A REVIEW OF CARBAMAZEPINE'S HEMATOLOGIC REACTIONS AND MONITORING RECOMMENDATIONS

Jenelle L. Sobotka, Bruce Alexander, and Brian L. Cook

ABSTRACT: Early case reports of fatal hematologic effects attributed to carbamazepine (CBZ) resulted in extensive monitoring recommendations by the manufacturer. The rarity of blood dyscrasias led many authors to question the manufacturer's guidelines. Thus the manufacturer removed specific monitoring guidelines, allowing physicians to monitor CBZ using their clinical judgment. This article reviews case reports and studies of CBZ's hematologic effects. Due to their rapid onset, daily laboratory checks would be necessary to monitor for aplastic anemia, agranulocytosis, and thrombocytopenia. These adverse effects are best monitored by informing patients and physicians to carefully watch for signs and symptoms. Leukopenia develops more slowly, occurring in approximately 12 percent of children and 7 percent of adults. Its onset is typically within the first three months of treatment, with patients at risk having a low or low-normal pretreatment white blood cell (WBC) count. Leukopenia often reverses, even if CBZ is continued. Based upon our review of the literature, we recommend monitoring of those high-risk patients during the first three months of treatment with the frequency being determined by results of each laboratory value. WBC counts $<3000/mm^3$ or neutrophil counts below $1000/mm^3$ warrant a decrease in dose with frequent monitoring or CBZ discontinuation, if necessary.

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EARLY REPORTS of fatal hematologic effects attributed to carbamazepine (CBZ) resulted in manufacturer recommendations for extensive laboratory monitoring. Several alternative monitoring protocols have been published, indicating disagreement with the manufacturer's recommendations. The manufacturer has, therefore, made significant changes in its recommendations. This article focuses on those changes and CBZ's hematologic effects, and provides a suggested monitoring protocol.

Review of Monitoring Protocols

From 1969 to 1974 the *Physicians' Desk Reference (PDR)* recommended hematologic monitoring of Tegretol with platelet and complete blood counts (CBCs) before treatment, weekly during the first month of therapy, every two weeks during the second and third months, and monthly for the duration of treatment. De Vries' recommendations published in 1965 for monitoring all anticonvulsants is quoted as the source of this schedule.[1,2] Interestingly, De Vries' protocol was less stringent as CBCs were recommended at baseline, weekly during the first month, monthly through the first year, and quarterly thereafter. In addition, he recommended intensified monitoring following dosage changes.

In 1975, the manufacturer's recommended monitoring frequency was increased to weekly for the first three months of treatment, then monthly for a period of at least two to three years.[3] Recommendations to obtain baseline reticulocyte counts and serum iron were added. These recommendations did not change through the 1988 *PDR*. All *PDR*s from 1975 through 1988 recommended CBZ discontinuation if blood indices decreased below the following minimums: "erythrocytes less than $4\,000\,000/mm^3$, hematocrit less than 32 percent, hemoglobin less than 11 gm%, leukocytes less than $4000/mm^3$, platelets less than $100\,000/mm^3$, reticulocytes less than 0.3 percent (20 000), or serum iron levels greater than 150 μg/100 mL."[4]

The rarity of severe blood dyscrasias attributed to CBZ led many authors to question the necessity of the manufacturer's 1975–88 monitoring schedule.[2,5-12] Alternative recommendations published between 1974 and 1988 vary widely,[2,5,7,13-15] ranging from baseline only,[7] monthly for the first year,[14] to routinely during the first 12 weeks of treatment.[5]

Starting with the 1989 *PDR* and Tegretol's current package insert dated September 1989, specific hematologic monitoring guidelines have been removed. Only pretreatment CBC, platelet count, and possibly reticulocyte count and serum iron are specifically mentioned.[16,17] Thus, prescribers are allowed to determine monitoring frequency during treatment based on their clinical judgment. The 1989 *PDR* also indicates, "if blood indices are below baseline levels at any time during CBZ treatment, the patient should be closely monitored." In place of a regular monitoring schedule, the revised guidelines suggest patients should be informed of the early signs and symptoms of hematologic problems, such as fever, sore throat, ulcers in the mouth, easy bruising, and petechial or purpuric hemorrhage and should report to the prescriber immediately if these signs or symptoms appear.[16]

The manufacturer justifies the change in recommendations by stating in its package insert, "the risk of develop-

JENELLE L. SOBOTKA, Pharm.D., at the time of writing was a Doctor of Pharmacy Student at the University of Iowa; she is now a Clinical Pharmacist, Departments of Pharmacy and Medicine, Iowa City Veterans Affairs Medical Center, and a Clinical Assistant Professor, College of Pharmacy, University of Iowa; **BRUCE ALEXANDER,** Pharm.D., is a Clinical Pharmacist, Departments of Pharmacy and Psychiatry, Iowa City Veterans Affairs Medical Center, and a Clinical Associate Professor, College of Pharmacy, University of Iowa, 2255 Quadrangle, Iowa City, IA 52242; and **BRIAN L. COOK,** D.O., is a Staff Psychiatrist, Iowa City Veterans Affairs Medical Center, and an Assistant Professor, Department of Psychiatry, College of Medicine, University of Iowa. **Reprints:** Bruce Alexander, Pharm.D.

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ing [aplastic anemia and agranulocytosis] is 5–8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia."[17]

Hematologic Reactions

CBZ's hematologic effects can be divided into bone marrow suppressive and proliferative effects. In a 1981 review, 78 percent of the adverse reactions were related to bone marrow suppression, presenting as leukopenia, anemia, neutropenia, thrombocytopenia, or aplastic anemia. A proliferative effect occurred in 14 percent of the cases as eosinophilia, lymphocytosis, leukocytosis, or macrocytosis. The remaining eight percent were unspecified hematologic complications.[18]

Although many CBZ reports have found hematologic laboratory abnormalities, many more studies have reported no evidence of clinically significant hematologic effects.[13,19-28] Based on case reports and CBZ tablets dispensed from 1972 to 1979, Pisciotta calculated an incidence rate for all hematologic disorders to range from 1:10 800 to 1:38 000 per year.[5] Ballenger in 1987 reported the rate of bone marrow suppresion to be between 1:10 000 and 1:50 000 cases.[6] In a 1982 review, a prevalence of aplastic anemia of <1:50 000 and an incidence of 0.5:100 000 per year was calculated.[2] Pellock indicated that 2.2 deaths per million exposures were associated with aplastic anemia and agranulocytosis.[19] Thrombocytopenia prevalence rate has been estimated to be two percent.[2]

APLASTIC ANEMIA

In 1982, Pisciotta reviewed 22 case reports of aplastic anemia in patients receiving CBZ.[5] These and five additional case reports are summarized in Table 1. No relationship between daily dose or total cumulative dose and aplastic anemia was detected.

Twenty-five of 27 cases listed in Table 1 specified duration of treatment, which ranged from 4 to >1500 days (average ± SD 4.4 ± 3.3 months). Ninety-five percent occurred within 11 months of treatment initiation. However, this figure may be misleading as aplastic anemia occurring beyond 11 months may be less likely to be attributed to CBZ and thus not reported.

Pisciotta considered most cases of aplastic anemia to be only possibly related to CBZ as 19 of the 22 cases had confounding variables.[5,38] Coincidental disease (e.g., hepatitis, lupus, tuberculosis, leukemia) or concurrent medications (e.g., phenytoin, mephenytoin, ethotoin, aminopyrine, primidone, chlorpropamide, ethosuximide, primaquine phosphate) may have adversely influenced the hematologic system in these cases.

AGRANULOCYTOSIS

In 1982, 16 case reports of agranulocytosis associated with CBZ were reviewed.[5] These appear in Table 2 with seven additional cases.

Agranulocytosis was unrelated to daily dose or total cumulative dose. Onset of agranulocytosis ranged from 6 to 1100 days following CBZ initiation. In 18 of 20 cases that reported duration of treatment, agranulocytosis occurred within four months of starting CBZ.

Table 1. Cases of Aplastic Anemia Associated with Carbamazepine

REF	AGE (y)	SEX	DOSE (mg/d)	TREATMENT DURATION (d)	OUTCOME
5	52	F	300–1200	180	died
5	90	F	800	40	recovered
5	75	F	600	18	died
5	54	M		20	died
5	51	M	600	30	died
5	18	F	200–400	16	died
5	45	F	800	330	died
5	44	F	800	180	died
5	32	M	500	120	died
5	32	M	500	30–90	died
5	62	F		15	died
5	30	F		months	on treatment
5	15	F	600	120	died
5	63	F		4	recovered
5	32	M	600	120	on treatment
5	17	F	100–300	120	recovered
5	21	F	200	>1500	recovered
5	2	F		90	
29	52	F	800	270	died
30	69	F	400–800	240	died
31	48	F	600–800	270	recovered
32					recovered
33	59	M	200–600	>90	died
34	53	M		210	recovered
35	30	F	1600	240	on treatment
36	24	F	800	170	died
37	52	F	600	270	died

Table 2. Cases of Agranulocytosis Associated with Carbamazepine

REF	AGE (y)	SEX	DOSE (mg/d)	TREATMENT DURATION (d)	OUTCOME
5	62	M	600	60	recovered
5	2			90	recovered
5	59	M	300	120	recovered
5	57	F			recovered
5	9	M	1400	120	recovered
5	40	F	600	75	died
5	7	M	400	150	recovered
5	29	F	800		on treatment
5	13	F	400	1100	on treatment
5	42	F	200–600	7	recovered
5	5	F	700		
5	31	M	900	30	recovered
5	2	M	200	6	recovered
9	1	F		61	recovered
9	6	F		21	recovered
39	11	F	15 mg/kg	30	recovered
40	47	M	400–600	56	recovered
41	31	M	600–900	34	recovered
42	49	F	600	32	recovered
43	61	M	600	48	recovered
44	48	M	400	32	died
45	73	M	600	11	died
46	38	M	600	21	recovered

LEUKOPENIA

Several studies in adults have reported a clinically insignificant leukopenia occurring in 2–14 percent (average 6.5

percent) of the patients.[10,14,47-49] For example, in one study, mean white blood cell (WBC) counts in 155 patients decreased significantly ($p<0.01$) after one month of treatment from 7500 to 6900/mm^3.[50] Thereafter, mean WBC counts stabilized at values lower than baseline but still within the normal range. Four patients had one or more WBC counts between 2000 and 3000/mm^3. Drug treatment was not discontinued in any patient.

Studies in children have demonstrated an incidence rate of 2–17 percent (average 12 percent).[7,13,19,28,51] The leukopenia usually resolves with continued treatment.[7,13,19,27] One study of 120 children reported the pretreatment WBC counts to be significantly lower ($p<0.05$) in those children who developed leukopenia compared with those who did not (6058 ± 1980/mm^3 vs. 8517 ± 3044/mm^3, respectively).[51] Also, the WBC and neutrophil counts in those patients who developed leukopenia, although reduced, were not significantly different during treatment with CBZ compared with pretreatment values. CBZ was discontinued in three children for a persistent neutrophil count <1000/mm^3. Another study of 220 children also found that those who developed leukopenia had either lower pretreatment WBC counts, a concomitant viral infection, or both.[19]

In summary, a benign or clinically unimportant leukopenia, where the leukocyte count drops to 4000/mm^3 has been reported in approximately 12 percent of children and 7 percent of adults treated with CBZ.[2,7,10,13,19,27,28,47,48,50,51] Typically, the WBC count may be decreased by as much as 25 percent[6] and this usually occurs within the first three months of treatment.[10] However, in almost all cases the WBC count returns to baseline with treatment continuation.[2,7,11,13-15,19,21,22,24,25,49,52-58] In some cases, the leukopenia is persistent but without clinical significance.[10,13,49,53,56,58,59] The leukopenia and neutropenia are more common in patients with low-normal pretreatment WBC or neutrophil counts.[2,49,51-53]

Three studies found no relationship between CBZ dose or blood concentration and changes in total WBCs.[14,20,51] However, a number of studies have reported that dose reduction can increase the WBC count.[49,53,56-59] In a recent case report of significant leukopenia, CBZ was successfully reinstituted at a lower dose and gradually increased with prevention of the leukopenia.[59]

THROMBOCYTOPENIA

Case reports have linked CBZ with both a mild transient decrease in platelets and a severe isolated thrombocytopenia. Thrombocytopenia was the most common CBZ-related hematologic reaction reported to the manufacturer from 1985 to 1987 as 31 of 80 reports involved platelets.[19] Published cases of isolated thrombocytopenia are listed in Table 3. An additional case of a reduction in platelet and WBC counts has been reported, but the lowest counts of 158 000 platelets/mm^3 and 4400 WBCs/mm^3 were still within normal limits.[68] Several studies have reported thrombocytopenia with CBZ.[14,22,47,52] The minor decrease in platelets occurred in approximately two percent of the patients and reversed with CBZ discontinuation.

Table 3. Cases of Thrombocytopenia Associated with Carbamazepine

REF	AGE (y)	SEX	DOSE (mg/d)	TREATMENT DURATION (d)	OUTCOME
60	79	F	800	300	recovered
61	49	F	800	7	recovered
62	16	F	600	14	recovered
63	31	F	400	60	recovered
64	15	M	750	6	recovered
65	33	F	800	24	recovered
66	66	F	600	17	recovered
67	4	F	300	14	recovered

MISCELLANEOUS

Individual case reports of miscellaneous hematologic reactions associated with CBZ appear in Table 4. One study reported eosinophilia in 5.5 percent of 653 CBZ-treated patients.[76] In five cases, the concentration returned to normal. However, in the other 31 cases the concentrations remained elevated. Davis found eosinophilia in 17 (24 percent) of 71 subjects followed for three years. Though the differential count was usually less than 10 percent, two patients had eosinophil values of 18 and 21 percent. Unlike the previous study, eosinophilia cleared spontaneously without CBZ discontinuation.[47]

Demographic Risk Factors

Patients with low pretreatment WBC counts are at increased risk of developing leukopenia.[2,19,28,49,51-53] There is no evidence that age or gender affects the incidence of CBZ-associated hematologic effects.[19,28,54]

As of 1974, aplastic anemia was reported in 11 patients with trigeminal neuralgia and four patients with epilepsy.[14] This report suggested that patients with trigeminal neuralgia, being older, may be more susceptible to this adverse effect. In a 1981 review, patients receiving CBZ for epilepsy accounted for 78 percent of all hematologic reactions although epilepsy was the indication for CBZ in only 52 percent of the sample.[18] In patients with epilepsy, the hematologic changes occurred in WBCs, red blood cells, and platelets; in other diagnoses, almost all reported cases were leukopenia. A possible explanation for an increased risk in patients with epilepsy would be the use of multiple anticonvulsants with additive hematologic effects.

In a 1982 review, the number of case reports of hematologic disorders were equal for epilepsy and trigeminal neuralgia.[5] Hematologic effects occurred at an equivalent rate in the psychiatric population when compared with earlier studies.[25] Thus, no disease state can be asso-

Table 4. Miscellaneous Cases of Hematologic Reactions with Carbamazepine

REF	REACTION	AGE (y)	SEX	DOSE (mg/d)	TREATMENT DURATION (d)	OUTCOME
69	eosinophila	8	M	200	35	recovered
70	eosinophila	12	M			recovered
	leukocytosis				21	desensitized
71	eosinophilia	35	F	600	21	died
72	red cell	45	F	1000		
	aplasia				30	recovered
73	hemolytic	63	M	300		
	anemia				20	recovered
74	leukocytosis	26	F	600	11	recovered
75	reticulocytosis	34	F	800	17	recovered

ciated with an increased risk of hematologic adverse effects with CBZ.

Mechanism

Though the mechanism of carbamazepine-induced blood dyscrasias is unknown, it is proposed to be an allergic or toxic reaction.[1,5,25,35,41,49,54,77,78] An inherited abnormality in CBZ metabolism resulting in formation of toxic CBZ metabolites has been postulated as the cause of hematologic dyscrasias.[79] The lymphocytes of patients with hypersensitivity reactions to CBZ showed susceptibility to toxic arene oxide metabolites of carbamazepine in vitro. Parents of the patients also had lymphocytes which were more susceptible to this metabolite than normal controls. Cross-sensitivity with other anticonvulsants which are metabolized to the same arene compound has been noted.

Kornberg and Kobrin identified CBZ-dependent antiplatelet antibodies in a patient who developed thrombocytopenia ten days after starting CBZ.[64] This finding provides support for an immune mechanism of thrombocytopenia.

It has also been postulated that hematologic effects reported in the early 1960s were due to impurities in the original manufactured tablet. Due to refined manufacturing techniques, impurities have since diminished.[11] As several generic products are available, future case reports should identify the manufacturer.

A case of persistent neutropenia with a normal bone marrow suggests that CBZ causes a shift in the circulating pool of WBCs or has a direct suppressive effect on the neutrophils.[49,53] CBZ did not suppress cell proliferation or function in an in vitro study.[5]

Discussion

All anticonvulsants have been associated with hematologic reactions.[7,19,54,80-82] Several authors indicate CBZ, when compared with phenytoin, is associated with an equal or fewer number of blood dyscrasias.[8,52,54,77] In a 1986 review of drug-induced hematologic reactions, both CBZ and phenytoin were associated with agranulocytosis but only phenytoin was listed as a cause of drug-induced aplastic anemia.[83] The 1987 editions of *Harrison's Principles of Internal Medicine* and *Oxford Textbook of Medicine* list phenytoin associated with aplastic anemia; CBZ is not listed. Neither drug is associated with agranulocytosis in these texts.[84,85]

Although phenytoin has been associated with leukopenia, granulocytopenia, agranulocytosis, pancytopenia, and thrombocytopenia, the manufacturer has never recommended routine hematologic monitoring. Parke-Davis has advertised that Dilantin does not require "routine" hematologic monitoring.[7,86]

The abundance of literature regarding the clinical course of the more serious hematologic dyscrasias occurring with CBZ supports the manufacturer's recent changes in monitoring recommendations. The progression of leukopenia or isolated thrombocytopenia to irreversible bone marrow suppression is debatable.[87] The 1975 *PDR* stated "early detection of hematologic change is important since, in some patients, aplastic anemia is reversible" with CBZ discontinuation.[3] The 1989 *PDR* states "the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis."[16] Studies have shown many cases of leukopenia which did not progress.[7,10,13,15,28,49,53,55] In a 1987 review Pellock stated leukopenia will "rarely" progress to agranulocytosis or aplastic anemia.[19] Considering the higher incidence rate of leukopenia in comparison with agranulocytosis and aplastic anemia, if progression does occur, it is extremely rare.[87]

Due to the rapid onset of agranulocytosis and aplastic anemia, effectiveness of routine counts in their early detection is doubtful.[6,7,19] Reports suggest aplastic anemia[6,38] and agranulocytosis[54,78] may occur within a few days of obtaining a normal CBC. Thus, laboratory monitoring would need to be very frequent, perhaps daily, to detect toxicity early in its development. It is unknown if CBZ discontinuation and/or specific drug treatment early in the reaction alters its progression.[2,5,7,30,38]

At what point CBZ should be discontinued following identification of decreased blood counts varies widely among authors. Pisciotta agreed with the 1975-88 *PDR* minimums on blood indices for drug discontinuation, including a lower limit of 4000 WBCs/mm^3.[5] Sillanpaa stated values below the *PDR* limits warrant frequent blood checks but not drug discontinuation.[18] Others believe a lower limit of 3000 WBCs/mm^3 or 1000–1500 neutrophils/mm^3 are more appropriate guidelines for drug discontinuation.[1,2,6,7,13,15,19,25] Joffe indicated CBZ should be discontinued only if a decrease in WBCs is associated with "symptoms of impaired hematologic function or other hematologic indices are also abnormal."[25] Considering laboratory costs, some authors report waiting until the WBC count is <4000/mm^3 before ordering a differential.[11,13] Others report watching only the granulocyte count of WBC, discontinuing CBZ when the granulocyte count drops below 1000/mm^3.[13,56]

Due to its ability to induce leukocytosis, lithium has been added to CBZ treatment in psychiatric patients to prevent leukopenia.[15,88] Brewerton suggested adding lithium to the patient's drug regimen when the WBC count falls below 4000/mm^3 as an alternative to CBZ discontinuation.[88] Lithium has also been used to successfully treat a case of agranulocytosis associated with CBZ.[46]

Concern with blood dyscrasias should not limit use of CBZ,[89] nor should early hematologic changes lead to premature treatment discontinuation.[7] With adequate neutrophils, treatment can be continued with frequent monitoring and the blood count may recover. Depending on the necessity of CBZ, it could also be restarted at a lower dose with frequent monitoring as an alternative to treatment discontinuation.

Recommendations

In the past if an adverse event occurred, the *PDR*'s recommendations for regular monitoring of CBZ had potential legal implications for prescribers who did not follow the stringent guidelines. Because detailed hematologic monitoring guidelines are no longer specified by the manufacturer, a standard approach is needed to establish consistent and adequate monitoring of all patients. This would be cost-effective and provide legal support for prescribers. The following recommendations are offered:

1. All patients should have a pretreatment CBC with differential and platelet counts. If all indices are in the middle

or upper normal range, no further laboratory checks are necessary. The patient should be educated to report signs and symptoms of possible hematologic abnormalities.

2. Patients with low-normal or below-normal pretreatment WBC and neutrophil counts are at increased risk of developing leukopenia. These patients should be monitored every two weeks for the first one to three months of treatment, covering the highest risk period for leukopenia. Subsequent monitoring must be individualized based on previous blood counts. If the WBC count falls below 3000/mm^3 or the neutrophil count falls below 1000/mm^3, the dose should be decreased or CBZ discontinued, if necessary. The benefits of CBZ must be carefully evaluated in patients with dangerously low counts as alternative treatments may be available.

3. Reticulocyte count and serum iron offer little benefit in the detection of hematologic toxicities, and significantly add to the cost of monitoring.[2] They should be reserved for follow-up of abnormal screening tests.

4. Due to their rapid onset, aplastic anemia, agranulocytosis, and thrombocytopenia are best monitored by early recognition by the patient and prescriber of signs and symptoms such as infections, fever, fatigue, ecchymosis, and bleeding through mucous membranes. It is very important to instruct the patient to seek medical care immediately upon development of any of these symptoms. The period of risk for such reactions is primarily during the first year of treatment. ≏

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EXTRACTO

Reportes tempranos de efectos hematológicos serios y fatales atribuidos a carbamazepina (CBZ) resultaron en recomendaciones de seguimiento extenso por parte del manufacturero. La rareza de discrasias sanguíneas motivaron a que muchos autores se cuestionaran las guías del manufacturero. Recientemente, el manufacturero retiró las guías específicas sobre el monitoreo de CBZ dejando a los médicos evaluar segun sus criterios clínicos. Este trabajo revisa reportes de casos y estudios sobre los efectos hematológicos de CBZ. Debido a su rápido comienzo de acción es necesario hacer pruebas de laboratorio a diario para monitorear anemia aplástica, agranulocitosis, y trombocitopenia. Estos efectos adversos son monitoreados mejor informando a los médicos y pacientes que vigilen los signos y síntomas de estas condiciones. La leucopenia se desarrolla lentamente y ocurre en un 12 por ciento de los niños y un 7 por ciento de adultos. Su comienzo ocurre tipicamente dentro de los primeros tres meses y pacientes a riesgo de desarrollarla tienen contaje de células blancas bajo o bajo/normal previo al tratamiento. La leucopenia muchas veces es reversible, aún si la CBZ es continuada. Basado en nuestra revisión de la literatura recomendamos monitorear todos aquellos paciente de alto riesgo durante los primeros tres meses de tratamiento con una frecuencia determinada por los resultados de cada laboratorio. Con un contaje de células blancas menor de 3000/mm³ o contaje de neutrofilos por debajo de 1000/mm³ se recomienda una disminución en dosis con monitoreo frecuente o descontinuación de CBZ si es necesario.

WILMA M. GUZMAN DE VALINES