night.

After 48 hours of this treatment adjustment, the patient is much calmer, is able to connect with the environment, recognizes their relatives and does not need mechanical restraint. During this time, he only required propofol during the night to facilitate rest and one haloperidol administration every 24 hours.

After 72 hours of our adjustment, the patient is focused, calm and cooperative with his care; he begins to tolerate oral diet and is able to sit down and respond to simple orders. He does not require treatment with propofol or other similar drugs and does not require haloperidol either.

Discussion

Antipsychotics are the mainstay of the treatment of delirium, except for the one that is produced by an abstinence of alcohol or benzodiazepines. Haloperidol is the most frequently used drug. Recent studies have compared the role of other antipsychotics, both typical and atypical, in the management of this pathology[4].

Tiapride is an atypical antipsychotic belonging to the family of benzamides. At the receptor level, it is a neuroleptic with selectivity for the D2 and D3 dopaminergic receptors, lacking any affinity for the receptors of the main central neurotransmitters (including serotonin, noradrenaline or histamine). The drug's technical data shows that the elimination half-life, both orally and intramuscularly, is 3-5 hours in healthy young volunteers, and that one of its most frequent indications is the treatment of behavior disorders in adults (demented patients or in alcoholic detoxification)[5].

The short half-life of the drug leads us to believe that its dispensation as a continuous perfusion may favor a better and more stable plasma concentration of the drug, with some studies stating that it is a safe administration and that the drug maintains its stability, both physical and chemical, for 48 hours when dissolved in solutions of 0.9% physiological saline or 5% glucoside[6]. Given these findings, and the good evolution of our case, we consider that it should be a drug to be taken into account for the treatment of delirium.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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