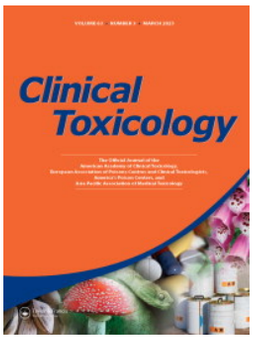

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CLINICAL RESEARCH

Clinical effects of acute lamotrigine overdose (ATOM-10)

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ABSTRACT

Introduction: Lamotrigine overdose is not typically associated with severe toxicity. However, both severe toxicity and serotonin toxicity is occasionally reported following large ingestions. We aimed to investigate the clinical effects of lamotrigine overdose.

Methods: This was a prospective observational study from July 2020-March 2024. Patients >14 years-old with acute lamotrigine overdose (≥2 g ingestion) were recruited from the Australian Toxicology Monitoring study or identified from three toxicology units. Data extracted included clinical features, lamotrigine concentrations, management, and outcomes.

Results: Fifty-four patients were included, median age 29 years (IQR: 21–42 years), 37 (69%) were female. The median ingested dose was 4.8 g (IQR: 3.2-6.3 g) and 41 patients (76%) co-ingested other substances. The median maximum lamotrigine concentration was 18.5 mg/L (IQR: 12.4–25.0 mg/L) at a median time of 4.3 h (IQR: 3.2–10.8 h) post-ingestion. Clinical effects and their management included sedation in 44 (81%) with 29 patients (54%) endotracheally intubated, tachycardia in 39 (72%), hypotension in 21 (39%) with 15 (28%) receiving inotropes, and seizures in 11 (20%). Serotonin toxicity occurred in 23 (43%) patients with four having severe toxicity characterised by temperature >38.5 °C and/or rigidity treated with muscle paralysis. Higher peak lamotrigine concentrations were correlated with severe outcomes such as endotracheal intubation for coma (P <0.0001), patients with hypotension receiving inotropes (P=0.0269) and patients developing seizures (P=0.0002). Patients who co-ingested another serotonin agent (some in therapeutic doses) had a higher incidence of developing serotonin toxicity (22/33 [67%]) versus those who had not (1/21 [5%]); P <0.0001).

Discussion: Severe toxicity was associated with higher peak lamotrigine concentrations. Serotonin toxicity was common in those who were exposed to another serotonergic agent.

Conclusion: Coma, seizures and hypotension following lamotrigine overdose appeared to be concentration dependent. Serotonin toxicity occurred in those who co-ingested another serotonergic agent and was unrelated to lamotrigine concentration.

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Lamotrigine; overdose; poisoning; serotonin syndrome; serotonin toxicity

Introduction

Lamotrigine is a broad-spectrum anticonvulsant and mood-stabiliser, whose clinical use has expanded over the last 30 years. Lamotrigine was traditionally used for the treatment of focal seizures, generalised tonic-clonic seizures, Lennox-Gastaut syndrome and the prevention of depressive episodes in bipolar disorder [1,2]. Recent literature has indicated potential benefits of lamotrigine in a variety of other disorders such as schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, autism and many other psychiatric disorders, increasing its indications and overall use [3]. Lamotrigine has various mechanisms of action. It primarily exerts its anticonvulsant effects by blocking voltage-gated sodium channels, thereby reducing neuronal depolarisation and suppressing epileptic activity [3,4]. Additionally, lamotrigine blocks calcium channels leading to decreased neurotransmitter release, particularly glutamate and aspartate, which are crucial in the excitation of seizure activity [1,3]. Beyond its anticonvulsant effects, lamotrigine exhibits antidepressant effects, possibly through inhibition of serotonin reuptake and reversible monoamine oxidase inhibitor activity [5–8]. It is these multiple mechanisms of actions that result in the many clinical effects seen following lamotrigine overdose.

There are limited data on the clinical effects of lamotrigine in overdose, and what is known is predominantly based on case reports and series [9–11]. These reveal a wide range of toxicity, varying from no or minimal symptoms following overdose, to severe toxicity including dysrhythmias, seizures,

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hypotension, cardiac arrest and death [9–12]. We observed cases of serotonin toxicity with larger lamotrigine overdoses and in combination with other serotonergic agents, which has only been reported sporadically, and does not appear to be common, based on case series [10,13–15]. This is likely because most cases report lamotrigine only ingestions, or there are few that also co-ingest a serotonergic agent. We hypothesized that large lamotrigine overdoses and those in combination with other serotonergic agents would result in more severe effects.

We aimed to investigate the clinical effects seen in lamotrigine overdose (≥2 g), in particular serotonin toxicity, and the association between serum concentration and different toxic effects.

Methods

Study design and setting

This was a prospective observational study identifying patients with lamotrigine overdoses from the New South Wales and Queensland Poison Information Centres and three clinical toxicology units. Patients ingesting >2 g of lamotrigine were either enrolled via the Australian Toxicology Monitoring (ATOM) study or from three clinical toxicology units.

The ATOM study is a prospective observational cohort designed to investigate a range of clinically important drugs in overdose that commenced in 2013. It utilizes a multi-centre collaboration recruiting patients from three clinical toxicology units and patients from calls to the New South Wales and Queensland Poison Information Centres. Within ATOM, specific prospective studies are designed and undertaken focusing on specific drugs or treatment types, such as paracetamol overdose [16–18] and digoxin immune Fab in digoxin toxicity [19,20]. For each study the inclusion criteria and data collection are determined prior to commencing and a pre-formatted data sheet is used for ATOM patients and similar data elements are used from the three toxicology units. The study investigators are notified by the Poison Information Centre staff when patients meet inclusion criteria. The treating doctor is contacted, and patients are consented to have clinical data recorded and serum samples collected for the measurement of drug concentrations (at least two in the first 24 h post admission). In circumstances in which the patients cannot consent, consent is obtained from a relative or next of kin and from the patient once able. The ATOM study allows the testing of any remaining serum collected during the patient's admission for drug concentrations.

The three toxicology units (Hunter Area Toxicology Service [Newcastle], South Eastern Area Toxicology Service [Sydney], and Princess Alexandria Hospital [Brisbane] prospectively collect data using a purpose-built database on drug exposures and doses and enter the same clinical data as patient recruited to ATOM. The clinical toxicology units treat approximately 1,000–2,000 toxicology patients per year. The New South Wales Poison Information Centre receives approximately 65,000 calls per year and Queensland Poison Information Centre 35,000 calls per year [21].

Selection of participants

We included patients (≥14 years old) with an acute (single ingestion) lamotrigine overdose of ≥2 g (five times the maximum recommended daily dose) from July 2020 to March 2024. Patients were informed about the research and then provided signed consent (once awake and alert). Patients were excluded if they had undetectable lamotrigine concentrations. Lamotrigine concentrations may be measured in most hospitals, but the results are often not available to clinicians for days.

Data collection

Australian Toxicology Monitoring clinical data were prospectively collected on a pre-formatted clinical datasheet (Supplementary Data). For those additional patients included from toxicology units the same data were collected from the database. Data from all patients were collated in REDCap and included demographic information, exposure details (time of ingestion and dose ingested), co-ingestions, clinical effects, lamotrigine concentrations (collected on admission and every 6-12 h for 48 h), management (endotracheal intubation, inotrope therapy, activated charcoal, and extracorporeal treatment) and outcomes (intensive care unit [ICU] admission, length of stay) (Supplementary Data). If the time of ingestion was uncertain the earliest possible time of ingestion was used. Patient medical records were used to extract any data that were missing. Data were extracted by investigators (AC, KN, KM and UNI), with all data entries checked by AC for accuracy.

Outcomes included occurrence of clinical effects and their association with median lamotrigine dose and median peak (highest recorded) lamotrigine concentration. Cardiovascular effects included tachycardia [heart rate >100 beats/min], hypotension [systolic blood pressure <90 mmHg] and QRS complex duration ≥120 msec. Central nervous system effects included a decreased level of consciousness (Glascow Coma Scale [GCS] <15) and coma (GCS <9) [22], agitation (as determined by the treating doctor) and seizures. The occurrence of serotonin toxicity was determined by the Hunter serotonin toxicity criteria [23] and was diagnosed by the treating clinician or toxicologist. Severe serotonin toxicity was defined as a temperature >38.5 °C and/or rigidity treated with muscle paralysis [24]. A serotonergic agent was defined as those agents that inhibit serotonin metabolism or decrease serotonin reuptake (e.g., selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and monoamine oxidase inhibitors) [25]. Agents which increase serotonin receptor sensitivity (e.g., lithium) and direct serotonin agonists (e.g., lysergic acid diethylamide [LSD]) were not classified as serotonergic agents as on their own rarely cause serotonin toxicity [25].

Laboratory assays

Lamotrigine concentrations in New South Wales and Queensland for clinical purposes are performed by one hospital laboratory in each state. These laboratories performed the ATOM lamotrigine concentrations by reverse-phase ultra

performance liquid chromatography (UPLC) coupled with the QDa mass spectrometer (UPLC MsMS System, Waters Milford, MA, USA).

Data analysis

Continuous data were reported as medians and interquartile ranges (IQR) for non-normally distributed data, and frequencies with percentages for categorical data. Continuous variables were compared using Mann–Whitney test (nonparametric data) with 95% confidence intervals [CI] and categorical variables were compared using Fisher's exact test. The association between dose of lamotrigine ingested and serum concentration was assessed with Pearson's correlation coefficient. All analyses were performed using GraphPad PRISM® software version 10.0.2.1.

Ethics

Ethics approval was obtained from the corresponding health district ethics committees, including Australian Toxicology Monitoring (ATOM) Study (HREC/12/POWH/165, HREC/14/QRCH/105), Australian Drug Intoxication and Treatment (AuDIT) Program of Research (2021/ETH00165), South Eastern Area Toxicology Service database (LNR/12/POWH/355) and Princess Alexandria Hospital (HREC/14/QPAH/308). The Hunter Area Toxicology Service database has been granted exemption by the local Human Research Ethics Committee to use de-identified patient information as an audit and has an ethics exemption.

Results

A total of 62 patients were identified for the study, but three patients were excluded due to undetectable lamotrigine concentrations and five additional patients were excluded because their serum was unavailable for analysis (misplaced samples or collection error). This left 54 patients (33 recruited from ATOM) who were included according to the outlined selection criteria.

Patient characteristics

The median age of the patients was 29 years (IQR: 21-42 years) and 37 (69%) were females. The median time to presentation was 2.3 h (IQR: 1.2-4 h). The median ingested lamotrigine dose was 4.8 g (IQR: 3.2-6.3 g, range: 2-16.8 g) of the immediate-release preparation (extended-release preparations are not available in Australia). Forty-one patients (76%) reported co-ingesting other medications, most commonly serotonergic agents (e.g., selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, moclobemide) in 18 (33%), antipsychotics in 17 (31%), benzodiazepines/Z class drugs in nine (17%), ethanol in eight (15%) and lithium in five (9%). Of the serotonergic agents co-ingested the most common were selective serotonin reuptake inhibitors in ten and serotonin and noradrenaline reuptake inhibitors in seven. Lamotrigine was prescribed to 49 (91%) of the patients. All cases were deliberate self-poisonings.

A median of two (IQR: 1–4) lamotrigine concentrations were collected in each patient. The median maximum lamotrigine concentration was 18.5 mg/L (IQR: 12.4–25 mg/L, range 6.1–131 mg/L; therapeutic range: 2.5-15 mg/L) at a median time of 4.3 h (IQR: 3.2–10.8 h) post-ingestion. There was a moderate correlation between ingested dose and maximum lamotrigine concentration (Pearson r = 0.6296, 95% CI: 0.435-0.768) (Figure 1).

Clinical effects

Thirty-eight (70%) of the 54 patients were symptomatic on presentation, and 51 (94%) developed symptoms during their admission. The most common clinical features were an altered level of consciousness (GCS <15) in 44 (81%) patients and tachycardia in 39 (72%) patients (Table 1). Seizures occurred in 11 patients (20%), coma (GCS <9) in 25 patients (46%), serotonin toxicity in 23 patients (43%) (Figure 2) and hypotension in 21 patients (39%). Eight patients had a QRS compex duration ≥120 msec within 24 h of presentation, with a median QRS complex duration of 133 msec (IQR: 127–148 msec, range: 120–160 msec). Six of the eight patients were also hypotensive, four had seizures, one developed atrial flutter, but none developed ventricular tachycardia. The 13 patients ingesting lamotrigine alone displayed similar clinical symptoms and signs, to those who co-ingested other agents (Table 1). Seizures and hypotension were associated with a higher median peak lamotrigine concentration (Figure 2).

Serotonin toxicity

In the 23 patients (43%) developing serotonin toxicity, the most common criteria met were tremor with hyperreflexia and inducible clonus with agitation or diaphoresis (Figure 3). Four had severe toxicity and three of these were paralysed for severe muscular rigidity. There was no association between median peak lamotrigine concentration in those who

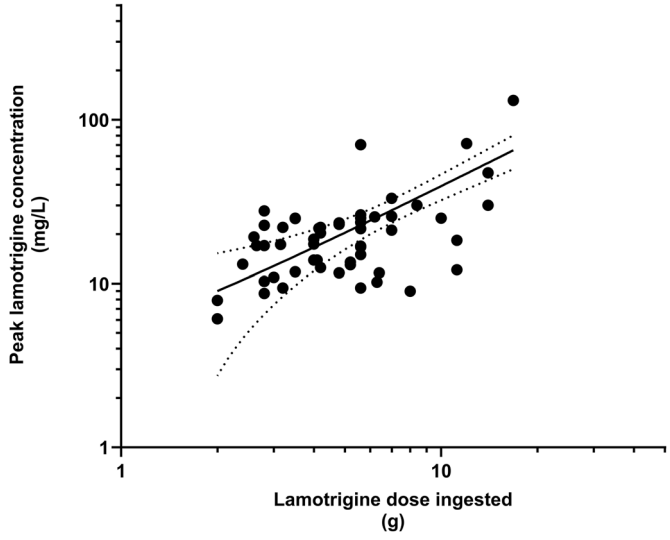

Figure 1. Peak lamotrigine concentration (mg/L) versus lamotrigine dose ingested (g).
Pearson r = 0.6296; 95% CI: 0.435–0.768

Table 1. Patient characteristics, outcomes and treatments of lamotrigine only ingestions and those co-ingesting another substance in overdose (excluding alcohol only).

	Lamotrigine only ingestion* ($n=13$)	Lamotrigine overdose with co-ingestion ($n=41$)
#Therapeutically taking a serotonergic agent, *n* (%)	9 (69%)	23 (56%)
Median lamotrigine dose ingested, g (IQR)	5.6 (3.9– .2)	4.8 (3.1–5.9)
Median lamotrigine peak concentration, mg/L (IQR) (therapeutic range: 2.5-15 mg/L)	21.1 (16.7–28.1)	17 (11.6–23.5)
Time to maximum lamotrigine concentration, h (IQR)	3.8 (2.0–12.4)	4.4 (3.5–10.0)
Central nervous system effects		
Decreased level of consciousness (GCS <15), *n* (%)	10 (77%)	34 (83%)
Coma (GCS <9), *n* (%)	6 (46%)	19 (46%)
Seizures, *n* (%)	4 (30%)	7 (17%)
Serotonin toxicity, *n* (%)	8 (61%)	15 (37%)
Severe serotonin toxicity, *n* (%)	0	4 (10%)
Cardiovascular system effects		
Tachycardia (heart rate >100 beats/min), *n* (%)	9 (69%)	30 (73%)
Hypotension (systolic blood pressure <90 mmHg), *n* (%)	5 (38%)	16 (39%)
QRS complex duration ≥120 msec, *n* (%)	3 (23%)	5 (12%)
Treatment		
Activated charcoal, *n* (%)	9 (69%)	23 (56%)
Multiple-dose activated charcoal, *n* (%)	5 (38%)	8 (20%)
Continuous kidney replacement therapy, *n* (%)	1 (8%)	5 (12%)
Endotracheal intubation, *n* (%)	8 (62%)	21 (51%)
Inotropes, *n* (%)	5 (38%)	10 (24%)
Serotonin antagonist, *n* (%)	1 (8%)	6 (15%)

*Four patients co-ingested with ethanol only.
#Serotonergic agent was defined as those substances that inhibit serotonin metabolism or decreased serotonin reuptake (e.g., selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and monoamine oxidase inhibitors).

developed serotonin toxicity compared to those who did not (Figure 2). All but one of the 23 patients with serotonin toxicity co-ingested or were already therapeutically on a serotonergic agent. Serotonin toxicity occurred in 22/33 (67%) of lamotrigine overdose patients co-ingesting or therapeutically taking a serotonergic agent, compared to 1/21 (5%) of patients not taking serotonergic agents (absolute difference: 62%; 95% CI: 46-90%; $P<0.0001$).

Management

Decontamination with activated charcoal was administered in 32 (59%) patients at a median time of 5 h (IQR: 2.5–7.0 h) post ingestion. Enhanced elimination (to increase clearance of lamotrigine) included multiple-dose activated charcoal in 13 (24%) patients and extracorporeal elimination in six (11%) patients, of whom all had continuous kidney replacement therapy.

Endotracheal intubation was performed in 29 (54%) patients for a decreased level of consciousness. The median duration of intubation was 39 h (IQR: 23–78 h, range: 12–305 h). Fifteen patients received inotropes with six receiving more than one inotrope. Being endotracheally intubated or receiving inotropes was associated with a higher median peak lamotrigine concentration (Figure 3). Seven were treated with a serotonin antagonist, five with cyproheptadine and two with chlorpromazine. Of the eight patients with a prolonged QRS complex duration, four received intravenous sodium bicarbonate boluses (50 to 100 mmol) and one received a bolus of 3% sodium chloride.

Eight of the 11 patients with seizures were treated with benzodiazepines either intravenous midazolam or diazepam. Ten of the 11 patients were endotracheally intubated and five received extracorporeal elimination. Four had recurrent seizures (more than one) and were loaded with intravenous

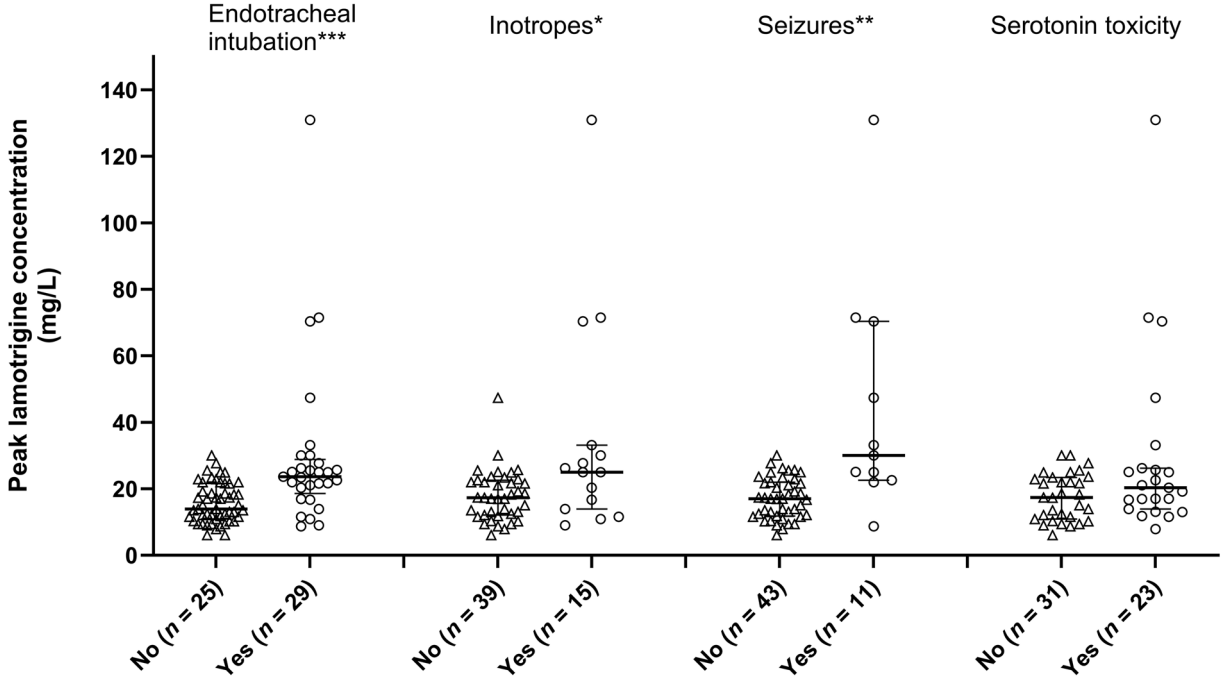

Figure 2. Comparison of median peak lamotrigine concentration in those patients who were endotracheally intubated, received inotropes, had seizures or developed serotonin toxicity compared to those who did not.
*$P<0.05$; **$P<0.01$; ***$P<0.0001$

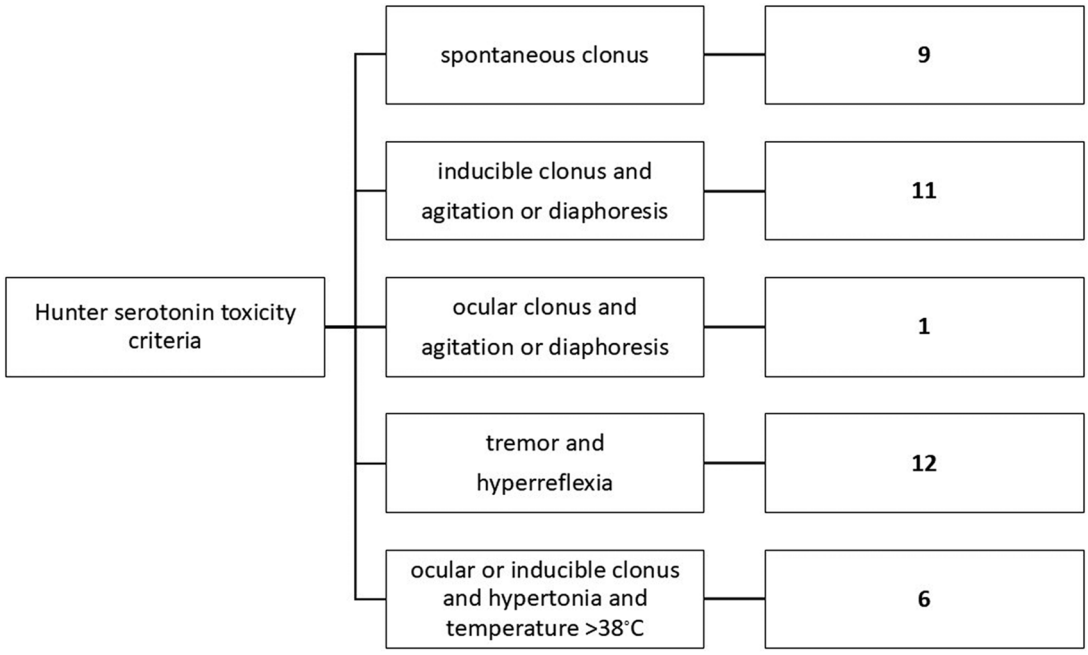

Figure 3. Hunter serotonin toxicity criteria met among the 23 patients with serotonin toxicity.
Note: 12 patients meet more than one criteria.

levetiracetam (four) and one also received a bolus of thiopentone. One patient with recurrent seizures developed status epilepticus and was managed with levetiracetam, phenobarbital, a midazolam infusion and neuromuscular blockade.

Outcome

All patients survived to discharge, with a median length of stay of 45 h (IQR: 27–111 h). Complications included aspiration pneumonitis (as diagnosed by an intensive care physician) in 13 patients, all of whom were endotracheally intubated. A further three developed ventilator-acquired pneumonia of which one was complicated by a pulmonary abscess. Two cases of dysrhythmia occurred which were unlikely related to lamotrigine: one had an episode of atrial flutter that was managed with cardioversion and one patient had an asystolic arrest secondary to hypoxia during an attempted endotracheal intubation, with a return of circulation after 15 min of resuscitation and a complete recovery.

Discussion

Lamotrigine overdose can cause a range of cardiac and neurological toxic effects. Decreased level of conscious, tachycardia and hypotension were common in this study of lamotrigine ingestions ≥2 g regardless of co-ingestion. Higher lamotrigine concentrations were associated with more severe toxicity including coma undergoing endotracheal intubation, hypotension receiving inotropes, and seizures. In contrast, serotonin toxicity occurred frequently in those who co-ingested another serotonergic agent and appeared unrelated to lamotrigine dose or concentration.

Case series and single case reports of lamotrigine overdose suggest that most lamotrigine exposures result in mild or no toxicity [11,12]. In those who become symptomatic, the most common clinical effects are altered level of consciousness, seizures, agitation and tachycardia [11]. We report a similar pattern of toxicity with the predominant clinical manifestations being central nervous and cardiovascular toxicity. In contrast most patients in our series were symptomatic (drowsy and/or tachycardia). The higher rate of clinical toxicity can be likely explained by the exclusion of ingestions <2 g. The largest study of lamotrigine exposures reports data from America's Poison Centers® National Poison Data System® and comprised 493 exposures the majority which (52.1%) remained asymptomatic [11]. This study included 173 (35.1%) children ≤4 years who were all unintentional exposures [11]. In contrast, our study only included adults with deliberate self-poisonings ≥2 g and the majority had co-ingested other agents. Even though lamotrigine only ingestions represented only 24% ($n = 13$) of ingestions, they had a similar toxicity profile to mixed ingestions.

We found higher peak lamotrigine concentrations were associated with coma, seizures and patients who developed hypotension and received inotropes (Figure 2). The association of higher lamotrigine concentrations and more severe central nervous system and cardiovascular toxicity likely reflects the sodium and calcium channel blocking effects of lamotrigine. In contrast, there did not appear to be an association between lamotrigine dose ingested or peak concentration and the development of serotonin toxicity. Rather, serotonin toxicity occurred in the presence of serotonergic co-ingestions or therapeutic use. There are limited available data regarding the incidence and risk factors associated with serotonin toxicity following lamotrigine overdose [10,13–15]. A case series of 57 patients (over a 10-year period) from a toxicology unit, of which nine were lamotrigine only, reported two incidences of serotonin toxicity [10]. Both cases met the Hunter criteria. One involved a 1-year-old child who had

ingested an unknown quantity of lamotrigine and subsequently developed agitation, clonus, and diaphoresis. The second case involved an adult, with limited published details. In contrast, in the 493 cases reported from America's Poison Centers® there were no documented cases of serotonin toxicity [11]. This contrasts with our study in which the occurence of serotonin toxicity was higher. This may be explained by most of our cases being polypharmacy overdoses and many patients co-ingested serotonergic agents (e.g., selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and/or monoamine oxidase inhibitors) or were taking them therapeutically.

The high occurrence of serotonin toxicity in our study in those co-ingesting or therapeutically on another serotonergic agent can be explained by the effect of lamotrigine on serotonin. *In vitro* and *in vivo* data has demonstrated that lamotrigine inhibits serotonin reuptake and has reversible monoamine oxidase inhibitor activity [5–8]. *In vitro* in both rat and human tissues at concentrations in the therapeutic range lamotrigine inhibits monoamine oxidase activity. However in *in vivo* rat studies, lamotrigine did not seem to affect monoamine disposition, indicating that its interaction with both monoamine oxidase-A and monoamine oxidase-B isoforms is competitive and highly reversible [6]. In contrast moclobemide (reversible monoamine oxidase inhibitor) has slow reversibility of monoamine oxidase inhibition in animal models. A study in bipolar patients, using platelet monoamine oxidase-B as a peripheral marker for brain monoamine oxidase-B activity, following six weeks of lamotrigine treatment showed a significant decrease in platelet monoamine oxidase-B activity [5].

In this study lamotrigine had similar risk factors and incidence of serotonin toxicity to moclobemide. A study by Isbister and colleagues [24] of 106 moclobemide overdoses found that 11 (55%) of 21 patients co-ingesting a serotonergic agent (even in therapeutic range) developed serotonin toxicity (using Sternbach's criteria), of whom six developed severe serotonin toxicity (defined as temperature >38.5 °C or muscle rigidity requiring endotracheal intubation and paralysis). In contrast only one (3%) of 33 moclobemide-alone overdoses developed serotonin toxicity, despite a larger median ingested dose [24].

Limitations

There are multiple limitations to this study including the restriction of participants to those with an ingestion ≥2 g. This was initially chosen as an inclusion criterion as previous studies had reported minimal toxicity with low dose ingestions. Hence, we are unable to conclude if a similar occurrence of serotonin toxicity is seen with ingestions of <2 g. Furthermore, this study found a correlation between serotonergic co-ingestion (overdose or therapeutic) and serotonin toxicity. It was not possible to distinguish whether serotonin toxicity resulted from the therapeutic use of serotonergic medications or from overdose, as all but one individual who overdosed on a serotonergic agent and developed toxicity were also taking a serotonergic medication at therapeutic doses. Furthermore, co-ingestions were determined from patient history and laboratory confirmation was not performed due to the wide range of medications co-ingested.

Furthermore, lamotrigine concentrations were not collected at set times post-ingestion but rather on arrival and then every 6–12 h. Several patients ($n = 14$) typically those with minimal symptoms had shorter length of stays and often only had one lamotrigine concentration measured. This will limit the accuracy of the maximum lamotrigine concentration calculated and may not correspond to the true peak.

As lamotrigine ingestion is uncommon and to get a better representation of ingestions, data from ATOM and toxicology databases were utilised. Although the majority of the data were prospectively collected missing clinical details were obtained from medical notes which may have not recorded all symptoms or complications. However, all patients were managed by a clinical toxicologist in person or via phone advice.

Conclusion

Severe toxicity, including coma, seizures and hypotension, following lamotrigine overdose appeared to be drug concentration dependent. Serotonin toxicity occurred commonly in this series in those who co-ingested another serotonergic agent and was unrelated to concentration.

Trial registration

Australian Toxicology Monitoring (ATOM) Study – Australian Paracetamol Project: ACTRN12612001240831 (ANZCTR) Date of registration: 23/11/2012

Authors contribution

AC, KI, GI: were involved in the design, data collection and analysis and drafting the manuscript. UNI, KM: were involved in the data collection; KN: were involved in the data collection and drafting the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The de-identified data we analysed are not publicly available, but requests to the corresponding author will be considered on a case-by-case basis.

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