

Levetiracetam Induced Steven Johnson Syndrome with Acute Kidney Injury

Dhananjay Gupta¹, Nikith Shetty^{2,3}, Mahendra Javali², Pradeep R², Anish Mehta², Purshottam T. Acharya² and Srinivasa Rangasetty²

¹MD, Ramaiah Medical College, Bengaluru, Karnataka, India

²DM, Ramaiah Medical College, Bangalore, Karnataka, India

³DM, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

Correspondence to:

Dr. Mahendra Javali

Associate Professor, Department of Neurology

Ramaiah Medical College and Hospitals

Bengaluru, Karnataka, India, 560054

Tel: +91-9731878817

E-mail: mahendrajv@gmail.com

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Abstract

Levetiracetam is a newer anti-epileptic drug and has a novel mechanism of action, that is modulation of synaptic neuro-transmitter release. Due to its good oral tolerability, wide therapeutic range and minimal systemic adverse effects, it is gaining popularity in a wide spectrum of seizure disorders. Cutaneous adverse effects are uncommon with levetiracetam, with sparse reports of reversible maculopapular rashes, Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia Syndrome (DRESS). Previously, cases of Levetiracetam induced SJS have been reported, but none in association with severe renal dysfunction. Here we report a patient who developed SJS associated with acute kidney injury, secondary to levetiracetam, which recovered spontaneously after stopping the drug.

Keywords

Levetiracetam, SJS-TEN, Steven Johnson syndrome, Acute kidney injury, Anti-epileptic drugs

Introduction

Levetiracetam (LEV) is a novel second generation anti-epileptic which has been extensively marketed and prescribed since the turn of the century. A favourable pharmacokinetics coupled with a wide safety margin and minimal adverse effects have made it a popular choice among physicians, both as a first line and as an add-on drug for partial onset as well as generalized onset seizures. The commonly encountered side effects are generalized asthenia, somnolence, infections and headache, though behavioural and psychiatric side effects (including aggressiveness and suicidal ideations) may necessitate drug discontinuation [1]. Several rare adverse effects like interstitial nephritis, renal failure [2], anhedonia and loss of libido [3] in men have also been reported previously. In contrast to other anti-epileptic drugs, cutaneous reactions to levetiracetam are considered rare. Here we report a case of Steven Johnson syndrome (SJS) with acute kidney injury, secondary to the use of levetiracetam.

Case History

A previously healthy 43-year-old man, developed sudden onset giddiness, vomiting and weakness of the right half of body. Clinical examination revealed blood pressure of 220/100 mmHg, left eye ptosis, left horizontal gaze restriction,

left LMN facial weakness and right hemiparesis (power 3/5). CT brain plain (done initially by the referring physician) showed an acute brainstem haemorrhage involving the left midbrain, pons and extending to the cerebellar peduncles (Figure 1). Routine metabolic workup was normal. Patient was initially managed in a primary care centre, where he was treated with anti-edema measures (3% hypertonic saline), anti-hypertensives and Levetiracetam (at a dose of 500 mg twice daily). Levetiracetam was started prophylactically due to large brainstem haemorrhage with low GCS. Thereafter, the patient was referred to our tertiary care centre. On the 7th day (after starting levetiracetam), he developed an acute febrile illness with body temperature of 39.6 °C. On the 9th day, he was noticed to have maculo-papular erythematous rash over the face, chest and trunk along with oral ulceration. Blood investigations revealed elevated blood urea nitrogen and serum creatinine (4.94 mg%) levels (Table 1). Blood

these drugs have been previously implicated in the causation of SJS, the anti-hypertensives amlodipine and clonidine as well as ondansetron do not cause worsening of renal function. Thus, by the principle of Occam's razor, these were excluded. A recent population case study from Europe studied the incidence of SJS-TEN among new drug users and suggested that pantoprazole and related drugs are usually innocent bystanders rather than causative agents for SJS [4]. Hence out of all these medications, Levetiracetam was thought to be the most likely culprit and was stopped immediately. The patient continued to receive amlodipine, clonidine and pantoprazole daily. Gradual clinical improvement with healing of the skin rashes was noted and the patient became afebrile on the 13th day. His kidney functions started improving and serum creatinine normalized on the 17th day.

Discussion

Amongst the anti-seizure drugs, older aromatic compounds- phenytoin, carbamazepine, phenobarbital and primidone are more likely to cause hypersensitivity reactions. Recent population-based studies from Europe have found phenytoin and lamotrigine to have the highest risk of Steven Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) amongst new drug users (68.9 and 45 cases/100,000 new users) [4, 5]. Contrarily, newer drugs like levetiracetam, topiramate, gabapentin and tiagabine are not known to have significant risk of skin rashes.

Used in doses of 1-3 gm/day, levetiracetam is considered to be a very well tolerated drug with good oral bioavailability and minimal drug interactions. It is predominantly renal-excreted drug and hence renal toxicities are being increasingly reported [6-9] (Table 2). Traditionally not considered to carry a major risk of allergic skin rashes; recent reports have associated the use of levetiracetam with dose-related reticular eruptions [10], maculo-papular exanthems [11], DRESS syndrome [12] and SJS [13, 14] (Table 3). None of these Levetiracetam induced SJS patients had associated kidney injury. Ours is probably the first case reported to have these co-existing severe adverse reactions in the same patient. The presence of renal dysfunction excluded amlodipine, clonidine and ondansetron and left levetiracetam as the likely offending drug. The cause of cutaneous reactions with levetiracetam remains speculative and whether kidney injury exacerbates skin reaction is debatable. It has been thought that allergic reactions with levetiracetam occurs in patients with a history of hypersensitivity to other anti-seizure medication. Role of cross-reactivity to phenytoin, carbamazepine and phenobarbital is also postulated. Human Leucocyte Antigen (HLA) predisposition to cutaneous drug reactions has been extensively studied for older aromatic compounds, however, these are lacking for levetiracetam. Ethnic variations due to HLA association have been reported with HLA-B*15:02, and this has been demonstrated to be a strong risk factor for carbamazepine induced SJS in Indian population [15]. Similar studies in patients on levetiracetam are lacking. Consequently, HLA testing prior to starting levetiracetam is presently not recommended.

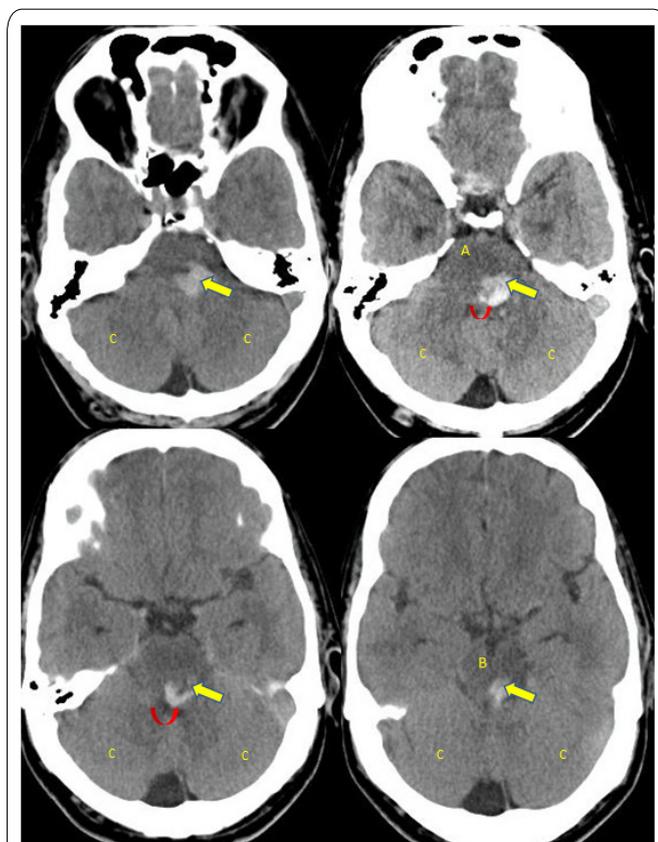


Figure 1: Neuro-Imaging in IIH. A-B: MRI Sagittal FLAIR images showing empty sella; C-D: MRI axial cuts showing tortuous and distended optic nerves (arrows); E: MRI orbit sagittal cuts showing flattening of posterior part of globe and tortuous optic nerve; F: MRI venogram showing right transverse sinus stenosis (arrow).

and urine cultures, including testing for malaria, dengue, chikungunya, enteric fever, mycoplasma and rickettsial fever were negative. In view of this, a possibility of drug induced rash was considered and his treatment chart reviewed. The patient was on Amlodipine 10 mg/day, Clonidine 0.3 mg/day (both via naso-gastric tube), intravenous Pantoprazole 40 mg/day, intravenous Ondansetron 8 mg (SOS, last received on day 4 and intravenous Levetiracetam 500 mg BD. Though all

Table 1: Laboratory parameters in our patient.

	(Normal values)	Day 0	Day 7	Day 13	Day 17
Haemoglobin	13.5-17.5 g/dL	14.5 g/dL	13.6 g/dL	13.5 g/dL	13.8 g/dL
White cell counts	4500-11000/mm ³	8960/ mm ³	9570/ mm ³	9730/ mm ³	9190/ mm ³
Platelet count	150-400 x 10 ⁹ /mm ³	430 x 10 ⁹ /mm ³	490 x 10 ⁹ /mm ³	350 x 10 ⁹ /mm ³	370 x 10 ⁹ /mm ³
Blood urea nitrogen	7-20 mg/dL	23 mg/dL	72 mg/dL	59 mg/dL	35 mg/dL
Serum creatinine	0.6-1.2 mg/dL	0.9 mg/dL	4.94 mg/dL	3.16 mg/dL	1.03 mg/dL
Uric acid	3.5-7 mg/dL	6.9 mg/dL	7.2 mg/dL	-	7.1 mg/dL
S. Bilirubin	0.1-1.2 mg/dL	1.2 mg/dL	1.5 mg/dL	1.4 mg/dL	1.4 mg/dL
Blood glucose	80-140 mg/dL	150 mg/dL	210 mg/dL	-	-

mg/dL- milligrams per decilitre; g/dL- grams per decilitre; /mm³- per cubic millimetre

Table 2: Previously reported cases of Levetiracetam induced Kidney dysfunction.

Author	Patient [#]	Dose [^]	Clinical syndrome	Latency to kidney injury	Serum creatinine [*]
Kathleen A. Hurwitz ²	17/F	250 mg twice daily	Interstitial nephritis	10 days	3.3 mg/dL
Katrina Chau ⁶	69/F	500 mg twice daily	Granulomatous interstitial nephritis	14 days	4.44 mg/dL
Ali Mahta ⁷	45/M	3000 mg/ day	Interstitial nephritis	7 days	3.59 mg/dL
Danielle Spengler ⁸	23/F	500 mg twice daily	Acute Kidney injury	2 days	2.76 -4.22 mg/dL
Mathieu Leblanc ⁹	75/M	500 mg twice daily	DRESS [*] and Acute kidney injury	10 weeks	1.22-5.16 mg/dL

[#]M- male, F- female, age in years; [^]- Dose in milligrams, for paediatric patient, dose in milligrams per kilogram body weight; ^{*}- Drug reaction with eosinophilia and system symptoms; ^{*}- Serum creatinine levels in milligrams per decilitre

Table 3: Previously reported cases of Levetiracetam induced SJS-TEN^{*}.

Author	Patient [#]	Dose [^]	Clinical syndrome	Latency to skin rash
Li-Ping Zou ¹³	2.25/F	30 mg/Kg/day	SJS	9 days
Bhargavi ramanujam ¹¹	18/F	250 mg twice daily	SJS	10 days
	24/M	500 mg twice daily	SJS	7 days
Tu Duong ¹⁴	20/F	-	TEN	26 days
	29/F	-	TEN	19 days

^{*}- SJS- Steven Johnson Syndrome; ^{*}TEN- Toxic Epidermal necrolysis;

[#]M- male, F- female, age in years; [^]- Dose in milligrams, for paediatric patient, dose in milligrams per kilogram body weight

Our patient did not have a previous history of intake of any anti-seizure medication and showed a temporal relation of appearance of skin rashes to levetiracetam administration. There was spontaneous resolution of both the skin rashes and the kidney dysfunction after stopping Levetiracetam. Whether the concomitant use of other drugs played a part in triggering or aggravating renal toxicity and/or skin rashes is difficult to comment upon. But clinical improvement following discontinuation of levetiracetam without stopping the other drugs possibly leaves levetiracetam as the cause of SJS and AKI. As clinicians using levetiracetam day in and day out, we need to be aware of this potentially life-threatening adverse reaction of levetiracetam. Moreover, prophylactic use of anti-

seizure medication in patients of cerebral stroke and intracerebral haemorrhage is widely prevalent amongst primary care physicians, but this is not a recommended practice and should be strongly discouraged.

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