Case Report

Diffuse alveolar hemorrhage due to valproic acid: Case report and review of the literature

Francesco Inzirillo, Casimiro Giorgetta, Eugenio Ravalli, Claudio Della Pona

Department of Thoracic Surgery, Morelli Hospital, AOVV, Sondalo, Italy

ABSTRACT

Valproic acid (VPA) is one of the most frequently used antiepileptic drugs for the treatment of focal and generalized epilepsies, absence seizures, and Lennox-Gastaut syndrome (LGS). VPA has been demonstrated to have a negative effect on both the intrinsic and extrinsic coagulation systems and controversy exists about the clinical relevance of such hematological abnormalities. We describe a case of reversible lung hemorrage due to VPA. In English-language literature only two other similar cases (one of which fatal) have been described so far.

KEY WORDS: Alveolar hemorrhage, coagulation disorders, valproic acid

Address for correspondence: MD. Francesco Inzirillo, Department of Thoracic Surgery, E Morelli Hospital, Via Zubiani 33, Sondalo - 23035, Italy.
E-mail: francescoinzirillo@gmail.com

INTRODUCTION

Valproic acid (VPA) is an antiepileptic drug for the treatment of epilepsy, absence seizures and Lennox-Gastaut syndrome.[1] VPA has a negative effect on coagulation and may cause thrombocytopenia (TCP), platelet abnormalities, alterations of concentrations of various coagulation factors.[2,3] Such hematological abnormalities may rarely lead to a large hemorrhage and may have a role in increased risk of bleeding after surgery. We describe a case of reversible lung hemorrhage due to VPA. Only two other similar cases have been described in literature.

CASE REPORT

A 51-old-year female patient treated with VPA, at a dose of 1000 mg per day, for depressive and bipolar disorder, since 2008, was admitted to our hospital with a diagnosis of hemoptysis. Pulmonary bleeding was causing anemia (up to four episodes of hemoptysis a day with the emission of bright red blood and fresh clots). Blood tests showed mild anemia (hemoglobin 9.6 g/dl; hematocrit 28,2%). Bronchoscopy detected diffuse bronchial wall blood painting. The bronchoalveolar lavage (BAL) examination showed a proportion of hemosiderin-laden macrophage (approximately 20%) cultures for bacteria and fungi, mycobacteria, and the autoimmune tests were all negative. The CT scan of the chest showed ground-glass areas localized in the right upper lobe [Figure 1]. Spirometry revealed restrictive abnormality, with diffusion capacity of the lung for carbon monoxide (DLCO) being 70% of the predicted value. A CT scan repeated after six days showed a reduction of the lesions in the upper lobe and the appearance of bilateral ground-glass opacity, mainly in the middle lobe. Only supportive therapy was carried out. VPA was suspended and the result was an immediate disappearance of hemoptysis, without recurrence. Hematological dosage of VPA was 54.7 μg/ml (range 50 to 100 μg/ml). VPA was effectively replaced with carbamazepine and the patient had no psychiatric disorders. After 20 days, the radiological and clinical follow-ups were normal [Figure 2].

DISCUSSION

Valproic Acid is used for the treatment of various forms of epilepsies and seizures, especially in the pediatric population. A variety of coagulation disorders, as side effects, have been demonstrated.[4] Some studies have showed a correlation between coagulation disorders and blood drug dosage, while others did not show any relation[2] A significant reduction in platelet count and platelet

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.152646

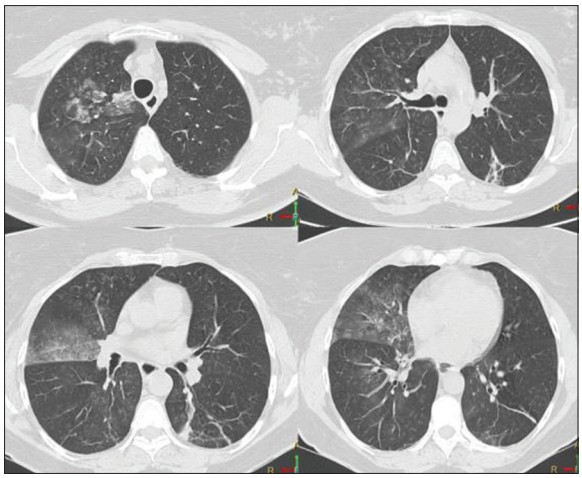

Figure 1: CT scan of the thorax showing confluent nodular opacities and ground-glass areas

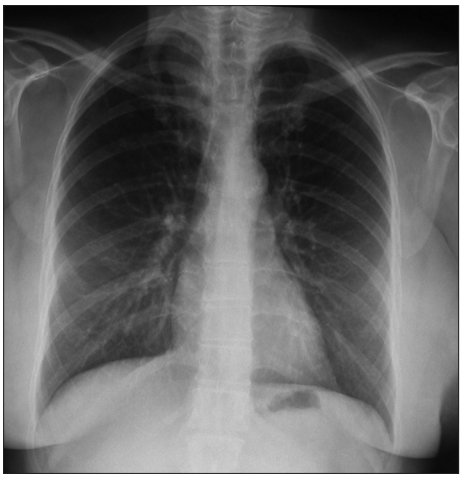

Figure 2: Follow-up chest X-ray

dysfunction are the most common hematological adverse effects of VPA (incidence range: 5-60%).[1,5] TCP has been explained by the induction of an immune response against platelets or by the direct toxic effect on bone marrow.[1] Factor XIII-deficiency syndrome was related to the VPA treatment and associated with an increase in perioperative bleeding risk.[3,6] Acquired von Willebrand disease was demonstrated in 67% of children during VPA treatment.[1] Vitamin K-dependent coagulopathies have been described, but the pathogenetic mechanisms have not been elucidated. The immediate improvement in prothrombin time (PT) after oral vitamin K administration, suggests an exogenous lack of vitamin K; anyway, under normal nutritional conditions, the daily intake is much higher than the daily need of vitamin K, and VPA seems not to influence the intestinal uptake of Vitamin K. A competitive rivalry for some metabolic steps seems to be more reliable.[1] Hypofibrinogenemia is another alteration that has been described.[7] Despite the reported abnormalities, the clinical consequences related to VPA treatment have been described infrequently. There are some reports about hematomas, epistaxis, and increased bleeding after neurosurgery. A review of the English-language Medical Literature revealed the description of only two other cases of VPA treatment–related alveolar bleeding. Diffuse alveolar hemorrhage (DAH) is a life-threatening disorder characterized clinically by hemoptysis, in approximately one-third of the cases,[8] falling hematocrit, diffuse pulmonary infiltrates, and hypoxemic respiratory failure. Bleeding is caused mainly by injury, which causes alterations in the pulmonary microcirculation and subsequently increases permeability, similar to immune-mediated capillaritis and the treatment consists of supportive care, cessation of offending drugs, and if necessary, high-dose steroids, immunosuppressants, and plasmapheresis.[8] One described case,[9] reported a 15-year-old boy receiving VPA treatment since the age of 10 years for myoclonic epilepsy. He developed dyspnea and hemoptysis and radiological examinations revealed bilateral lung infiltrates, suggestive of DAH. The bronchoscopic examination and the BAL fluid study were performed for alveolar hemorrhage. No alterations of coagulation were discovered, but the immediate disappearance of the symptoms and the sudden radiological improvement after two days and seven days, after discontinuation of the drug, were considered as a close association between bleeding and VPA. A platelet dysfunction without thrombocytopenia was the primary hypothesis.

The second case[10] is of a 30-year-old woman, who was receiving valproic acid since the age of 20 years for generalized seizure disorder, and was hospitalized for severe anemia. Laboratory data showed hemoglobin of 4.9 g/dl, hematocrit of 15%, platelet count of 15,000/μl, and a serum VPA level of 124 μg/ml. The radiological reports showed that she had lower lobe infiltrates and a bone marrow aspirate, which were consistent with the myelodysplastic syndrome. Bronchoscopy and BAL studies implied that it was probably DAH. Unfortunately, the patient died because of respiratory failure due to the evolution of bilateral diffuse pulmonary infiltrates. In the reported case, the bleeding was related to bone marrow suppression. Our clinical case is similar to the first described. In fact the CT scan of the lung showed bilateral ground-glass infiltrates localized first in the right superior lobe and later in the middle lobe, with other diffuse ground-glass opacities bilaterally. Bronchoscopic evaluation revealed the presence of blood in the middle lobe bronchus with a proportion of hemosiderin-laden macrophages (approximately 20%) and all BAL specimens were negative for infection. Autoimmune antibody tests were negative and the platelet count was always normal (the lowest value recorded was 2,43,000/μl). Alterations or deficiency of coagulation factors were not found and a pre-existing disease, predisposing to DAH, (pulmonary or cardiac disorders, especially heart failure or interstitial lung diseases) was not present. An increase in DLCO is usually seen in cases with fresh DAH. Due to the increased availability of intra-alveolar hemoglobin that combines with carbon monoxide. However, our case had reduced

DLCO. This may be because the DLCO measurements in our case were done more than 48 hours after admission. The association between bleeding and VPA treatment was diagnosed indirectly, because hemoptysis suddenly disappeared after cessation of VPA therapy and never recurred, with the radiological examinations normalizing after a week.

CONCLUSION

The alterations of pulmonary microcirculation can cause DAH, a life-threatening disease, which requires specific supportive treatment. In our case an association between VPA and DAH was suspected and indirectly confirmed by the successful outcome, with no bleeding recurrence after cessation of the drug. VPA therapy is a common cause of various disorders of coagulation that is rarely associated with clinically significant spontaneous bleeding, but rather with an increased risk of postoperative bleeding. DAH is one of the rare VPA-related complications, probably secondary to a combination of several hemostatic disorders. DAH in patients under VPA treatment could disappear with VPA cessation.

ACKNOWLEDGEMENT

Simon Tiberi (Revisor and Language Reviewer)

REFERENCES

1. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, *et al*. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia 2006;47:1136-43.
2. Igrutinović Z, Obradović S, Vuletić B, Marković S. Impact of valproates on haemostasis and blood cell count in children. Srp Arh Celok Lek 2008;136:267-73.
3. Teich M, Longin E, Dempfle CE, König S. Factor XIII deficiency associated with valproate treatment. Epilepsia 2004;45:187-9.
4. Banerjea MC, Diener W, Kutschke G, Schneble HJ, Korinthenberg R, Sutor AH. Pro- and anticoagulatory factors under sodium valproate-therapy in children. Neuropediatrics 2002;33:215-20.
5. Zeller JA, Schlesinger S, Runge U, Kessler C. Influence of valproate monotherapy on platelet activation and hematologic values. Epilepsia 1999;40:186-9.
6. Pohlmann-Eden B, Peters CN, Wennberg R, Dempfle CE. Valproate induces reversible factor XIII deficiency with risk of perioperative bleeding. Acta Neurol Scand 2003;108:142-5.
7. Köse G, Arhan E, Unal B, Ozaydin E, Guven A, Sayli TR. Valproate-associated coagulopathies in children during short-term treatment. J Child Neurol 2009;24:1493-8.
8. Newsome BR, Morales JE. Diffuse alveolar hemorrhage. South Med J 2011;104:269-74.
9. Choi KH, Nam TS, Kim JT, Choi SM, Park MS, Kim BC, *et al*. Valproate associated diffuse alveolar hemorrhage. Eur J Neurol 2011;18:e98-9.
10. Sleiman C, Raffy O, Roué C, Mal H. Fatal pulmonary hemorrhage during high-dose valproate monotherapy. Chest 2000;117:613.

How to cite this article: Inzirillo F, Giorgetta C, Ravalli E, Pona CD. Diffuse alveolar hemorrhage due to valproic acid: Case report and review of the literature. Lung India 2015;32:175-7.

Source of Support: Nil, **Conflict of Interest:** None declared.