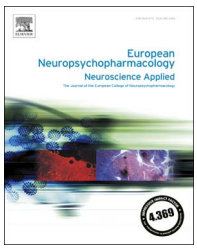
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



A study on the bioequivalence of lithium and valproate salivary and blood levels in the treatment of bipolar disorder

A. Murru[a], M. Torra[b], A. Callari[c], I. Pacchiarotti[a], S. Romero[d], B. Gonzalez de la Presa[e], C. Varo[a], J.M. Goikolea[a], V. Pérez-Sola[f], E. Vieta[a], F. Colom[f,*]

[a]*Bipolar Disorders Unit, Institute of Neuroscience, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, Villarroel 170, Barcelona 08036, Catalonia, Spain*
[b]*Pharmacology and Toxicology, Biomedical Diagnosis Department, Hospital Clínic, University of Barcelona, IDIBAPS, Villarroel 170, Barcelona 08036, Catalonia, Spain*
[c]*Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, Lungarno Pacinotti 44, I-56126 Pisa, Italy*
[d]*Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, CIBERSAM, Hospital Clínic of Barcelona, Villarroel 170, Barcelona 08036, Catalonia, Spain*
[e]*CORE Laboratory – Centre de Diagnòstic Biomédic Hospital Clinic, IDIBAPS, Villarroel 170, Barcelona 08036, Catalonia, Spain*
[f]*Mental Health Group, IMIM Hospital del Mar, CIBERSAM, Plaza Charles Darwin, sn, 08003 Barcelona, Catalonia, Spain*

Received 7 February 2017; received in revised form 11 May 2017; accepted 10 June 2017

KEYWORDS
Lithium;
Valproate;
Salivary;
Bioequivalence;
Bipolar disorders;
Serum levels

Abstract
Lithium (Li) and valproate (VPA) are used in the treatment of bipolar disorder (BD), with narrow therapeutic window requiring periodic control of serum levels. This prevents intoxication, lack of efficacy due to low serum concentrations, and allows monitoring adherence. We aimed at evaluating the bioequivalence of salivary and blood levels of LI or VPA in a sample of adult BD patients. Secondarily, lithium bioequivalence was evaluated across different patients' life-spans. BD patients treated with either Li or VPA underwent contemporary standard serum and salivary measurements. Blood levels of both drugs were taken according to standard procedures. Li salivary levels were performed by an adapted potentiometric method on the AVL9180 electrolyte analyzer. VPA salivary levels were taken with an immune-assay method with turbidimetric inhibition. A total of 50 patients (38 on Li, 12 on VPA) were enrolled. Blood-saliva bioequivalence for VPA was not found due to a high variability in salivary measures. Li measures resulted in a high correlation ($r=0.767$, $p<0.001$), showing no partial correlation

*Corresponding author. Fax: +34 933160410.
E-mail address: fcolom@imim.es (F. Colom).

http://dx.doi.org/10.1016/j.euroneuro.2017.06.003

Please cite this article as: Murru, A., et al., A study on the bioequivalence of lithium and valproate salivary and blood levels in the treatment of bipolar disorder. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.06.003

with age (r=0.147, p=0.380). Li salivary test is a reliable method of measuring Li availability and is equivalent to serum levels. Potential advantages of Li salivary testing are its non-invasive nature and the possibility of doing the test during the usual appointment with the psychiatrist.

1. Introduction

Bipolar Disorder (BD) is a highly prevalent and chronic condition, with high risk of relapses into acute episodes within 5 years (Keller et al., 1993; Merikangas et al., 2011). For this reason, an appropriate long-term treatment with mood stabilizers aimed at preventing recurrences is necessary (Grande et al., 2015).

In the last twenty years several drugs for the treatment of acute phases and for the prevention of relapses in BD have been introduced (Carvalho et al., 2015). Along with newer agents, "classical" mood stabilizers such as lithium (Li) and valproate (VPA) are still widely used, alone or in combination, in the long term treatment of BD (Samalin et al., 2016). Lithium still represents a cornerstone in the treatment of BD, and the long clinical experience associated with the use of this drug makes it a relatively safe tool to prevent recurrences of BD (Geddes and Miklowitz, 2013; Nivoli et al., 2010). Valproate is also considered by most clinical guidelines as a first-line option in the maintenance phase, although some concerns on tolerability have been raised (Murru et al., 2015; Yatham et al., 2013). As both lithium and valproate have a relatively narrow therapeutic window, therapeutic ranges need to be routinely checked. Blood sampling and subsequent measuring -generally twice a year- are the methods used to check for Li and VPA levels in everyday clinical practice (NICE, 2014).

Unfortunately, Li has a high discontinuation rate, with an average time of adherence as short as 76 days at 6-year follow-up (Johnson and McFarland, 1996). To date there are no similar data for VPA. Poor adherence is a common issue in BD patients, with rates of 20–40% (Colom et al., 2000; Murru et al., 2013; Sajatovic et al., 2009) in euthymic patients, and up to 40–64% among acute manic patients (Keck et al., 1997; Montoya et al., 2007). Poorly adherent BD patients suffer from greater chronicity, worse functioning, an increased number of visits to emergency units and increased and longer acute admissions, with subsequent higher health expenses (Gianfrancesco et al., 2008; Lew et al., 2006). The risk of poor adherence has been documented in BD patients within the first weeks after initiating or changing treatment due to a manic or mixed relapse (González-Pinto et al., 2010). This is a delicate moment, in which poor illness awareness and need for effective treatment should lead clinicians to require a frequent monitoring of mood stabilizers in order to assess therapeutic blood levels, reduce risks of toxicity as well as ensuring treatment adherence.

The literature on the subject of salivary measures of drugs in patient populations affected by BD is almost nonexistent. Saliva was initially investigated as an alternative fluid for therapeutic monitoring of some anticonvulsants in the late 1970s until recent years on epileptic samples (Danhof and Breimer; Mucklow et al., 1981; Patsalos and Berry, 2013; Tonic-Ribarska et al., 2012), showing a low correlation for salivary/serum valproate levels (al Za'abi et al., 2003). On the other hand, the use of Li salivary monitoring instead of serum dosages has been deemed possible, but high interpersonal variability was reported, so that its possible use in clinical practice was questioned (Moody, 1999; Spencer et al., 1990). Recently, the feasibility of measuring salivary concentration of Li in 50 BD patients was tested, and results did not allow for supporting saliva monitoring as a substitute of serum Li estimation (Shetty et al., 2012). Also, it is commonly known that interpersonal variability in drug volumes of distribution get increased as people get older (Mangoni and Jackson, 2004).

The aim of the present study was to evaluate the bioequivalence of salivary and blood levels of Li and VPA in a sample of adult BD patients. Secondarily, Li bioequivalence in saliva and serum was evaluated across different patients' lifespans.

2. Experimental procedures

2.1. Subjects and study design

A study on the correlation between serum and salivary levels of lithium and valproate was performed in a group of BD patients who attend the Bipolar Disorder Unit of the Hospital Clínic of Barcelona.

Inclusion criteria were: 1. A diagnosis of BD, type I, II or NOS (American Psychiatric Association, 2000). 2. Age between 10 and 80 years old. 3. Being on maintenance treatment, in mono- or polytherapy, with lithium or valproate, and stable on treatment with Li or VPA for at least 4 weeks. 4. Not with signs, symptoms or actual history suggesting ongoing dehydration. 5. Renal function within normal limits. 6. Written informed consent provided. Exclusion criteria referred to factors possibly modulating volume distribution or excretion of the studied drugs: 1. Factors affecting normal salivary secretion (active oral infections, occasional or chronic xerostomia). 2. Alcohol consumption. 3. Pregnancy. 4. Drugs affecting Li/VPA pharmacokinetics such as those significantly affecting extracellular water or kidney function. 5. Concurrent urinary tract infection.

As a secondary objective of the study was to evaluate the effect of age in saliva-blood lithium concentrations, we recruited 5 patients aged under 18.

2.2. Procedure

A single visit for each patient was scheduled, in which salivary and blood sample were taken. Patients were asked to fast since the night before. All extractions were performed by a nurse. Serum levels were extracted by standard procedure. Saliva was collected by chewing parafilm wax for 1 min before spitting into tubes (Salivette ® SARSTEDT). After centrifugation, the saliva samples were stored in a freezer (−20 °C) before analysis at the Centre de Diagnòstic Biomédic, Hospital Clinic Barcelona.

Please cite this article as: Murru, A., et al., A study on the bioequivalence of lithium and valproate salivary and blood levels in the treatment of bipolar disorder. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.06.003