

INTRODUCTION

Diagnosing and managing patients with altered mental status creates one of the greatest challenges to physicians. Difficulties exist due to the vast etiologies of coma and depressed mental status ranging from metabolic derangements to endogenous or exogenous central nervous system (CNS) toxins (2,3). Additionally, there may be limited time in which to make an appropriate diagnostic and therapeutic judgment (1).

When initially working up an altered patient, it is rare for any physician to have complete, accurate or even reliable information. As poisonings continue to be a significant source of morbidity and mortality, an especially challenging task for the physician is the management of a patient with a suspected overdose from an unidentified medication or substance.

The Annual Report of the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) consistently reports sedatives, hypnotics, antipsychotics and anticonvulsants as frequently involved in human exposures and fatalities (4,5,6). Recognizing the seemingly ubiquitous nature of these commonly prescribed medications, the aim of this study is to report cases of supratherapeutic valproic acid (VPA), lithium (Li) or carbamazepine (CZP) concentrations in those patients being managed for altered mental status who had no history of being prescribed or ingesting these agents.

MATERIALS & METHODS

After Institutional Review Board approval, we performed a retrospective case review utilizing our regional poison center data. All cases coded as “valproic acid”, “lithium”, and “carbamazepine”, from January 1, 2006 to December 31, 2008, were obtained and considered. Utilizing Crystal Reports (Version 11), a retrospective search of these cases were queried for analysis. Inclusion criteria were all cases with supratherapeutic concentrations of VPA, Li, and CZN (VPA >100 mcg/mL, Li >1.2 mEq/L, CZN >12 mcg/mL). These cases were subsequently scrutinized and reported if they met the following criteria: 1) those with altered mental status and an unclear history of psychiatric diseases or seizure disorder and 2) an unknown medication history regarding the use of VPA, Li, or CZN. Exclusion criteria included patients who were not evaluated in a healthcare facility, had known history of psychiatric disease or seizure disorder and a history of ingesting one of the three medications as an intentional overdose, or did not have quantitative serum concentrations of VPA, Li, or CZN.

RESULTS

Our poison center received 2182 cases coded as either VPA (1012), CZN (572), or Li (598) between January 1, 2006 through December 31, 2008. Twenty-six patients ultimately met our stringent inclusion criteria: 8 patients in the VPA group (113-247 mcg/ml; mean 158; Figure 1), 9 patients in the Li group (1.9-5.2 mEq/L; mean 2.9; Figure 2), and 9 patients in the CZN group (13.4-38.8 mcg/ml; mean 23.2; Figure 3). All

patients survived and one patient had a Li concentration of 5.2 mEq/L and received hemodialysis.

DISCUSSION

There have been significant advances in the treatment of bipolar disorder, which includes new medications for the various subtypes of bipolar disorder such as bipolar depression and acute mania. Whereas lithium is still considered a first line agent for acute and prophylactic treatment of bipolar depression and mania, contemporary anticonvulsant agents such as valproic acid and carbamazepine have been successfully used in the treatment of patients with mixed mania, rapid cycling and concurrent substance use (7).

Carbamazepine is an iminobenzyl derivative that is structurally similar to the tricyclic antidepressants. It is extensively metabolized in the liver, primarily by CYP 3A4, to carbamazepine 10, 11 epoxide which is pharmacologically active (8). Because of its lipophilic nature, it is absorbed erratically and peak plasma levels can be delayed up to 24 hours especially with a large overdose or an overdose of a sustained release formulation (9, 10).

Valproic acid is a simple branched-chain carboxylic acid. VPA indirectly increases the amount of gamma-aminobutyric acid (GABA) in the CNS by increasing the activity of glutamic acid decarboxylase and inhibiting GABA transaminase (11, 12). VPA also alters free fatty acid metabolism by impairing beta oxidation and disrupting the urea cycle. This can lead to hyperammonemia, hepatitis, pancreatitis and renal insufficiency (11).

While the mechanism of action for Li has not been completely elucidated, recent research suggests that the therapeutic action of Li results from a complex interaction of events affecting multiple target sites. These interacting systems likely readjust the balance between excitatory and inhibitory activities while the decrease in glutamatergic activity may contribute to its neuroprotection (13). With a significant overdose, Li is characterized by altered mental status, stupor, seizures or coma.

Further highlighting the pervasive nature of these commonly prescribed medications, during the years 2006-2008 the Annual Reports of the AAPCC NPDS repeatedly reported that sedative/hypnotics/antipsychotics and anticonvulsants are among the top 25 substances most frequently involved in human exposures. Additionally, sedative/hypnotics/antipsychotics were noted to be associated with the largest number of fatalities and anticonvulsants among the top 10 reported (4,5,6).

The poisoned patient can present with a number of clinical symptoms—from minor presentations such as nausea and vomiting to the devastating including seizures, cardiac dysrhythmias, seizures, coma or even death. In the patient with altered mental status, there may be few clues at the time of initial presentation but fortunately, the toxin may be rapidly identified with a careful history, a focused physical exam and commonly available laboratory tests (3, 14).

While qualitative urine or blood tests rarely affect patient management, quantitative blood tests such as acetaminophen, salicylate, theophylline, lithium, lead, iron, toxic alcohols, digoxin and anticonvulsants, are easily accessible and can be useful for the clinician (3,12,15,16,17).

The findings of this study yield several important implications. Many clinicians in our group have adopted the practice of measuring concentrations of VPA, Li, and CZN in patients that present altered and may have a remote history of psychiatric disease or seizure disorder. A concentration of one of these agents is much more advantageous in directing care and disposition in contrast to a qualitative urine toxicology screen which has many potential problematic false positive results and nuances when interpreting the results. Obtaining a quantitative concentration however may drive a second concentration to elucidate any ongoing absorption which activated charcoal could prevent. Additionally, multiple doses of activated charcoal is utilized to enhance elimination of CZN (ie. serum levels will decrease with multiple doses of activated charcoal which interrupts enterohepatic recirculation and uses the gut as a modified hemodialysis procedure). Patients poisoned by any of these 3 medications (VPA, Li, and CZN) are sometimes requiring hemodialysis when severe. While only 1 patient in our series required hemodialysis, good supportive measures such as repeat doses of activated charcoal and close medical monitoring (in contrast to clearance to a psychiatric facility) may benefit this patient population.

There are a number of limitations worthy of note relating to this preliminary data. The retrospective nature of this study yields itself to possible coding errors and potential omissions in the poison center record. Additionally, our analysis of the clinical information was limited to documentation available from the RPC record. While our RPC manages 80,000 to 100,000 exposures annually, and the majority of our clinical toxicologists have adopted the practice of obtaining these serum drug concentrations in such patients, our total number of cases meeting criteria was relatively small. The

denominator of patient calls to our RPC was much larger than those meeting criteria for study, however our goal was to report the possible cases that otherwise may have been missed. One cannot conclude that any change in outcome was made in diagnosing poisoning by these agents in our study, but can assert that this phenomenon is real and is worthy of prospective analysis.

In conclusion, our RPC detected 26 patients with supratherapeutic VPA, Li, or CZN concentrations in patients with potential indications for the agent, but no available or known history of either ingestion or access to these agents. Our clinical toxicology group will continue the practice of obtaining quantitative concentrations of these medications in this patient population.

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