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CARBAMAZEPINE OVERDOSE: A PROSPECTIVE STUDY OF SERUM LEVELS AND TOXICITY

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ABSTRACT

A cooperative prospective study of consecutive cases of carbamazepine overdose was conducted to determine if serum levels were predictive of toxicity and if risk factors such as age, chronic exposure, or previous disorder or cardiovascular disease could be used as prognostic indicators. Seventy-three consecutive cases were collected from two regional certified poison control centers from January 1989 to August 1989. There were 25 exposures in children < 6 yrs., 11 exposures in adolescents, and 37 exposures in adults. Ten adult cases and one adolescent case were excluded from the study due to the presence of coingestants or inadequate information. Peak measured serum levels ranged from 0.3 to 56 mcg/ml. Using the presence of coma, seizure activity or respiratory depression requiring mechanical ventilation as measures of toxicity, we found poor correlation between rising serum levels of carbamazepine and toxicity. Increased serum levels of carbamazepine did appear to correlate with increased hospital stay, but not with ICU stay. History of a seizure disorder appears to pose increased risk of a seizure in carbamazepine overdose. In this series chronic exposure to carbamazepine did not appear to increase the risk of coma or respiratory depression for a

given toxic serum level and may add some protective effect. Serum levels below 40 mcg/ml do not appear to accurately predict the severity of toxicity. Cardiac conduction defects were rare (one child). Anticholinergic findings, as evidence by decreased bowel motility and sinus tachycardia were common. Previous cardiovascular disease and age did not appear to be important prognostic indicators.

INTRODUCTION

Carbamazepine (Tegretol™) was first approved in the United States for use as an antiepileptic agent in 1974. It is the drug of choice for the treatment of trigeminal neuralgia for which it has been used worldwide since the 1960s. In recent years its use has expanded to the treatment of depression and affective disorders, as well as to unapproved uses such as treatment of phantom limb pain, postherpetic neuralgia and cocaine abuse. Carbamazepine (CBZ) is a synthetic iminostilbene derivative that is chemically and structurally related to tricyclic antidepressants and spatially related to phenytoin. In overdose CBZ often exhibits toxicities shared by these compounds (1,2).

In 1988 over 2880 CBZ exposures were reported to the national data collection system of the American Association of Poison Control Centers (AAPCC), with roughly equal distribution into child, adolescent and adult age groups (3). Of these exposures over 1900 were treated in a health care facility. Three hundred and eighty six were determined to have a moderate medical outcome (severe but not life threatening) and 89 had a major medical outcome (life threatening). It is unclear how many of these cases experienced seizures, coma, respiratory depression or cardiac arrhythmias, but both of these categories could include such event (total = 475 cases). Three fatalities were reported.

METHODOLOGY

Data were collected on a prospective basis from all carbamazepine exposures reported to the Delaware Valley Regional Poison Control Center

and the Pittsburgh Poison Center from January 1, 1989 to August 31, 1989. The entrance criteria for this study were: all intentional ingestions for the purpose of suicide, misuse or abuse and all accidental ingestions or therapeutic misadventures that the participating center determined would require treatment in a hospital. Recommendations for the medical management of these patients was based on the participating center's judgement. Only those patients who had at least two successive serum carbamazepine levels and had been observed in a health care facility for a minimum of six hours were included in this study. Polydrug ingestions were excluded from the analysis of the data.

The specific data collected were: 1) drug and amount of drug ingested by history, 2) time of ingestion and time of arrival at health care facility, 3) dosing method: (i.e. single acute ingestion vs acute increase over a previous chronic level vs slow chronic rise [chronic misdosing]), 4) pertinent medical history (i.e. previous neurologic or cardiovascular disorder), 5) initial patient presentation including blood pressure, heart rate, temperature, EGG changes if noted, and neurologic status, 6) serial patient assessment every 4-8 hours, including blood pressure, heart rate, temperature, EGG (if monitored), and neurologic status until patient was considered medically stable, 7) initial recorded serum CBZ level, 8) serial serum CBZ levels, 9) any medical interventions used to treat the patient, 10) medical outcome including: days spent in hospital, days spent in ICU, use of mechanical ventilator and any sequelae noted. Neither the treatment administered to the patient nor the timing of such treatment were altered by participation in this study. Statistical analysis was performed by using Chi Square on the 2 x 2 tables (Tables 1, 3) and on the rectangular table (Table 2) Chi Square test for trend was used because of the ordinal sequence of the independent variable.

RESULTS

Seventy three consecutive cases were collected from 1/1/89 to 8/31/89. There were 25 exposures in children < 6 years (34.2%), 11 exposures in adolescents (15.1%), and 37 exposures in adults (50.7%). Ten

TABLE 1

Acute vs Previous Chronic Exposure to Carbamazepine

	Acute	Chronic	Total	P*
Coma	7/21	5/37	13/62	>.05
Ventilation	4/21	3/37	8/62	>.05
Seizure	1/21	8/37	9/62	>.05

* Chi Square

TABLE 2

Peak Measured Serum Level vs Coma, Seizures and Mechanical Ventilation

PMSL (mcg/ml)	Patient Total	Coma		Seizures		Mechanical Ventilation		Mean Stay (days)	
		Yes	No	Yes	No	Yes	No	ICU	HOSP
0 - 9.9	10	1	9	0	10	1	9	0.9	1.4
10 - 19.9	16	0	16	1	15	0	16	0.8	1.6
20 - 29.9	21	5	16	3	18	2	19	1.4	2.4
30 - 39.9	12	4	8	4	8	2	10	1.4	2.8
40 - 49.9	2	2	0	0	2	2	0	4.5	6.0
50 - 59.9	1	1	0	1	0	1	0	2.0	3.0
Total	62	13	49	9	53	8	54		

TABLE 3

History of Seizure Disorder vs Seizure Occurrence

	Seizure		
	Yes	No	Total
Seizure History			
Yes	8	23	31
No	1	25	26
Unknown History	0	5	5
Total	9	53	62

Chi Square P < .05 (.03)

adult cases and one adolescent case were excluded from analysis due to the presence of coingestants or inadequate information. Peak measured serum levels (PMSL) of total carbamazepine ranged from 0.3 to 56 mcg/ml. Thirty one patients (50%) had a history of a seizure disorder, 10 of whom were children < 6 years. Thirty seven patients (60%) used CBZ chronically for therapeutic reasons prior to entering the study. Using the presence of coma, seizures or respiratory depression requiring mechanical ventilation we found poor correlation between rising PMSL and toxicity.

Of the 62 cases analyzed, 13 became comatose (21%) (Tables 1,2). Patients who used CBZ chronically prior to the development of toxicity had a somewhat lower incidence of coma ($p > .05$). Increases in PMSL below 40 mcg/ml did not correlate with the incidence of coma ($p > .05$), but when levels above 40 mcg/ml were included a significant correlation was found ($p < .05$). No correlation between duration of coma and PMSL was found in the 10 patients with a known length of coma (Figure 1). Three patients presented already in coma and we were unable to determine the time of onset of coma by history.

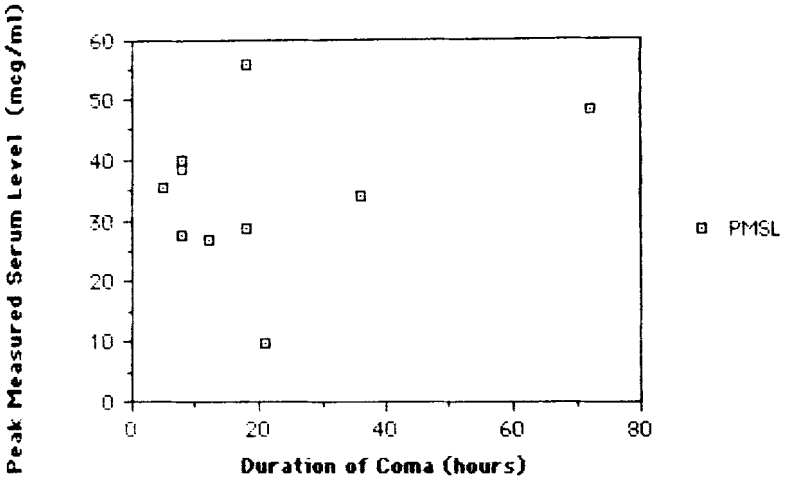

Figure 1: Duration of Coma Versus PMSL

Nine patients had seizures (14.5%). No correlation was found with rising PMSL and seizure incidence (Table 2). Seizures occurred in patients with recorded PMSL ranging from 18.0 mcg/ml to 56.0 mcg/ml. A significant relationship was found when we compared seizure incidence in patients with and without a history of a seizure disorder ($p < .05$) (Table 3). However, no correlation was discovered when we compared previous chronic use and the occurrence of seizures (Table 1). Only two patients with recorded seizures experienced coma or respiratory depression requiring mechanical ventilation.

Eight patients required mechanical ventilation (12.9%). No correlation was found for the need for mechanical ventilation and patients with previous chronic use ($p > .05$) (Table 1). PMSL up to 40 mcg/ml did not correlate with an increased incidence of respiratory depression ($p > .05$), but when levels above 40 mcg/ml were included a significant correlation was found ($p < .05$) (Table 2). Seven of these patients received multiple dose activated charcoal (MDAC), while one patient received only a single

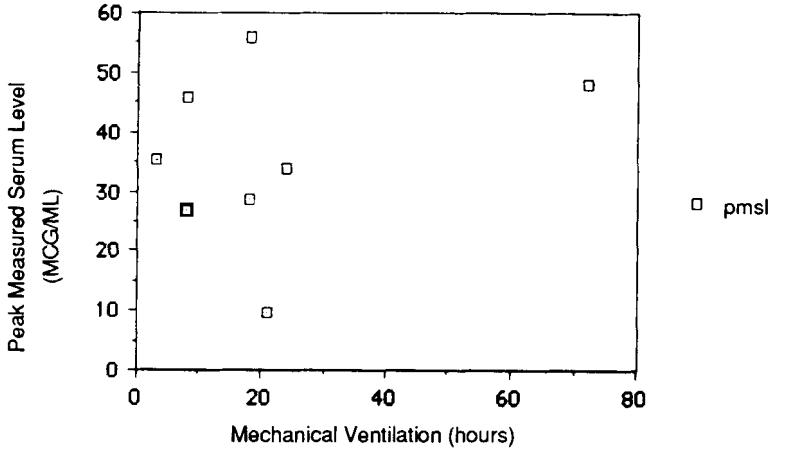

Figure 2: Duration of Mechanical Ventilation Versus PMSL

dose. The mean and median duration of mechanical ventilation with MDAC was 23 hrs and 18 hrs, respectively (PMSL range 9.6-56 mcg/ml). The duration of mechanical ventilation for the patient receiving a single dose of activated charcoal was 12 hours (PMSL 46 mcg/ml). There was no correlation between the PMSL and duration of mechanical ventilation (Figure 2).

Sinus tachycardia (> 100 bpm in adults and adolescents, > 160 bpm in children < 2 yrs, > 130 bpm in children 2-5 yrs) was noted in 22 patients (35.5%). Cardiac conduction defects were rare (one child). This was a Mobitz type II block and did not compromise the patient's cardiovascular condition. Hypotension was not seen in this study. Increased temperature (> 38.3°) was observed in five patients (8%). No correlation was found when we compared the rising PMSL and the incidence of increased temperature. One child had a recorded temperature of 35.4°. There appeared to be a trend for a longer mean ICU stay and total hospital stay with rising PMSL (Table 2). However, there were such wide intra and interpatient variations in PMSL with the patients in ICU, as seen in Figure 3, that this appears to be an unreliable indicator. Increased hospital stay

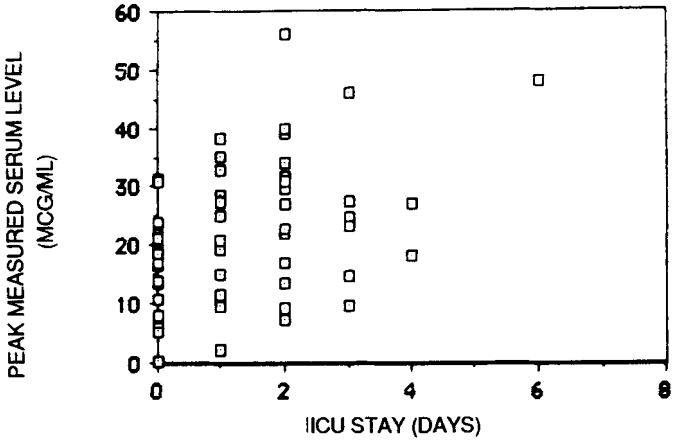

FIGURE 3: ICU STAY VERSUS PMSL

did appear to correlate well with rising PMSL (Figure 4). The mean hospital stay was 2.26 days (SD = 1.46), while the mean ICU stay was 1.27 days (SD = 1.31). Twenty four patients (38.7%) were never admitted to an ICU and a total of 35 patients (56.5%) stayed one day or less.

The thirteen patients who developed coma and/or respiratory depression were analyzed for time of onset of serious symptoms. Seven of these patients had acute ingestions without previous chronic use. The time of onset of coma in these patients was 4.1 hours ($\pm$ 1.9). The time of onset of respiratory depression was 4.2 hours ($\pm$ 2.8). The remaining six patients either had a slow chronic rise of serum level or we were unable to determine time of ingestion.

Cyclical coma with alternate waxing and waning of consciousness, occurred in two patients. One was a mentally retarded adult with previous chronic exposure and the second was a child with no previous exposure. Multiple dose activated charcoal was used in both patients without apparent benefit.

Treatment in this series was mainly supportive, treatment for seizures was administered to two patients. One child, without a history of a seizure

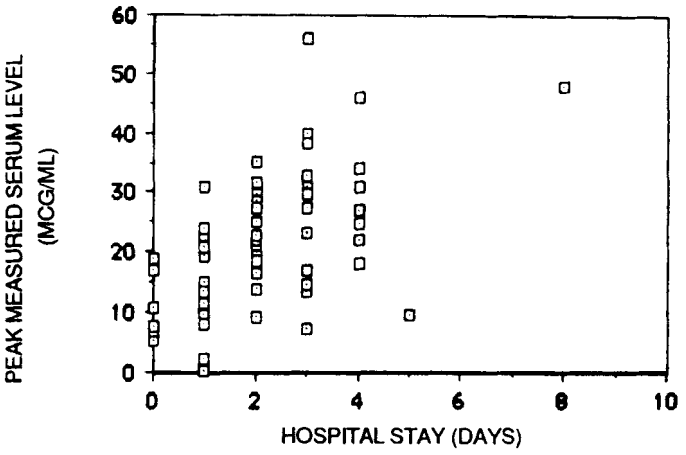

FIGURE 4: HOSPITAL STAY VERSUS PMSL

disorder, was treated with lorazepam with success. A second child, with a history of seizure disorder, was treated with diazepam and phenytoin, also with success. The remaining seven patients with seizures did not require treatment. Multiple dose activated charcoal was administered to 32 patients, while 25 received only a single dose of activated charcoal and six patients received no charcoal.

DISCUSSION

As a result of the increasing and widespread use of CBZ, intentional and accidental overdoses with CBZ have become much more common. It is essential, therefore, to adequately characterize the symptomatology of the overdose situation and its correlation with serum CBZ levels. To date, a prospective analysis of this type has not been performed. We prospectively and consecutively assessed 62 toxic CBZ ingestions in order to determine the validity of correlating toxicity of CBZ ingestion with serum CBZ levels as well as to discover if certain patient risk factors could serve as prognostic indicators.

Many case reports exist in the literature which cite the various signs and symptoms that have been associated with toxic ingestions of CBZ (3-24). These include: drowsiness and stupor which may lead to coma in some patients; respiratory depression, which may result in the need for assisted ventilation; tachycardia, hypotension, hypertension; nausea, vomiting, decreased bowel sounds; hypersensitivity skin reactions; and hypothermia. Several deaths associated with toxic carbamazepine ingestions have been reported (7,25,26).

Weaver et al. attempted to correlate the degree of symptomatology in CBZ overdose with CBZ serum levels by assessing four of their own cases of CBZ toxicity as well as reviewing the existing literature on this topic (24). They concluded that clinical events in CBZ overdose can be characterized by a four stage sequence related to measured serum levels of CBZ. We believe that a prospective and consecutive assessment of all toxic CBZ ingestions more successfully reduces the bias inherent in a retrospective, nonconsecutive analysis. Our findings revealed no correlation between severity of toxicity and CBZ serum levels less than 40 mcg/ml. A significant relationship between severity of toxicity and serum levels greater than 40 mcg/ml did occur but the small number of patients with serum levels > 40 mcg/ml evokes a cautious interpretation. Furthermore, it should be noted that 26 of our patients (42%) had PMSL < 20 mcg/ml, a generally accepted threshold for toxicity.

Protein binding of CBZ has been reported to be 70% to 80% (23,27). However wide interpatient variation of protein binding of CBZ, ranging from 52.2% to 90%, has been reported (28). This may be a dose dependent phenomenon (27). CBZ has a brain concentration to serum free drug concentration ratio of only slightly above one (29). A large interpatient variation in free serum drug concentration possibly could alter brain concentrations of CBZ. This might explain the wide variation of symptomatology seen in our study at similar toxic ranges.

Carbamazepine-10,11-epoxide (CBZ-E), the active metabolite of CBZ has anticonvulsant activity and in overdose must be considered to possibly

have toxic properties as well (13,19). Protein binding of CBZ-E in overdose has been reported to be approximately 50%, but this may also be dose dependent (19,23). A brain to blood concentration ratio for CBZ-E has been reported to be approximately one (29). We did not measure CBZ-E levels and so cannot comment if it would be a useful prognosticator alone or in conjunction with CBZ levels.

Several other authors have questioned the validity of correlating serum CBZ levels with severity of overdose symptomatology (30-32).

In our patient population, chronic CBZ use did not seem to alter the risk of toxic effects. The incidence of coma and respiratory depression in chronic users did not differ from that of the larger group. A slight tolerance to CNS depression was noted with chronic CBZ use, but the difference was not statistically significant. As noted by several authors, CBZ induces liver enzymes to more rapidly metabolize CBZ (1,2,13). Thus with chronic use, the elimination half-life of CBZ decreases significantly from 20-65 hours in normal adults to approximately 12 hours (1,2,13).

Toxic effects were uncommon at PMSLs < 20 mcg/ml. However, one incident of coma with respiratory depression occurred at a PMSL of 9.6 mcg/ml in a two year old child without previous exposure. This child deteriorated from increasing lethargy to a point where he was responsive to deep pain, with periods of apnea. At 2.5 hours post-ingestion he was intubated and placed on a ventilator. Serial CBZ levels were 8.9, 9.6, 9.0, 8.1, and 1.3 mcg/ml at 1, 5.5, 9.5, 13.5, and 41.5 hours post-ingestion, respectively.

It is unclear if CBZ in toxic doses is epileptogenic, but it appears to have caused a seizure in one patient without a previous seizure disorder. The incidence of paradoxical seizures in patients with toxic levels of CBZ and with histories of a seizure disorder may perhaps indicate a loss of seizure control when serum levels rise above 20 mcg/ml.

CONCLUSION

In this series of carbamazepine overdose in 73 subjects, we did not find serum carbamazepine levels < 40 mcg/ml to be predictive of toxicity.

We concur that management decisions should be based on the patients clinical presentation (33). A history of a seizure disorder was found to be predictive of increased risk of a seizure. The risk of cardiovascular complications was low and may relate to the young age of the subjects. The incidence of minor neurologic symptoms such as nystagmus, ataxia, intention tremor, dysarthria, and drowsiness was not tabulated. Major neurologic effects occurred infrequently (coma 21%, seizures 14.5% and respiratory depression 12.9%) and responded well to supportive care. No fatalities occurred.

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