Journal of Clinical Toxicology
ISSN: 2161-0495
Becker et al., J Clin Toxicol 2019, 9:4
Case Report Open Access

Intermittent Haemodialysis in Lamotrigine Poisoning

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Received date: July 25, 2019; **Accepted date:** August 20, 2019; **Published date:** August 30, 2019

Abstract

Lamotrigine poisoning is usually benign causing only mild to moderate neurological and cardiovascular effects. However, there have been case reports of lamotrigine poisoning leading to intractable seizures, sudden cardiovascular collapse and death. It has not been clear if haemodialysis can effectively remove lamotrigine. We provide pharmacokinetic data on a large lamotrigine overdose that was managed with intermittent haemodialysis.

We present a case of a 23-year-old (90 kg) female who presented to hospital 2 hours post ingestion of 17.8 g of lamotrigine and 9 g of quetiapine. Her initial Electrocardiogram (ECG) showed a sinus tachycardia with normal intervals. Over time this progressed to a right bundle branch pattern progressive QRS widening and T wave changes. She was commenced on Continuous Veno-Venous Heamodiafiltration Therapy (CVVHDF) but the circuit clotted. Eleven hours post ingestion she still had ongoing ECG changes despite a bolus of 100 mmol of 8.4% sodium bicarbonate. She was commenced on Intermittent Haemodialysis (IHD) 16 hours post ingestion. Lamotrigine levels were collected and the extraction ratio of lamotrigine during IHD was 0.4 with a mean clearance of 78 ml/min. The half-life of lamotrigine was significantly shorter during IHD, 4.1 hours versus 30.4 hours post IHD. She was extubated 42 h post ingestion and made a full recovery. She acknowledged at that time she only took 9 g of lamotrigine.

This case demonstrates that intermittent haemodialysis is effective in removing lamotrigine in acute overdose.

Keywords: Lamotrigine; Overdose; Intermittent haemodialysis

Introduction

A 23-year-old female presented to emergency 2 hours post a reported ingestion of 17.8 g of lamotrigine and 9 g of quetiapine immediate release. On arrival her Glasgow Coma Score was 12, heart rate 150 bpm, blood pressure 136/90, respiratory rate 18 bpm and oxygen saturations 97% on room air. She had slurred speech, normal tone and no hyperreflexia or clonus.

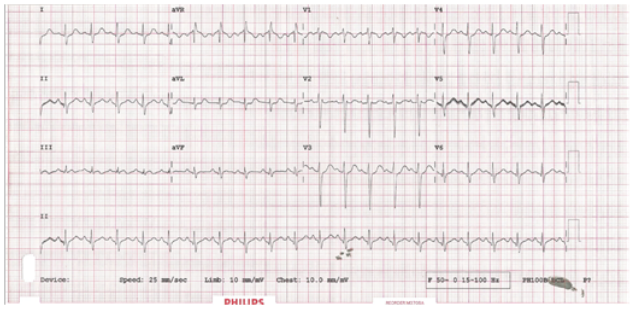

Figure 1: Initial ECG 2.5 hours post ingestion.

Her initial ECG showed a sinus tachycardia with a dominant R wave of 5 mm in lead aVR, an absolute QT interval of 330 ms and QRS interval of 96 ms. Given the large amount of lamotrigine ingested and predicted clinical course she was intubated and ventilated to allow for decontamination. Activated charcoal 50 g was given 3.5 hours post ingestion via a nasogastric tube. She received three further doses of activated charcoal including 50 g at 8 h, 25 g at 10 h and 25 g at 17 h post ingestion. 4-6 hours post ingestion she developed a right bundle branch pattern on her ECG, with gradual widening of her QRS to 120 ms with subsequent T wave inversion in leads V1 and V2 (Figures 1 and 2).

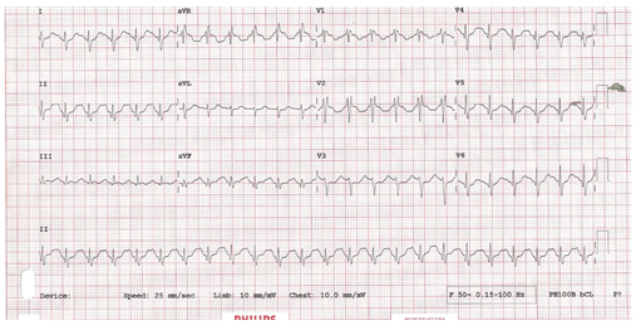

Figure 2: ECG 4.5 hours post ingestion.

Given the ongoing ECG changes she was started on Continuous Veno-Venous Haemodiafiltration (CVVHDF) at 7.5 h post ingestion. Forty-five minutes after commencing CVVHDF the circuit clotted and required changing. It was restarted but clotted a further 2 times. 11 hours post ingestion because of ongoing ECG changes (QRS 120 ms),

100 mmol of 8.4% sodium bicarbonate was administered. There was no improvement in QRS width on the ECG. At 12 hours post ingestion she required a low dose noradrenaline (max 3 mcg/min) infusion for hypotension. This was required for 3 hours only. Due to concerns with ongoing dynamic ECG changes, the large dose ingested and the need for low dose noradrenaline, Intermittent Haemodialysis (IHD) was commenced at 16 h post ingestion. IHD was performed with blood flow rates ranging from 230-300 ml/min, dialysate flow rate of 500 ml/min and ultrafiltration rate of 125 ml/h. She was dialysed for 4.5 hours in total. Lamotrigine levels were taken on admission, during haemodialysis and for 24 hours post. Quetiapine levels were taken on admission at 7.5 hours post ingestion. She developed aspiration pneumonia and was treated with intravenous ceftriaxone. She was extubated 42 hours post ingestion. Once awake she stated she had only taken 9 g in total of lamotrigine and 9 g of quetiapine. She made a full recovery.

Time post ingestion	Blood flow rate (ml/h)	Dialysate flow rate (ml/h)	Serum Lamotrigine Concentrations	Pa	Pv	Extraction Ratio	Clearance mL/min
2.6	-	-	21.5	-	-	-	-
7.75	-	-	16.3	-	-	-	-
10.25	-	-	15.4	-	-	-	-
16.25*	250	500	-	14	8.4	0.4	67
16.75	250	500	-	13	8.2	0.37	63
17.75	250	500	-	11	5.8	0.47	80
19.75	300	500	-	7.4	4.3	0.42	85
20.75	300	500	-	6.9	4	0.42	85
23.25	-	-	-	6.2	-	-	-
27.75	-	-	-	5.8	-	-	-
32.85	-	-	-	5.2	-	-	-
35.75	-	-	-	4.5	-	-	-
52.5	-	-	-	3.5	-	-	-
61.75	-	-	-	2.4	-	-	-

Table 1: Lamotrigine concentration and clearance data before, during and after intermittent haemodialysis.

During this patient's admission lamotrigine concentrations were measured.

The extraction ratio, clearance and half-life of lamotrigine were calculated while the patient was receiving IHD. The half-life was calculated using the equation:

$T1/2=In2/ke$

The ke (elimination rate constant) was determined using linear regression to calculate the slope of the log transformed Y-axis of lamotrigine serum concentrations versus time curve (Graphpad Prism 7 Software). The recovery method could not be used as the lamotrigine concentrations were below the limit of detection in the effluent fluid collected.

Clearance was calculated by the A-V pair or difference method. As the lamotrigine concentrations are serum concentrations, this method allows us to determine the plasma clearance of lamotrigine via IHD. The following equations were used:

Extraction ratio=Pa-Pv/Pa

Plasma flow rate=blood flow rate x (1-Hct)

Plasma clearance=extraction ratio x plasma flow rate.

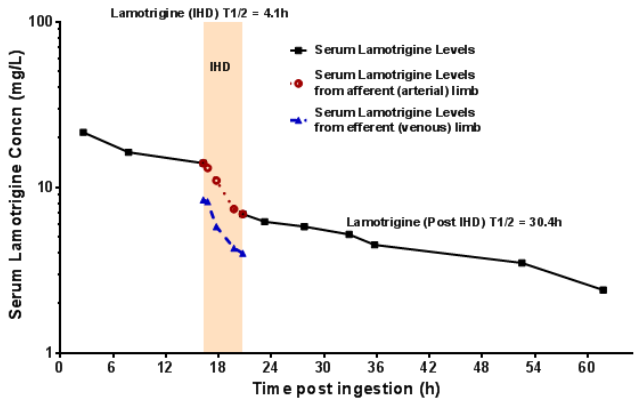

Figure 3: Serum Lamotrigine Concentration (mg/L) Vs Time Post ingestion (h).

Where Pa is the lamotrigine serum concentration from the arterial (afferent) limb; Pv is the lamotrigine serum concentration from venous (efferent) limb, Hct is the hematocrit [1].

Serum quetiapine concentrations taken at 2.5 h and 7.5 h post ingestion were measured using liquid chromatography mass spectrophotometry.

Lamotrigine concentrations, IHD blood, dialysate flow rates, calculated extraction ratios and clearances are shown in (Table 1).

During IHD the mean calculated half-life of lamotrigine was 4.1 hours. The mean clearance calculated was 78 ml/min with a mean extraction ratio of 0.4. Post dialysis the half-life of lamotrigine was 30.4 hours (Figure 3). Quetiapine levels at 2.5 and 7.5 h post ingestion were found to be 1.4 mg/L and 1.7 mg/L respectively (therapeutic range: 0.1-1 mg/L).

Case Report

We report a patient who presents 2 h post an overdose of 9 g lamotrigine and 9 g quetiapine immediate release. On presentation, the patient was obtunded and it was thought she had ingested 17.8 g of lamotrigine, a point she clarified after recovery. In overdose, lamotrigine usually causes mild to moderate neurological and cardiovascular symptoms [2]. In some cases however and at variable doses, intractable seizures, hypotension, QRS and QT prolongation, cardiac arrhythmias and death occur which can often be delayed [3-5]. Quetiapine in overdose causes vasodilation and hypotension mediated by alpha-1-adrenoreceptor and H1-histamine receptor antagonism, but no significant QRS or QT prolongation [6]. Her quetiapine levels 2.5 and 7.5 hours post ingestion were 1.4 mg/L and 1.7 mg/L respectively (therapeutic range: 0.1-1 mg/L), only just above the therapeutic range.

Cardiovascular instability has been reported with lamotrigine overdoses of 3.5 g [7] and death at 4 g [3]. Lamotrigine inhibits voltage-gated sodium channels and attenuates release of glutamate and aspartate [4]. It inhibits serotonin, noradrenaline and dopamine reuptake [2]. It is also a reversible non-selective monoamine oxidase inhibitor but no interactions with serotonergic agents have been reported [8]. The cardiovascular toxicity and QRS prolongation is thought to be mediated by cardiac sodium channel blockade [9]. This sodium channel inhibition does not appear to have any response to sodium bicarbonate [3,5,7]. With sodium channel blockers, it has been shown that the acidic dissociation constant (pKa) is strongly correlated with the pH-dependence potency [9]. Lamotrigine has a pKa of 4.7 while amitriptyline is 9.8. At a pH of 8, lamotrigine has a higher affinity while amitriptyline has a lower affinity for the sodium channels when compared with an acidic pH of 6. This may partially explain why alkalinisation may not work in lamotrigine poisoning.

Discussion

How to best predict which patients with lamotrigine overdose will deteriorate is unknown. In this case, ECG changes suggestive of sodium channel blockade in a large overdose were used to trigger the need for haemodialysis. Lamotrigine levels were not available in a timely manner to guide management and were only available a week after the presentation. Three hours post overdose her lamotrigine level was 21.5 mg/L (therapeutic range: 3-13 mg/L) and just prior to IHD 14 mg/L.

Lamotrigine has a low molecular weight of 256 g/mol, a bioavailability of 98%, protein binding of 56% and a low volume of distribution of 1.2 L/kg [3,4]. It is metabolised in the liver predominately to glucuronide metabolites that are excreted in the urine [4]. It has a long half-life that varies from 22-36 hours in therapeutic use [10]. This half-life has been shown to be more variable and prolonged in acute overdose [3]. In patients on therapeutic doses of lamotrigine with renal insufficiency, haemodialysis shortened the elimination half-life from 59.6 ± 28.1 h to 12.2 ± 6.4 h [11]. The literature reports a 17-20% extraction factor with haemodialysis [11,12]. A published systemic review on lamotrigine poisoning concluded there was no published data in this setting on the benefit of extracorporeal elimination [13].

This patient did not develop severe toxicity and IHD most likely did not alter her clinical course. It does however provide information regarding how dialyzable lamotrigine is in an acute overdose. In this case we were able to calculate the extraction ratio, clearance and half-life of lamotrigine during IHD.

It has been proposed that activated charcoal and multi-dose activate charcoal can reduce absorption and increase elimination of lamotrigine through interference with entero-hepatic circulation [14,15]. This patient was given multi-dose activate charcoal which was commenced prior to IHD. Multiple dose activated charcoals may also be of benefit in increasing the total clearance of lamotrigine and may account for the low lamotrigine level at 16 h post ingestion prior to commencing IHD. This may also have had an additive effect in shortening the half-life during IHD.

There are various limitations in this case report. This patient has a small amount of fluid (125 ml/h) removed during IHD, Fluid was removed before the efferent lamotrigine serum concentration was measured, thereby leading to a small overestimation of the efferent lamotrigine serum concentrations (approximately 5%). This will in turn lead to an underestimation in clearance, by the A-V pair method. Furthermore, we were unable to detect lamotrigine in the effluent fluid and hence could not calculate clearance via the recovery method. The likely reason for this is that only about 10-20 mL of effluent samples was collected from the effluent limb. The dialysate flow rate was 500 mL/min and this would result in 30 L of effluent fluid an hour that has low concentration of lamotrigine.

Conclusion

This is a case report of a patient who had a large lamotrigine and quetiapine overdose. Intermittent haemodialysis was undertaken and pharmacokinetic data was collected. In this patient the half-life of lamotrigine was substantially reduced to 4.1 hours during IHD compared to 30.4 hours post IHD. This demonstrates lamotrigine is dialyzable in overdose and should be considered as a management option in the unstable patient.

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