Psychiatria Danubina, 2019; Vol. 31, No. 3, pp 362-365 https://doi.org/10.24869/psyd.2019.362 *Case report*

USE OF CLOZAPINE FOR RESOLVING LAMOTRIGINE-INDUCED SKIN LESIONS CAUSED BY SCHIZOPHRENIA TREATMENT

Lee-Hou Tsai[1] & Jeng-Wen Lin[2]

[1]*Taichung Hospital, Ministry of Health and Welfare, Department of Psychiatry, Taichung, Taiwan*
[2]*Feng Chia University, Department of Civil Engineering, Taichung, Taiwan*

received: 26.6.2019; revised: 27.8.2019; accepted: 3.9.2019

* * * * *

INTRODUCTION

The causes of lamotrigine-induced rashes that develop during schizophrenia treatment are poorly understood. Although lamotrigine-induced Stevens-Johnson syndrome appears to be an idiosyncratic adverse drug reaction associated with rapid titration, its incidence has been remarkably reduced since the recommended starting lamotrigine dose was reduced and corrected by the effect of hepatic enzyme inhibitors, such as valproate (Kaur & Dogra 2013). Lamotrigine (LTG) is a phenyltriazine (non-aromatic) anticonvulsant that can be used to treat epilepsy, including partial seizures, primary generalized tonic-clonic seizures, Lennox-Gastaut syndrome, and bipolar disorder (Hodo 2017). LTG has been used as a maintenance treatment for bipolar disorder since 2003 and showed some efficacy for bipolar depression (Hodo 2017). Many treatments for bipolar disorder result in unwanted side effects. For example, valproate, a type of mood stabilizer, significantly increases the risk of obesity. Additionally, carbamazepine may be associated with lethal Steven-Johnson syndrome (SJS). Lithium, a non-antiepileptic drug, has a narrow safety range. Furthermore, the incidence of antidepressant-induced mania is high in bipolar disorder (Frye et al. 2009). LTG has also been used off-label as a treatment for schizophrenia and schizoaffective disorder (Poyurovsky et al. 2010, Kremer et al. 2004).

Here, the case report describes a subject with treatment resistant schizophrenia (TRS). There are several guidelines to asses TRS, and a Treatment Response and Resistance in Psychosis (TRRIP) working group was formed to establish consensus criteria to standardize the definition of treatment resistance (see for example Howes et al. 2017).

METHODS AND CASE DESCRIPTION

In this study, we describe a case of drug-refractory schizophrenia with vivid depressive features. In the past, the 36-year-old Taiwanese female patient had taken antipsychotics, such as risperidone, quetiapine, flupentixol, and zotepine, with concomitant use of antidepressants, such as citalopram, duloxetine, and fluoxetine. But all of the antidepressants didn't work. There were several occurrences of drug-related hyperprolactinemia, and LTG was used as a last resort for the augmentation effect. However, in these instances, rash / desquamation on the patient's face appears. As the LTG augmentation was not evident when treating patients with drug-refractory schizophrenia or schizoaffective disorder, clozapine was promptly used to treat psychotic symptoms.

The subject gave informed consent and her anonymity has been preserved. Since this was a case report of an inpatient, oversight by the institutional review board was not necessary. Because the patient was lying in bed almost all day, tired and stiff, meaning that zotepine had poor efficacy and had doubts about extrapyramidal symptoms (EPS) and rash / desquamation (Bujor et al. 2017). Thus zotepine was stopped and switched to clozapine. LTG was deactivated immediately on the next day because of suspicion that LTG still had the potential to cause a skin lesion. Eventually, her facial lesions cleared and remission of her mental illness was observed.

RESULTS AND DISCUSSION

Table 1 presents the treatment regimen of this patient after her admission to the psychiatry department of Taichung Hospital. It is highly likely that the rapid escalation in LTG dosage (from 25 (mg/d) on December 5, 2017 to 50 (mg/d) on December 8, 2017) triggered the rash. After taking LTG for nearly four weeks, the patient's rash worsened and her entire face became scaly. She felt tired, was almost completely bedridden, and had no appetite. We initially thought these symptoms were due to extrapyramidal symptoms (EPSs) caused by zotepine, so we replaced zotepine with clozapine. As her skin condition remained unchanged, we eventually discontinued LTG. There were obvious improvements in her skin by the following week.

LTG is a novel antiepileptic drug (AED) that causes skin rashes in 3-10% of new users (Kaur & Dogra 2013). Nearly all rashes occur within 2-8 weeks after the initiation of LTG treatment (Hodo 2017). Arif et al.

Table 1. The treatment regimen of the patient after her admission to the psychiatry department of Taichung Hospital

Admission date (2017)	Medication	Reason for changes in medication
1/25	Ris 4 (mg/d) → 6 (mg/d)	Vivid AH
3/06	Plus Citalopram 10 (mg/d)	Depression
3/17	Ris 6 → 2 (mg/d) + Aripiprazole 20 (mg/d)	Ris-induced hyperprolactinemia PRL=104.4 (ng/ml) →PRL=6.81 (ng/ml) (2017/3/25)
3/26	Que 400 (mg/d) + Flup 3 (mg/d)	Poor response to Aripiprazole, no insight
5/3	Que 400 (mg/d) + Flup 6 (mg/d)	Vivid AH
5/5	Duloxetine 30 (mg/d)+ Que 400 (mg/d) + Flup 6 (mg/d)	Depression then added Duloxetine
6/1	Que 400 (mg/d) + Flup 9 (mg/d) + Duloxetine 30 (mg/d)	Flare up of AH, Flup titration
6/7	Que 400 (mg/d) + Flup 6 (mg/d) + Duloxetine 30 (mg/d) + Lithium 600 (mg/d)	Poor response to Flup, depression with fear Added Lithium
6/20	Que 400 (mg/d) + Haloperidol 10 (mg/d) + Duloxetine 30 (mg/d) + Lithium 600 (mg/d)	AH, delusions of being controlled, replaced Flup with Haloperidol
7/6	Que 400 (mg/d) + Haloperidol 10 (mg/d) + Duloxetine 30 (mg/d)	AH, delusions of being controlled, tap water intoxication Na=118 (mmol/u) K= 3.2 (mmol/u) Cl=8.6 (mmol/u)
8/5	Que 600 (mg/d) + Flup 3 (mg/d) (removed Haloperidol and Duloxetine)	AH, depression hyperprolactinemia (PRL=146 (ng/ml)
8/8	Que 600 (mg/d) + Flup 6 (mg/d)	AH
8/11	Que 600 (mg/d) + Flup 6 (mg/d) + Chlorpromazine 50 (mg/d)	AH, more bedridden, poor response
11/8	Que 600 (mg/d) + Flup 9 (mg/d) + Chlorpromazine 50 (mg/d)	Commenting AH(+) 8/24 PRL=36.68 (ng/ml)
11/24	Que 800 (mg/d) + Flup 9 (mg/d) + Chlorpromazine 50 (mg/d) + Fluoxetine 40 (mg/d)	Commanding and commenting AH, low mood, poor impulse control 11/25 CPK=268 (IU/L)
11/27	Zotepine 75 mg + Que 600 (mg/d) + Flup 9 (mg/d) + Chlorpromazine 50 (mg/d)	Commenting AH, poor response to Que, will replace Que with Zotepine (want to simplify the drug and disable the antidepressant)
12/1	Zotepine 125 (mg/d) + Que 600 (mg/d) + Chlorpromazine 50 (mg/d)	AH, planned replacement of medications
12/4	Zotepine 175 (mg/d) + Que 400 (mg/d) + Chlorpromazine 50 (mg/d)	AH, planned replacement of medications
12/5	Added Lamotrigine 25 (mg/d) Zotepine 175 (mg/d) + Que 400 (mg/d)	Insomnia, AH, referential delusion
12/8	Lamotrigine 50 (mg/d) + Zotepine 175 (mg/d) + Que 400 (mg/d)	Queer behaviour, referential delusion 12/6 CPK=268 (IU/L), PRL=88.14 (ng/ml)
12/11	Lamotrigine 50 (mg/d) + Zotepine 150 (mg/d) + Que 200 (mg/d)	Planned replacement of medications: Betaxolol 20 (mg/d) (Replaced Propranolol 80 (mg/d)
12/18	Adding Citalopram 20 (mg/d) Lamotrigine 50 (mg/d) + Zotepine 150 (mg/d)	Depression, poor impulse control 12/17 CPK=457 (IU/L)
12/26	Trihexyphenidyl 6 (mg/d) + Citalopram 20 (mg/d) + Lamotrigine 50 (mg/d) + Zotepine 150 (mg/d)	Body rigidity, blunted affect

Ris: Risperidone; Que: Quetiapine; Flup: Flupentixol; Chlo: Chlorpromazine AH: auditory hallucination;
EPS : extrapyramidal symptoms; PRL: Prolactin; CPK: CK or CPK or Creatine Kinase

Table 1. Continues

Admission date (2017)	Medication	Reason for changes in medication
12/29	Biperiden 8 (mg/d) + Citalopram 20 (mg/d) + Lamotrigine 50 (mg/d) + Zotepine 150 (mg/d)	Dystonia/rigidity, delusional perception
2018/1/08	Clozapine 50 (mg/d) + Lamotrigine 50 (mg/d) + Citalopram 20 (mg/d) + Biperiden 6 (mg/d)	Zotepine-induced EPS and hyperprolactinemia, fatigue, hypoactivity, patient was bedridden, facial rashes and scaly skin
1/09	Deleted Lamotrigine Clozapine 50 (mg/d) + Fluoxetine 20 (mg/d) + Betaxolol 10 (mg/d)	LTG-induced skin rash, Clozapine-induced tachycardia
1/10	Clozapine 100 (mg/d) + Fluoxetine 20 (mg/d) + Betaxolol 10 (mg/d)	
1/15	Clozapine 100 (mg/d) + Fluoxetine 20 (mg/d) + Propranolol 30 (mg/d)	Hypotension due to Betaxolol, improvement of skin lesion, prominently decreased AH
1/22	Clozapine 100 (mg/d) + Fluoxetine 20 (mg/d) + Propranolol 30 (mg/d) + Clonazepam 2 (mg/d) (taken at bedtime as a sleep-aid)	Discharged

Ris: Risperidone; Que: Quetiapine; Flup: Flupentixol; Chlo: Chlorpromazine AH: auditory hallucination;
EPS : extrapyramidal symptoms; PRL: Prolactin; CPK: CK or CPK or Creatine Kinase

reported that AED rash rates were highest with phenytoin, lamotrigine, and carbamazepine (Arif et al. 2007). Notably, several factors increase the risk of developing an LTG-induced rash. These include a younger age, female, a high initial dose, a rapid escalation of dosage, concomitant use of hepatic enzyme inhibitor, previous history of another AED related rash, and the concomitant use of other drugs that may also cause adverse skin effects (Hodo 2017, Arif et al. 2007). Dermatological side effects of psychopharmacological drugs are mostly presented in the group of mood stabilizers and AEDs, particularly the carbamazepine and lamotrigine (Lasic et al. 2011).

CONCLUSION

Apart from which guideline the clinician wants to follow, clozapine seems of course the drug of choice in the case report described, considering the failure of other antipsychotics on remission of symptoms over the years. The use of LTG as augmentation therapy has been described in TRS patients, but mostly in cases in which clozapine itself was not completely working (some authors suggest that as a rationale the glutamatergic effects of LTG may be used in this population of non-responders), and so LTG was added to clozapine. Finally, the fact that the patient developed a skin rash is contemplated in LTG therapy, and is adding the use of the drug as an off label augmentation therapy in schizophrenia.

Although LTG has fewer side effects compared with other antiepileptic drugs, extra caution should be taken when determining the initial dose. Additionally, the dosage should be increased progressively. Side effects caused by cross-reactivity with concomitant drugs should be taken into consideration in order to reduce the risk of rashes. When treating patients with drug-refractory schizophrenia or schizoaffective disorder, if LTG augmentation is not evident, clozapine should be promptly used to treat psychotic symptoms.

Acknowledgements:

The work described in this paper was part of research sponsored by the Ministry of Science and Technology, Taiwan (Contract No. MOST 105-2221-E-035-074).

Conflict of interest: *None to declare.*

Contribution of individual authors:

Lee-Hou Tsai: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

Jeng-Wen Lin: Data collection and analysis, drafting and revision of manuscript.

References

1. *Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas Humara C, Bazil CW, Resor SR Jr, Hirsch LJ: Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007; 68:1701–1709*
2. *Bujor C-E, Vang T, Nielsen J, Schjerning O: Antipsychotic-associated psoriatic rash - a case report. BMC Psychiatry 2017; 17:242*
3. *Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE Jr, Nolen WA, Kupka R, Leverich GS, Grunze H, Mintz J, Post RM, Suppes T: Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 2009; 166:164–172*
4. *Hodo DW: Kaplan and Sadock's Comprehensive Textbook of Psychiatry. Tenth Edition. 2017; chapter 34.18: 3083–3088*
5. *Howes et al.: Treatment resistant Schizophrenia: TRRIP Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry, 2017*
6. *Kaur S & Dogra A: Toxic epidermal necrolysis due to concomitant use of lamotrigine and valproic Acid. Indian J Dermatol 2013; 58:406*
7. *Kremer I, Vass A, Gorelik I, Bar G, Blanaru M, Javitt DC, Heresco-Levy U: Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. Biol Psychiatry 2004; 56:441–446*
8. *Lasic D, Cvitanovic MZ, Uglesic B, Visic V, Hlevnjak I: Exanthema medicamentosum as a side effect of promazine. Psychiatr Danub 2011; 23:194–197*
9. *Poyurovsky M, Glick I, Koran LM: Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. J Psychopharmacol Oxf Engl 2010; 24:861–866*

Correspondence:

Jeng-Wen Lin, PhD
Department of Civil Engineering, Feng Chia University
100, Wenhwa Road, Taichung 40724, Taiwan
E-mail: jwlin@fcu.edu.tw