Seizure 1999; **8**: 250–252
Article No. seiz.1999.0281, available online at http://www.idealibrary.com on IDEAL®

CASE REPORT

Carbamazepine, hepatotoxicity, organic solvents, and paints*

KENNETH R. KAUFMAN

Departments of Psychiatry and Neurology, UMDNJ-Robert Wood Johnson Medical School, 125 Paterson Street, Suite #2200, New Brunswick, NJ 08901, USA

Hepatotoxicity secondary to carbamazepine is a serious condition which can be fatal. However, other concomitant medications or environmental factors may be the offending agents. In this case report, hepatotoxicity secondary to organic solvents and paints is described.

Key words: hepatotoxicity; carbamazepine; organic solvents; paints; bipolar disorder.

INTRODUCTION

Treatment of bipolar affective disorders has become more comprehensive during the past decade. Where, once, lithium was the only mood stabilizing psychotropic, anticonvulsants have become the treatment of choice for mixed/rapid cycling disorders and first line agents for classical manias and bipolar depressed patients[1,2]. Blood dyscrasias (neutropenia, thrombocytopenia, anemia) and liver function abnormalities to the point of frank hepatotoxicity are well-known complications associated with anticonvulsants monitored by epileptologists[3]. Furthermore, the fatality rate for hepatotoxicity associated with carbamazepine is 25%[4]. With the advent of anticonvulsants in the treatment of bipolar disorders, it is critical that similar monitoring be performed by psychiatrists. What is not appreciated is the potential for a concomitant chemical, be it pharmaceutical or environmental, to be the offending agent. In this case report, organic solvent and paint hepatotoxicity masquerading as carbamazepine hepatotoxicity is described.

CASE

This patient, a 48 year old white married male, has a 23 year history of bipolar affective disorder[5]. He first presented with a classic manic cluster, including increased creativity, pressured speech, flight of ideas, grandiosity, decreased sleep, decreased appetite and spending sprees which required hospitalization. The patient responded to lithium and remained symptom free for 5 years when, after being taken off lithium for 18 months, he had a recurrent manic episode. On that occasion he revealed cycling and was hospitalized three times within 6 months. Again, he was stabilized on lithium and was on 1500/1800 mg qd, when first seen by this physician in 1984. The patient's lithium level was 0.7 mEq/l. The same regimen was maintained through the spring of 1987. Liver function tests and CBC remained normal between 1984–1987. When seen on 19/5/87, the patient was in a hypomanic state and clearly escalating. His lithium was increased to 1800 mg qd with a resultant blood level of 1.1 mEq/l. Haloperidol was titrated up to 20 mg qd with benztropine prn. Unfortunately, in his increasingly confused state as his manic episode worsened, he took the benztropine on a regular basis and haloperidol prn. The patient was ultimately hospitalized from 2/6/87–15/7/87 with a complete manic cluster, marked confusion, and frank delusions. As the patient had had a lithium breakthrough episode with historical cycling, the patient was changed to carbamazepine which was titrated successfully to 200 mg qid. During the hospitalization, all chemistries were within normal limits excluding mildly elevated SGPTs—the admission value was 55 and the discharge value was 58.

* Presented at the 22nd Epilepsy International Congress, Dublin, Ireland, June 30, 1997.

1059–1311/99/040250 + 03 $12.00/0

Table 1: Serial liver enzymes on anticonvulsants with hepatotoxic agents.

Date	SGOT <50	SGPT <55	GGT <65	Alkaline phosphatase <140	Anticonvulsant
15/7/87	nl	58	nl	nl	CBZ
5/8/87	26	37	88	nl	CBZ
16/11/87	116	234	296	173	CBZ
23/11/87	109	213	256	149	CBZ
15/12/87	51	112	192	116	CBZ
22/12/87	47	95	196	131	CBZ
29/12/87	41	79	177	130	CBZ
5/1/88	33	63	155	128	CBZ
12/1/88	38	72	160	129	CBZ
19/1/88	32	49	133	118	CBZ
26/1/88	32	35	110	115	CBZ
1/2/88	27	43	108	123	CBZ
18/2/88	28	44	103	118	CBZ
2/3/88	22	31	85	111	CBZ
1/6/88	24	37	84	135	CBZ
22/11/88	23	32	87	122	CBZ
21/2/89	21	25	73	99	CBZ
17/7/90	23	32	79	124	CBZ
10/7/91	28	34	80	119	CBZ
24/9/92	27	31	107	138	CBZ
15/12/93	36	42	113	131	CBZ
29/9/94	21	19	105	87	CBZ
9/5/95	19	19	81	102	CBZ
22/12/95	21	25	93	60	CBZ + VPA [a]

[a] CBZ, carbamazepine; VPA, valproic acid.

The carbamazepine blood level on 200 mg qid was 6.5 mg/l.

As an outpatient following this hospitalization, the patient remained stable on the carbamazepine regimen. The first liver function tests drawn on 5/8/87, or three weeks after discharge, were all normal excluding a GGT of 88 (normal is <65). The patient did not have his next blood work drawn as scheduled, and his liver function tests drawn on 16/11/87 revealed marked abnormalities: SGOT 116 (normal is <50), SGPT 234 (normal is <55), GGT 296, and alkaline phosphatase 173 (normal is <140).

The patient had no jaundice, itching, change in the color of his stool or urine, or loss of appetite. At this juncture, a critical decision concerning the continuation of carbamazepine was required. Repeat liver function tests on 23/11/87 revealed continued significant abnormalities; however, the values of all four liver function tests decreased to 109, 213, 256, and 149, respectively. This physician pursued an in-depth evaluation of the patient for any other potential etiology and determined to continue this psychotropic regimen while closely monitoring the liver function tests as long as serial liver function tests continued to decrease. The internist in concert with a hepatology consultant recommended discontinuation of the carbamazepine.

The comprehensive history of potential occupational/environmental/medical offending agents revealed that the patient had recently painted his home prior to the initial transaminase spikes. More importantly, he had used paint thinner, carbon tetrachloride, organic solvents, and both acrylic and enamel paints in enclosed areas without ventilation. The other factor noted was a long-term history of drinking, 6–8 beers per week.

Hepatitis screen and abdominal ultrasound were both negative as were extensive chemistries. Absolute eosinophil counts were always normal. Regardless of instructions, the patient continued the same alcohol consumption. As noted in Table 1, all liver enzymes continued to improve even though the patient remained on carbamazepine.

During the past nine years, the patient has had further bipolar episodes requiring increased titration of carbamazepine to a maximum dosage of 1600 mg qd with clonazepam 2 mg qd and risperidone 4–6 mg qd. Ultimately, the patient was initiated on valproic acid with the intent of changing to valproic acid as monotherapy. When last seen by this physician on 1/2/96, the patient was on carbamazepine 1400 mg qd and valproic acid 2250 mg qd with normal liver function tests excluding a GGT of 93. Repeat hepatitis A/B/C screen remained negative for prior hepatitis. The patient had continued alcohol ingestion of 6–8 beers per week.

DISCUSSION

The patient's liver function abnormalities could have been secondary to carbamazepine. In that case, the consequences of marked morbidity, if not fatality, are significant[4, 6, 7]. Carbamazepine induced hepatotoxic-

ity appears to be immune mediated, presents as an acute granulomatous hepatitis, responds to drug withdrawal, and reoccurs with drug rechallenge[6–9]. In this case, the transaminase spikes occurred 4 months after initiation of carbamazepine and the eosinophil count was always normal. Furthermore, continued treatment with carbamazepine did not lead to increased liver dysfunction. A liver biopsy was not performed in this case since the liver function tests were improving. The patient's alcohol consumption remained constant before, during and following the period of elevated transaminases and, as such, alcohol was not considered to be the etiologic factor. Without any medical illness or known drug reaction, the abnormalities were presumed to be directly caused by paint, paint thinner, carbon tetrachloride and other organic solvent exposure.

This physician delayed discontinuing carbamazepine based upon the comprehensive history of other potentially offending agents and the patient's excellent response to this psychotropic. At the same time, serial liver function tests were performed in addition to abdominal ultrasound and absolute eosinophil count. Had increasing liver dysfunction, elevated eosinophil count, or abnormal abdominal ultrasound been noted, the carbamazepine would have been immediately discontinued. At that point, a liver biopsy would have been pursued. In such circumstances, this patient would have then been changed to valproic acid for his bipolar disorder. Had this been a patient with epilepsy who was exquisitely controlled with carbamazepine, a rechallenge at a very low dosage would have been considered.

The literature supports the association between hepatotoxicity and exposure to paints and organic solvents[10–12]. One negative study referred to the inhalation of non-chlorinated solvents, whereas carbon tetrachloride was involved in this case[13]. In another study, the liver function tests normalized within 6 weeks of discontinuation of exposure[12]. In this case, all liver function tests were within normal limits excluding GGT within 9 weeks. Furthermore, paint thinner has been shown to potentiate carbon tetrachloride hepatotoxicity[14]. None of the studies addressed exposure without adequate ventilation.

The patient continued to use paint after the episode of liver dysfunction, but only when there was adequate ventilation and he discontinued the use of paint thinner or carbon tetrachloride. He has not shown any further transaminase spikes. Even with the addition of valproic acid, there has been no change in liver function tests.

The author concludes that this isolated episode of elevated liver function tests was causally related to the use of paints, paint thinner, carbon tetrachloride, and organic solvents in enclosed areas without ventilation. Whether there was a synergistic effect among these agents and carbamazepine is unknown. The author recommends monitoring liver function tests in patients on carbamazepine, while always obtaining a complete history for any other potentially hepatotoxic agent. Furthermore, the patient on carbamazepine should be advised that exposure to other hepatotoxic medications or occupational agents should be as minimal as possible. Finally, the clinician must always remember that the true etiology will often masquerade.

REFERENCES

1. Frances, A., Doherty, J. P. and Kuhn, D. A. The expert consensus guideline series—treatment of bipolar disorder. *Journal of Clinical Psychiatry* 1996; **57**: 1–88.
2. Post, R. M., Altshuler, L. L., Ketter, T. A., Denicoff, K. and Weiss, S. R. Antiepileptic drugs in affective illness: clinical and theoretical implications. *Advances in Neurology* 1991; **55**: 239–277.
3. Wyllie, E. and Wyllie, R. Routine laboratory monitoring for serious adverse effects of antiepileptic medications: the controversy. *Epilepsia* 1991; **32** (Suppl. 5): S74–S79.
4. Dreifuss, F. E. and Langer, D. H. Hepatic considerations in the use of antiepileptic drugs. *Epilepsia* 1987; **28** (Suppl. 2): S23–529.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Washington, DC, American Psychiatric Association, 1994.
6. Horowitz, S., Patwardhan, R. and Marcus, E. Hepatotoxic reactions associated with carbamazepine therapy. *Epilepsia* 1988; **29**: 149–154.
7. Davion, T., Capron, J. P., Andrejak, M., Geoffroy, P., Capron-Chivrac, D. and Quenum, C. Acute hepatitis due to carbamazepine: study of a case and review of the literature. *Gastroenterologie Clinique et Biologique* 1984; **8**: 52–56.
8. Levy, M., Goodman, M. W., Van Dyne, B. J. and Sumner, H. W. Granulomatous hepatitis secondary to carbamazepine. *Annals of Internal Medicine* 1981; **95**: 64–65.
9. Levander, H. G. Granulomatous hepatitis in a patient receiving carbamazepine. *Acta Medica Scandinavica* 1980; **208**: 333–335.
10. Dossing, M., Arlien-Soborg, P., Milling Petersen, L. and Ranek, L. Liver damage associated with occupational exposure to organic solvents in house painters. *European Journal of Clinical Investigations* 1983; **13**: 151–157.
11. Chen, J. D., Wang, J. D., Jang, J. P. and Chen, Y. Y. Exposure to mixtures of solvents among paint workers and biochemical alterations of liver function. *British Journal of Industrial Medicine* 1991; **48**: 696–701.
12. Sotaniemi, E. A., Sutinen, S., Arranto, A. J. and Pelkonen, R. O. Liver injury in subjects occupationally exposed to chemicals in low doses. *Acta Medica Scandinavica* 1982; **212**: 207–215.
13. Lundberg, I. and Hakansson, M. Normal serum activities of liver enzymes in Swedish workers with heavy exposure to organic solvents. *British Journal of Industrial Medicine* 1985; **42**: 596–600.
14. Toskulkao, C., Nhongsaeng, J. and Glinsukon, T. Potentiation of carbon tetrachloride induced hepatotoxicity by thinner inhalation. *Journal of Toxicological Sciences* 1990; **15**: 75–86.