

Itching Skin Rash during Valproic Acid Therapy in Co-Administration with Silodosin: a Case Report and Review of Literature

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Abstract

Valproic acid (VA) is an antiepileptic drug commonly used in psychiatric setting as mood stabilizer. It is generally well-tolerated but, because of its pharmacodynamic properties, it may cause different adverse drug reactions, especially when it is co-administrated with other drugs.

Here we report the case of a 65 year old man with a Bipolar Disorder type I, according to DSM V, hospitalized for a depressive relapse and treated with Valproic Acid 300 mg/day, Lorazepam 2.5 mg/day, and Elopam 40 mg/ml intravenous daily infusions. When, one week after admission, Silodosin 8 mg/day was added for the management of Benign Prostatic Hyperplasia (BPH) symptoms, he developed an extensive pruritic and purpuric skin rash on his lower legs that subsided after valproic acid discontinuation and therapy with intravenous fluids and oral antihistamines. Therefore, valproic acid was replaced with Pregabalin, which was well tolerated by the patient who recovered quickly.

Our clinical experience and the pharmacologic mechanisms underlying the onset of this adverse drug reaction are discussed in detail. Since valproic acid inhibits the uridin-glucuronyl transferase-2B7 (UGT2B7) enzyme that is involved in the metabolism of silodosin, a likely interaction between valproic acid and silodosin elimination pathway has been considered as a possible precipitating factor in our case. The goal of this case report is to draw clinicians' attention on the significant risk of pharmacokinetic interaction in patients undergoing multiple treatments for different diseases.

Keywords: Valproic acid; Pharmacodynamic; Silodosine; Itching; Skin rash

Abbreviations

VA: Valproic Acid; AED: Antiepileptic Drugs; ADRs: Adverse Drug Reactions; LUTS: Low Urinary Tract Symptoms; BPH: Benign Prostatic Hyperplasia; UGT: Uridin-glucuronyltransferases; SSRI: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic antidepressants; LMT: Lamotrigine; CYP: Cytochrome P.

Introduction

Valproic Acid (VA) is a simple eight-carbon branched-chain fatty acid belonging to the category of the non-aromatic Antiepileptic Drugs (AED) able to reduce neuronal excitability by different mechanisms of action [1]. VA is largely used in the neurological setting as an anticonvulsant, and in psychiatry for the management of patients with dementia-related agitation, social anxiety, schizoaffective disorder and bipolar disorder [2]. It is very effective in controlling manic episodes occurring in bipolar disorder. Furthermore, it can be used for the prevention of either manic or depressive episodes relapse [3].

VA has good efficacy and low cost, as well as a relatively favourable safety profile. Cutaneous Adverse Drug Reactions (ADRs) have been reported with its use [4], and include, among others, Stevens-Johnson

syndrome [5], toxic necrolytic erythema [6], and leukocytoclastic vasculitis [7]. Overall, the cutaneous ADRs related to valproic acid are considered less common compared to other antiepileptic drugs. However, when VA is prescribed in poli-pharmacotherapy there is a high chance of pharmacological interactions, mainly due to its ability to inhibit key liver enzymes and to the complexity of its degradation pathways that make interactions with other drugs very likely [8].

Many of these interactions are widely known by clinicians and taken into account when a new treatment is added in patients taking VA. However, there are many other drugs interactions that are less well known and that can lead to toxicity or clinical inefficacy as a result of either a drastic increase or a reduction of drug blood levels, respectively.

Cutaneous reactions are the most likely ADR reported in the literature; in most cases they are benign but sometimes they may herald a life threatening disease. Acute cutaneous adverse reactions occur in 3% of hospitalized patients: usually, they rise up within a few days to 4 weeks after the beginning of the therapy and need a discontinuation of the offending drug to be solved. Many drugs are associated to a 1%-2% incidence of cutaneous reactions during clinic trial. Morbilliform rash (91%) and urticaria (6%) are the most frequent cutaneous reactions in hospitalized patients during pharmacotherapy [9].

Here we report a case of a 65 year old man affected of Bipolar Disorder, hospitalized for a depressive episode, and treated with Selective Serotonin Reuptake Inhibitors (SSRI) and Valproic Acid. After the introduction of Silodosin, he developed an extensive pruritic and purpuric skin rash on his lower legs.

Silodosin is a highly selective α 1A-adrenoceptor antagonist indicated for the treatment of Low Urinary Tract Symptoms (LUTS) in patients with Benign Prostatic Hyperplasia (BPH) [10]. Silodosin exposure may be increased by the co-administration of uridine-glucuronyl transferase-2B7 (UGT2B7) inhibitors (e.g. probenecid, valproic acid, fluconazole), furthering the onset of ADRs [11].

Case Report

A.C. is a 65 year old man suffering of Bipolar I Disorder according to DSM 5 criteria with onset of symptoms at age 40. The first episode was characterised by euphoric mood, easy distractibility, less need of sleep, psychomotor agitation and aggressiveness towards objects and people. He has had several hospitalizations over the past 25 years and

was tried on multiple medications as monotherapy or in combination (lithium, fluoxetine, nortriptyline, lorazepam, olanzapine, quetiapine). The predominant polarity was mania and relapses occurred mainly during the season change.

At the end of September 2014, A.C. was admitted to our Department for a depressive relapse including depressed mood, apathy, social withdrawal, insomnia, and deficit of attention. He was given pharmacological treatment with: Valproic Acid 300 mg/day; Elopam 40 mg/ml daily intravenous infusion for one week, followed by oral Elopam 40 mg/day; Lorazepam 2.5 mg/day. During hospitalization, the patient complained of nocturia, urgency, frequency, and sensation of not completely emptying the bladder. After one week from the admission, he underwent urological consultation, which revealed Benign Prostatic Hyperplasia (BPH); therefore, Silodosin 8 mg/day was prescribed. The day after starting treatment with Silodosin, the patient developed a pruritic skin rash on his right lower leg, which soon appeared also on the opposite leg (Figure 1). Skin lesions were not present at the admission and the patient denied any history of allergy to drugs or other substances.

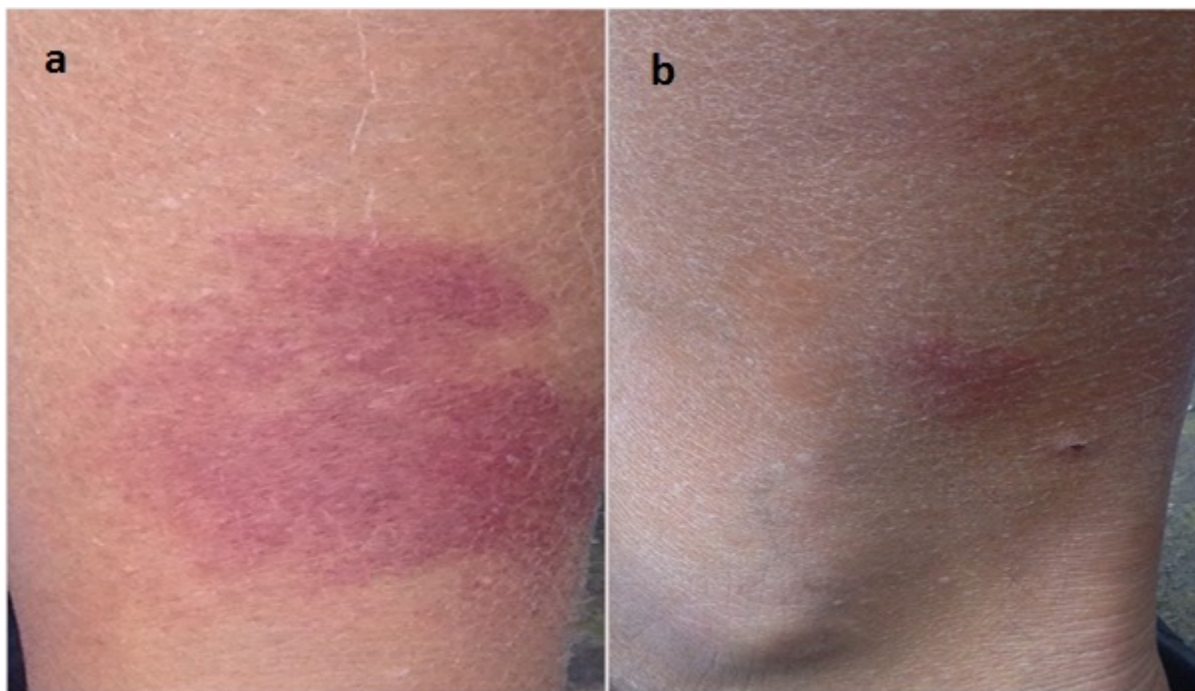


Figure 1: Pruritic skin rash at right (a) and left (b) lower leg at day 1.

At physical examination a symmetric skin eruption consisting of multiple, erythematous, purpuric patches coalescing in slightly infiltrated, pruritic plaques that did not blanch on diascopy, was evident on both legs. Laboratory investigations, including kidney and liver function tests, urinalysis, screening for hepatitis, autoantibodies, complement and immune complexes, were within normal range, and any other comorbidity was excluded. Permission for a skin biopsy was declined, and a provisional clinical diagnosis of drug-induced vasculitis was considered. VA, the likely offending drug, was withdrawn and intravenous fluid therapy with oral antihistamines was administered. Elopam, Lorazepam and Silodosin were not discontinued. VA was then replaced by Pregabalin 300 mg/day. In the

following two days, itching resolved and the skin rash improved (Figure 2). At discharge, two weeks later the admission, the patient experienced a partial remission of his psychiatric symptoms and the skin lesions were completely recovered, with no relapses at one-month follow-up (Figure 3).



Figure 2: Pruritic skin rash at right (a) and left (b) lower leg at day 3.

We considered the skin rash as a result of a drug interaction that involved VA and Silodosin. Since VA has an inhibitor effect on some enzymes, such as UGT2B7 which metabolite Silodosin, we hypothesized that this interaction leads to a Silodosin serum concentration increase and therefore to the skin rash.

Discussion

Our case is an example of skin rash due to drug administration, showing the importance for clinicians to be aware of pharmacodynamic interaction.

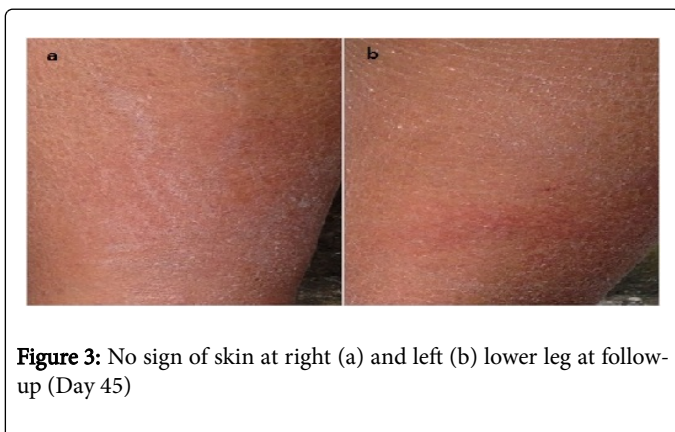


Figure 3: No sign of skin at right (a) and left (b) lower leg at follow-up (Day 45)

Skin rash is a mild ADRs of common observation during AEDs administration. Skin rash is generally exanthematous or maculopapular, but blistering eruptions such as erythema multiforme have also been recorded; it can occur usually within a few weeks after the administration of the offending drug and only requires withdrawal for resolution [7]. Some authors found higher benign rash rates in patients treated with aromatic AEDs (such as phenytoin, carbamazepine, and phenobarbital) with a frequency ranging from 5% to 15% of treated individuals [12], and lower rates with non-aromatic AEDs (such as levetiracetam, gabapentin, valproate and topiramate) [13].

The skin rash described in our case is probably due to an interaction between VA and Silodosin, because of the pharmacokinetic characteristics of both drugs.

Valproic Acid has an intricate interaction profile due to its pharmacokinetic and pharmacodynamic properties: it has liver metabolism that depends roughly for the 25% by Cytochrome P (CYP) 450 system [1]. Drugs, such as erythromycin, fluoxetine and

cimetidine, which inhibit CYP enzymes, can increase valproate levels. Nevertheless also valproate can increase the plasma levels of some drugs, possibly by inhibition/competitive inhibition of their metabolism; examples include Tricyclic antidepressants (TCAs), particularly clomipramine, lamotrigine, quetiapine, warfarin and phenobarbital [12,14]. Valproate may also induce significantly lower plasma olanzapine concentrations, but the mechanism is unknown [15].

Valproic Acid can be considered a broad-spectrum enzyme inhibitor of the uridin-glucuronyltransferases (UGT) [16] (Figure 4). Unlike enzyme induction, enzyme inhibition generally occurs immediately, although its magnitude may increase gradually in parallel with the increase in serum concentration of the inhibiting agent. Enzyme inhibition typically results in decreased metabolism of the affected drug, with an increase in serum concentrations to a new steady state, after four to five times the new half-life of the affected drug. Likewise, the time for enzyme inhibition to disappear after withdrawal of the inhibitor will depend on the half-lives of both the inhibiting drug and the affected drug [17].

Valproic acid pharmacokinetic shows a protein-binding saturation: it is highly protein bound and can be displaced by other protein-bound drugs, like aspirin. Other, less strongly protein-bound drugs, such as warfarin, can be displaced by valproate, leading to higher free levels and toxicity. Pharmacodynamic interactions also occur. Drugs, such as antipsychotic, could present an antagonism of the VA anticonvulsant effect, decreasing the seizure threshold [18]. Other drugs such as clozapine and olanzapine can lead to weight gain [15].

Many side effects of valproate are dose-related (peak plasma-level related) and increase in frequency and severity when its plasma level is >100 mg/L. The most common early symptoms of VA toxicity include anorexia, nausea, vomiting, and somnolence [19].

The risk of ADRs presentation is slightly different if VA is administered in mono or in poly therapy Zeng et al. [20] investigated the adverse effects correlated to VA monotherapy compared to other AEDs monotherapy (Carbamazepine, Phenytoin and Lamotrigine): they showed a good efficacy and safety of VA, since none of those patients observed have discontinued the intake during the two years of follow up. Making a comparison, VA has a lower percentage of ADRs than the other AEDs involved. In particular, rash related to AED treatment has been observed in seven patients during the first 2-8 weeks of monotherapy with Carbamazepine (n=2), Phenytoin (n=1) and Lamotrigine (n=4); none patients in treatment with VA have presented skin rash.

VA is most likely to be involved in ADRs when is co-administrated with other drugs because of its pharmacokinetic properties, as reported in literature [5,6,21].

Many studies have reported that VA in co-administration with Lamotrigine (LMT) increases the risk of Lamotrigine-induced ADRs [7,22-24].

The most likely explanation is that Valproic Acid inhibits N-glucuronidation metabolic pathway of lamotrigine, which leads to an increase in the concentration of glucuronate form of Lamotrigine by 30%-50% [14]. These data suggest that LMT has to be prescribed in a reduced dose when co-administered with valproic acid. In patients taking concomitant VA and LMT, the incidence of skin rashes is dependent on the starting dose: a high starting dose and a rapid dose

escalation have been identified as risk factors of ADRs, and can be reduced with low doses and slow titration [7,12].

Since Silodosin has a similar metabolic pathway to the one described for Lamotrigine, the co-administration of Silodosin in patients already treated with VA could increase the risk of ADRs.

Silodosin is a highly selective α 1A-adrenoceptor antagonist indicated for the treatment of the signs and symptoms in patients with Benign Prostatic Hyperplasia (BPH). Silodosin is metabolized by UGT2B7, alcohol and aldehyde dehydrogenases, and cytochrome P450 and 3A4 (CYP3A4) pathways, and is excreted in urine (34%) and feces (55%) [25-27].

Silodosin is generally well tolerated. After post-marketing experience, ADRs have been reported such as skin rash, pruritus, urticaria and immune system disorders of different severity [28].

Silodosin exposure may be increased by the co-administration of UGT2B7 inhibitors, such as Probenecid, Fluconazole and Valproic Acid, drawing to alteration in its serum concentrations and its active metabolite that could lead to the onset of different ADRs [11]. Furthermore, Silodosin is highly bound to serum proteins, and its displacement from protein binding sites may occur when is co-administrated with other highly protein bound drugs, like VA: this interaction is another mechanism that can lead to the increase of Silodosin serum concentration [29,30] (Figure 4).

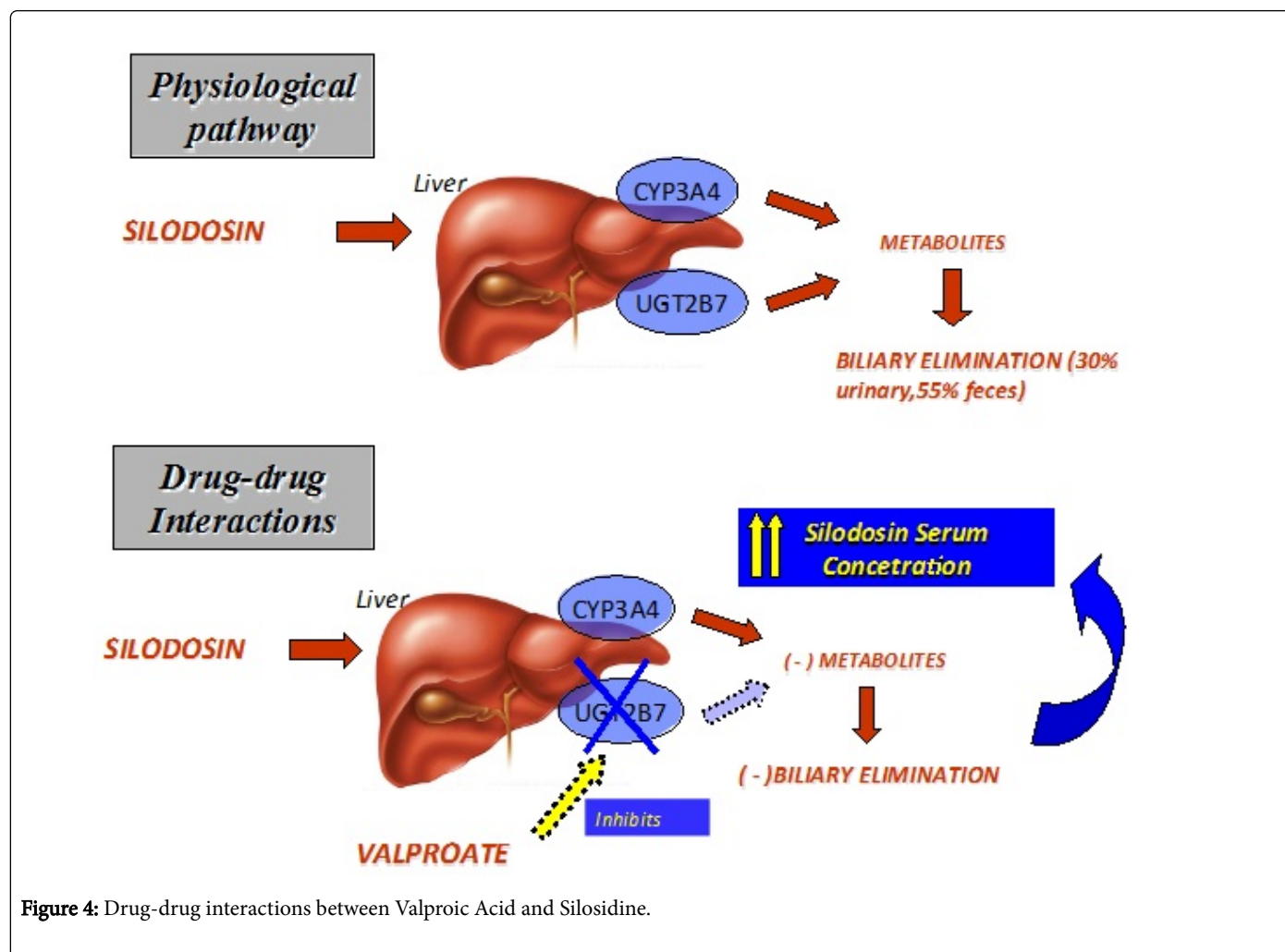


Figure 4: Drug-drug interactions between Valproic Acid and Silosidine.

In our case, we acknowledge that itching skin rash is due to the interaction between VA and Silodosin, since the presentation of the ADR appeared after the introduction of Silodosin and stopped as soon as VA treatment was discontinued, without any recurrence. We consider our case an example of a non-common drug reaction that has to be considered when poly-therapy is administrated.

Conclusion

This case report showed the importance of monitoring side effects, such as itching skin rash, due to VA administration, especially in poly-therapy. Cutaneous reactions are highly common during

pharmacotherapy and it is not always clear which could be the offending drug and the subtended mechanism.

This is the first case report in which the potential interactions between a widely prescribed Anti-Epileptic Drug, such as Valproic Acid, and a selective α 1A-adrenoceptor antagonist not commonly used in psychiatric setting, such as Silodosin, are presented. Clinicians should be aware of this possible interaction, which in our case caused the onset of the pruritic skin rash. The likely underlying mechanisms of this interaction have been discussed in detail, allowing a better understanding of pharmacokinetic and pharmacodynamic properties of these drugs when used in co-administration.

Also, we hope that our experience will be helpful in the future to promptly identify potential adverse drug reaction during co-administration of pharmacotherapy in elderly patient with Bipolar Disorder and Benign Prostatic Hyperplasia. A better knowledge of possible reactions is imperative to prevent and manage manifestations of ADRs induced by pharmaco-interaction with inhibitor of the uridin-glucuronyltransferases when VA are prescribed, taking into account that it is often necessary Valproic Acid discontinuation only in order to achieve patient's full recovery. Since prompt recognition of adverse drug reactions is essential for a better outcome, it is also crucial to advice patients under pharmacologic treatment about the chance of such potential events, recommending to immediately seek medical attention in case of any clinical change, including the onset of a cutaneous rash.

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