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Carbamazepine - hematologic effects of the use

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Abstract

Carbamazepine is an antiepileptic drug which exhibits a number of side effects, namely including a headache, abdominal pain, increased blood pressure, but also hematologic disorders. Thrombocytopenia, hypogammaglobulinemia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, pure red cell aplasia, leukemia or eosinophilia with DRESS syndrome belong to the latter. There is a low incidence of carbamazepine pharmacotherapy related symptoms and their exact mechanisms of action are still unknown.

Keywords: carbamazepine, thrombocytopenia, hypogammaglobulinemia

1. Introduction

Carbamazepine is an antiepileptic drug used in epilepsy, trigeminal neuralgia and bipolar disorder treatment [1-3].

This substance blocks the sodium channels [4] and it also inhibits serotonin reuptake [5, 6]. Although carbamazepine is widely used in the treatment of numerous medical disorders, it exhibits many side effect which include inflammation and hepatic insufficiency, cholestatic jaundice, pneumonia, dyspnoea, renal failure, polyuria, albuminuria, dizziness, headache, drowsiness, hallucinations, nausea, vomiting, abdominal pain, fever, heart failure, increased blood pressure. Side effects that may develop in response to the treatment with this anticonvulsant include hematopoietic disorders, such as agranulocytosis, thrombocytopenia, leukocytosis, leukopenia, aplastic anemia, eosinophilia or pancytopenia [7].

Currently, it is believed that carbamazepine therapy should be discontinued with the value of WBC less than 3,000 / mm3, thrombocytes level less than 100,000 / mm3 and neutrophils less than 1500 / mm3 [8].

2. Thrombocytopenia

In 1993, a case of carbamazepine-induced thrombocytopenia with coexisting leukopenia was reported in a patient with Henoch-Schönlein purpura. According to the researchers, this was due to an allergic reaction to the drug, and the suppression of bone marrow [9].

Ishikita et al. described a case of a boy, who had a substantial decrease in platelets count and had been treated for twelve days with carbamazepine. One week after therapy discontinuation, the level of thrombocytes normalized. carbamazepine challenge test was performed. It caused, again, a successive decrease in thrombocytes level. Platelet-associated IgG and serum interleukin-6 increased suggesting an allergic reaction [10].

Finsterer et al. presented a case of a 67-year-old woman with epilepsy. The patient was treated with combination therapy consisting of carbamazepine and valproic acid. Therapy resulted in a significant decrease in thrombocyte count. A few days after the withdrawal of medications, the number of platelets increased to the physiological level. Researchers have not determined

which drug was responsible for this phenomenon, but the fact that carbamazepine was used for a longer period than valproic acid might play a crucial role [11].

Tutor-Crespo et al. published, in 2007, the results of studies on the occurrence of thrombocytopenia in 137 patients treated with carbamazepine and in 60 patients treated with its derivative - oxcarbazepine. The estimated prevalence of thrombocytopenia for both drugs was 2.9% and 1.7%, respectively [12].

It has also been reported that carbamazepine induces thrombocytopenic purpura [13].

3. Hypogammaglobulinemia

Carbamazepine may also cause a hypogammaglobulinemia due to B cell aplasia [14]. According to Sorrell et al. hypogammaglobulinemia develops independently of drug concentration in blood, dose or therapy time [15].

In 1975, Sorrel et al. estimated the incidence of humoral or cellular response to the carbamazepine therapy to be as high as 47% of all patients treated [15]. In 2001 however, Tamada et al. described carbamazepine hypogammaglobulinemia as "very rare" [16].

In 2012, a case of a 37-year-old man suffering from Jacksonian seizures was described. He was treated with, among others, carbamazepine. Low platelets counts (up to 100,000/mm3), rash on the face and trunk, frequent urinary tract infections, and decreased levels of IgG 275 mg/dl (normal: 884- 1912 mg / dl) and IgM 31 mg/dl (n: 50- 196 mg/dl) was noted. After the discontinuation of carbamazepine treatment, the rash disappeared and the platelet count returned to a normal level. The patient was given intravenous immunoglobulin four times. After four months, the immunoglobulin level returned to normal and there was no urinary tract infections or rash during the follow-up of one year [17].

Castro et al. described a similar case. Their patient was 7 years old and underwent treatment with carbamazepine because of preexisting epilepsy. After a month of the treatment regimen, many infections had been reported, which required antibiotic therapy. The immunoglobulin essay revealed IgA levels dropped to 16 mg/dL and IgG to 594 mg/dL. The concentration of IgG2 subclass decreased to 82 mg/dL (with the lower limit being 119 mg/dL). IgM concentration remained normal [18].

In 2004, a case report was published of a boy treated with carbamazepine with no evident adverse symptoms, but the decrease in IgG, IgA, and IgM levels - of which only the first class of immunoglobulin fell below normal. IgG2 concentration remained below normal for 12 months after carbamazepine withdrawal [19].

Hayman et al. reported a case of carbamazepine-treated women who reported frequent respiratory infections. IgG, IgM and IgA deficiencies were detected in the immunoglobulin essay. Three months after the discontinuation of treatment IgG levels returned to normal and after seven months, IgM and IgA concentrations approached the reference values [20].

The co-occurrence of hypogammaglobulinemia with agranulocytosis as a complication of carbamazepine treatment has been reported [21].

It is believed that this anticonvulsant drug may have an effect on the interaction between the immune system and the CNS, which may be the cause of disorders [18]. There is also a possibility that there is a defect with regards to immunoglobulin synthesis, or B-class lymphocytes maturation [18]. Another possibility in terms of IgG decline is also the dysfunction of B-cells or the increase of CD8 + [19]. Another theory is that the drug metabolite: 9-Acridine carboxaldehyde in low concentrations increases the proliferation of lymphocytes, but in higher concentrations inhibits them [22].

Accurate carbamazepine-related mechanisms of action on the above-mentioned effects have not been established yet. Further studies are needed. Because carbamazepine may not alter IgG counts or might even contribute to its increase - it is necessary to clarify the carbamazepine's role in this process and to determine under what conditions it causes an increase of IgG levels [19].

An example of an inducible effect of this anticonvulsant drug is the case of an adult woman treated with carbamazepine, who developed the total disappearance of IgM, IgA decrease and IgG-kappa monoclonal gammopathy [23].

4. Leukopenia and neutropenia

Daughton et al. claim that leukopenia affects 10% of carbamazepine treated patients transiently and 2% permanently [8]. According to Sobotka et al. this disorder affects 7% of adults and 12% of children [24]. Carbamazepine-induced leukopenia most commonly

develops within three months after the treatment initiation. The WBC values decrease as a result of the colony-stimulating factor (CSF) inhibition [8].

In 2005, scientists analyzed 41 patients treated with carbamazepine. After an annual follow-up, 13 of them (31.7%) developed leukopenia. One patient had to discontinue the treatment after 6 months because of severe neutropenia [25].

According to another study, including 41 patients with epilepsy and treated with carbamazepine, leukopenia developed in 31.4% of them and neutropenia in 17.1% [26].

Hughes et al. compared two groups of 131 patients each. The first group was treated with carbamazepine, the second group with a different anticonvulsant. Leukopenia occurred in 21.4% of patients in the first group and in 13.7% of patients in the second group. It indicates that carbamazepine (out of all the substances used in epilepsy therapy) is associated with the highest risk of this hematologic side effect. Leukopenia usually develops several weeks after carbamazepine reaches the highest concentration in the blood. It has also been observed that the maximum drug concentration is inversely proportional to the level of white blood cells [27].

5. Agranulocytosis

Agranulocytosis caused by carbamazepine (CIA) is a relatively rare disorder characterized by an increased number of promyelocytes and myeloblast and disappearance of neutrophils. The bone marrow shows wide variability and may show pseudohypercellularity features. These deviations mimick acute myeloid leukemia [28]. Out of all psychotropic drugs, carbamazepine is second only to clozapine in terms of the frequency of agranulocytosis [8].

According to Daughton et al. agranulocytosis coexisting with thrombocytopenia and aplastic anemia occurs in 1-2% of patients treated with carbamazepine [8].

According to Furst et al. the mechanism attributed to the formation of agranulocytosis induced by carbamazepine is the formation of reactive metabolites, which are responsible for many side effects. The drug can bind to neutrophils and myeloperoxidase system, giving the same metabolites while following the same pathway. However, binding with neutrophils was approximately 500 times metabolically slower than that of myeloperoxidase. Myeloperoxidase contributes to carbamazepine’s metabolism to reactive metabolites. The

specific pathway of these changes has not yet been discovered [29]. Other researchers suggest that this drug inhibits the colony stimulating factor [30].

Lenograstim - granulocyte colony-stimulating factor, or lithium may be effective in the treatment of carbamazepine-induced agranulocytosis [30, 31].

6. Anemia

Tagawa et al. reported a case of a 7-year-old girl who had a red blood cell aplasia (known as pure red cell aplasia [PRCA]) and developed anemia as a result of carbamazepine administration. An absence of erythroblasts, with normal myelopoiesis and megakaryocytopoiesis, was observed. Following a discontinuation of the drug, the process of reticulocytosis intensified and the hemoglobin level returned to a normal [32]. A similar case has also been reported by Saikia et al. in 2010, who claim that this is the fifth only case of PRCA being a complication of carbamazepine therapy in world literature [33].

Carbamazepine therapy may also contribute to aplastic anemia [34].

7. Leukemia

It has been proven that carbamazepine administration can contribute to the development of acute lymphoblastic leukemia [35].

Silverman et al. investigated the effect of carbamazepine on lymphocyte levels in lymphocytic leukemia. By several replacements of carbamazepine therapy with other anticonvulsants, they have noted that carbamazepine causes a significant drop in the lymphocyte level (from 28,800 $x10^6$/L to 3,200 $x10^6$/L and from 23,200 $x10^6$/L to 10,700 $x10^6$/L respectively) [36].

Moreover, a situation when chronic myeloid leukemia is treated with imatinib in a patient with carbamazepine therapy for existing epilepsy may result in the interaction of these two substances (it reduces the activity and concentration of imatinib). Indirectly then, carbamazepine may contribute to the leukemia progression by inhibiting imatinib [37].

8. Summary

Carbamazepine, despite its widespread use in the treatment of epilepsy, contributes to many hematologic disorders. In addition to the adverse effects discussed above, this drug can also cause CD30+ pseudolymphoma [38], DRESS syndrome [39, 40], large-cell lymphoma or CD30+ lymphadenopathy [41]. Although all these side effects are described as very rare and some only occur as case reports, they are nonetheless a threat to the health and life of patients chronically treated with this drug. Most of the carbamazepine's mechanisms of these hematologic abnormalities development are unclear. Further research and analysis are needed.

References:

1. Eisenberg, E., River, Y., Shifrin, A., & Krivoy, N. (2007). Antiepileptic drugs in the treatment of neuropathic pain. Drugs, 67(9), 1265-1289.
2. Schneider, M. R., Klein, C. C., Weber, W., Bitter, S. M., Elliott, K. B., Strakowski, S. M., ... & DelBello, M. P. (2014). The effects of carbamazepine on prefrontal activation in manic youth with bipolar disorder. Psychiatry Research: Neuroimaging, 223(3), 268-270.
3. Mainerova, B., Prasko, J., Latalova, K., Axmann, K., Cerna, M., Horacek, R., & Bradacova, R. (2015). Alcohol withdrawal delirium-diagnosis, course and treatment. Biomedical Papers, 159(1), 044-052.
4. Rogawski, M. A., Löscher, W., & Rho, J. M. (2016). Mechanisms of action of antiseizure drugs and the ketogenic diet. Cold Spring Harb Perspect Med, 6(5).
5. Dailey, J. W., Reith, M. E., Steidley, K. R., Milbrandt, J. C., & Jobe, P. C. (1998). Carbamazepine-Induced Release of Serotonin from Rat Hippocampus In Vitro. Epilepsia, 39(10), 1054-1063.
6. Dailey, J. W., Reith, M. E., Yan, Q. S., Li, M. Y., & Jobe, P. C. (1997). Carbamazepine increases extracellular serotonin concentration: lack of antagonism by tetrodotoxin or zero Ca 2+. European journal of pharmacology, 328(2), 153-162.
7. Carbamazepine in dailymed. com https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7a1e523a-b377-43dc-b231-7591c4c888ea [02-11-2017]
8. Daughton, J. M., Padala, P. R., & Gabel, T. L. (2006). Careful monitoring for agranulocytosis during carbamazepine treatment. Primary care companion to the Journal of clinical psychiatry, 8(5), 310.
9. Kaneko, K., Igarashi, J., Suzuki, Y., Niijima, S., Ishimoto, K., & Yabuta, K. (1993). Carbamazepine-induced thrombocytopenia and leucopenia complicated by Henoch-Schönlein purpura symptoms. European journal of pediatrics, 152(9), 769-770.

10. Ishikita, T., Ishiguro, A., Fujisawa, K., Tsukimoto, I., & Shimbo, T. (1999). Carbamazepine-induced thrombocytopenia defined by a challenge test. American journal of hematology, 62(1), 52-55.
11. Finsterer, J., Pelzl, G., & Hess, B. (2001). Severe, isolated thrombocytopenia under polytherapy with carbamazepine and valproate. Psychiatry and clinical neurosciences, 55(4), 423-426.
12. Tutor-Crespo, M. J., Hermida, J., & Tutor, J. C. (2007). Relation of blood platelet count during carbamazepine and oxcarbazepine treatment with daily dose, and serum concentrations of carbamazepine, carbamazepine-10, 11-epoxide, and 10-hydroxycarbazepine. Biomedical Papers, 151(1), 91-94.
13. Straussberg, R., Harel, L., Ben-Amitai, D., Cohen, D., & Amir, J. (2000). Carbamazepine-induced Stevens-Johnson syndrome treated with IV steroids and IVIG. Pediatric neurology, 22(3), 231-233.
14. Yamamoto, T., Uchiyama, T., Takahashi, H., Himuro, K., Kanai, K., & Kuwabara, S. (2010). B cell aplasia and hypogammaglobulinemia after carbamazepine treatment. Internal Medicine, 49(7), 707-708.
15. Sorrell, T. C., & Forbes, I. J. (1975). Depression of immune competence by phenytoin and carbamazepine. Studies in vivo and in vitro. Clinical and experimental immunology, 20(2), 273.
16. Tamada, T., Nara, M., Tomaki, M., Ashino, Y., & Hattori, T. (2007). Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. Thorax, 62(1), 100.
17. Ozaras, N., Goksugur, N., Eroglu, S., Tabak, O., Canbakan, B., & Ozaras, R. (2012). Carbamazepine-induced hypogammaglobulinemia. Seizure, 21(3), 229-231.
18. Castro, A. P. B. M., Redmershi, M. D. G., Pastorino, A. C., Paz, J. A. D., Fomin, A. B. F., & Jacob, C. M. A. (2001). Secondary hypogammaglobilinemia after use of carbamazepine: case report and review. Revista do Hospital das Clinicas, 56(6), 189-192.
19. Go, T. (2004). Carbamazepine-induced IgG1 and IgG2 deficiency associated with B cell maturation defect. Seizure, 13(3), 187-190.
20. Hayman, G., & Bansal, A. (2002). Antibody deficiency associated with carbamazepine. Bmj, 325(7374), 1213.
21. Spickett, G. P., Gompels, M. M., & Saunders, P. W. (1996). Hypogammaglobulinaemia with absent B lymphocytes and agranulocytosis after carbamazepine treatment. Journal of neurology, neurosurgery, and psychiatry, 60(4), 459.
22. Yavaşoğlu, I., Sargın, G., & Demirbulat, A. (2013). Carbamazepine and hematological malignancies. Turkish journal of haematology: official journal of Turkish Society of Haematology, 30(4), 424-425.
23. Moreno-Ancillo, A., Martin, P. C., Dominguez-Noche, C., Martín-Núñez, G., Fernández-Galán, M. A., López-López, R., ... & Gil-Adrados, A. C. (2004). Carbamazepine induced transient monoclonal gammopathy and immunodeficiency. Allergologia et immunopathologia, 32(2), 86-88.

24. Sobotka, J. L., Alexander, B., & Cook, B. L. (1990). A review of carbamazepine's hematologic reactions and monitoring recommendations. DICP, 24(12), 1214-1219.
25. Asadi-Pooya, A. A. (2005). Risk factors for carbamazepine-induced leukopenia in children and adolescents. Journal of Pediatric Neurology, 3(04), 233-235.
26. Asadi-Pooya, A. A., & Ghetmiri, E. (2006). Folic acid supplementation reduces the development of some blood cell abnormalities in children receiving carbamazepine. Epilepsy & Behavior, 8(1), 228-231
27. Hughes, J. R., & DeTolve-Donoghue, M. (1995). Chronic leukopenia associated with carbamazepine and other antiepileptic drugs. Journal of Epilepsy, 8(4), 282IN1-288IN10.
28. Banfi, L., Ceppi, M., Colzani, M., Guzzini, F., Morena, R., & Novati, P. (1998). Carbamazepine-induced agranulocytosis. Apropos of 2 cases. Recenti progressi in medicina, 89(10), 510-513.
29. Furst, S. M., & Uetrecht, J. P. (1993). Carbamazepine metabolism to a reactive intermediate by the myeloperoxidase system of activated neutrophils. Biochemical pharmacology, 45(6), 1267-1275.
30. Avinash, A., Amberkar, V. M., Kunder, S. K., Madhyastha, S., & Meenakumari, K. (2016). Carbamazepine-induced Life-threatening Stevens-Johnson Syndrome and Agranulocytosis: The Maiden Case. Journal of clinical and diagnostic research: JCDR, 10(12), FD01.
31. Cambon, S., Rossi, P., Miliani, Y., Arnaud, S., & Albanese, J. (1999, May). Severe agranulocytosis induced by carbamazepine (Tegretol). In Annales francaises d'anesthesie et de reanimation (Vol. 18, No. 5, pp. 542-546).
32. Tagawa, T., Sumi, K., Uno, R., Itagakia, Y., Fujii, F., & Yamaguchi, H. (1997). Pure red cell aplasia during carbamazepine monotherapy. Brain and Development, 19(4), 300-302.
33. Saikia, B., Aneja, H., Manchanda, A., Patowary, R., & Barman, B. (2010). Carbamazepine-induced Pure Red Cell Aplasia in a young girl. Indian Journal of Medical Specialities, 1(2), 130-133.
34. Handoko, K. B., Souverein, P. C., Van Staa, T. P., Meyboom, R. H., Leufkens, H. G., Egberts, T. C., & Van Den Bemt, P. M. (2006). Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia, 47(7), 1232-1236
35. Goyal, C., Bhandari, V., & Rafi, M. (2013). Long term carbamazepine therapy induced acute lymphoblastic leukemia. International Journal of Basic & Clinical Pharmacology. 2013 Mar-Apr; 2(2): 222-223.
36. Silverman, D. A., & Chapron, D. J. (1995). Lymphopenic effect of carbamazepine in a patient with chronic lymphocytic leukemia. Annals of Pharmacotherapy, 29(9), 865-867.
37. Taguchi, K., Kouroki, M., Ohmura, T., Jono, H., Endo, F., & Saito, H. (2014). Carbamazepine–imatinib interaction in a child with chronic myeloid leukemia. Pediatrics International, 56(4).
38. Nathan, D. L., & Belsito, D. V. (1998). Carbamazepine-induced pseudolymphoma with CD-30 positive cells. Journal of the American Academy of Dermatology, 38(5), 806-809.

39. Allam, J. P., Paus T., Reichel C., Bieber T., Novak N. (2004). DRESS syndrome associated with carbamazepine and phenytoin. European Journal of Dermatology, 14(5), 339-342.
40. Di Lernia, V., Viglio, A., Cattania, M., & Paulli, M. (2001). Carbamazepine-induced, CD30+, primary, cutaneous, anaplastic large-cell lymphoma. Archives of dermatology, 137(5), 675-676.
41. Yeo, W., Chow, J., Wong, N., Chan, A. T., & Johnson, P. J. (1997). Carbamazepine-induced lymphadenopathy mimicking Ki-1 (CD30+) T-cell lymphoma. Pathology, 29(1), 64-66.