Phenytoin Hypersensitivity Syndrome Presenting as Multi-System Organ Failure
P Marik

Citation

Abstract
Phenytoin is a highly effective and widely prescribed anticonvulsant agent. Phe nytoin is however, associated with both dose related side effects and hypersens itivity reactions. We report a life-threatening case of phenytoin hypersensitiv ity syndrome, which was characterized by a skin eruption and multi-system organ failure.

INTRODUCTION:
Phenytoin (diphenylhydantoin; Dilantin(r)) is commonly used as first line therapy in patients with seizure disorders. Phenytoin is associated with both dose-related side effects and hypersensitivity reactions. Hypersensitivity reactions occur in up to 19% of patients receiving this medication, and range from a mild morbilliform eruption to more severe reactions, including erythroderma, erythema multiforme, and toxic epidermal necrolysis (1,2,3,4). A small percentage of patients will experience a distinctive reaction referred to as the phenytoin hypersensitivity syndrome. This syndrome can have a variable spectrum of clinical and laboratory findings. We report a patient with the phenytoin hypersensitivity syndrome who developed multi-system organ failure.

CASE REPORT:
The patient, a 64 year-old black male, was started on phenytoin six weeks prior to admission, following an alcohol withdrawal seizure. He was taking no other medication. Approximately four weeks after starting phenytoin, he was seen by his primary physician for a diffuse erythematous skin rash when the phenytoin was discontinued. One week prior to admission the patient developed fever and chills, and noted an increased severity of his rash. The patients’ past medical history was unremarkable except for a myocardial infarction 8 years previously. The patient was a retired baker with a history of moderate alcohol intake and no history of exposure to chemicals, wild animals, insect bites and no recent travel history.

On presentation to the emergency room the patient was found to be confused, hypotensive and in severe distress. Physical examination, upon admission to the Medical Intensive Care Unit, revealed a well-developed adult male, with labored respirations, a systolic blood pressure palpable at 80 mmHg and a pulse of 150 beats/minute. His respiratory rate was 30/minute and temperature 39.5oC. He was noted to have periorbital edema with a diffuse morbilliform maculo-papular rash covering his entire body including his palms and soles, with small follicular pustules on his face. His neck was supple with no jugular venous distention. He had normal fundi, jaundiced sclera with an injected soft palate. Enlarged, firm, discreet lymph nodes were palpable in the cervical, axillary, and inguinal regions. Auscultation of the chest revealed bilateral scattered crackles. The remainder of the physical examination was unremarkable.

Significant laboratory tests on admission included: hemoglobin 10.5g/dL; platelet count 105 x 109/L; leukocyte
Phenytoin hypersensitivity syndrome (PHS) is a reaction which typically develops within 3 weeks to three months after initiation of treatment with phenytoin (1-5). It is characterized by fever, exanthems that range from aceniform to erythema multiforme major, lymphadenopathy, and eosinophilia (1-5). In addition, patients may develop hepatitis and acute renal failure. There is no age or sex predilection. However the black population appears to be at increased risk for developing this syndrome (5,6). First order relatives of patients who have experienced this reaction have also been reported to have an increased risk (5-7). Sheara and Spielberg (6) have suggested that the PHS may be inherited as an autosomal co-dominant pattern. Of practical importance is the fact that re-exposure to the drug, or exposure to phenobarbital or carbamazipine, will result in reactivation of the syndrome with a potentially fatal outcome (5-7).

The exact incidence and mechanism of PHS is not known. However, several observations suggest that it is a result of an allergic hypersensitivity reaction (4,7). Phenytoin may act directly as antigen or indirectly as a hapten to trigger antibody production. In some patients circulatory IgG antibodies to phenytoin have been detected (4,7). It has also been suggested that some individuals may lack the enzyme epoxide hydrolase which is needed to detoxify arene oxides. These oxides, which are very highly reactive and potentially cytotoxic, are formed as a result of oxidative metabolism of phenytoin (6). Phenobarbital and carbamazepine share the same metabolic pathway as phenytoin. In addition to the clinical picture, and the absence of a septic focus, the probable response to corticosteroid therapy is compatible with the diagnosis of PHS.

DISCUSSION:
We present a case report of a patient with characteristic features of the phenytoin hypersensitivity syndrome (PHS), who developed multi-system organ failure after treatment with phenytoin. In addition to the clinical picture, and the absence of a septic focus, the probable response to corticosteroid therapy is compatible with the diagnosis of PHS.

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The clinical presentation of the PHS varies, however the most frequent finding are skin rashes, hepatitis and lymphadenopathy. A generalized macular papular eruption with follicles and pustules on the face and upper trunk is characteristic (4,7). However generalized erythroderma, patchy erythema, and less commonly, erythema multiforme and toxic epidermolysis have been reported (3-7,11).
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Hepatitis occurs in about 75% of the patients, and is characterized by hepatomegaly and a marked increase in serum aminotransferase values (7,8). Severe hepatitis is associated with a prolonged hospital stay and a mortality of up to 50% (4,7). Additional findings that have been reported in some cases include interstitial nephritis, myopathy, Coomb’s negative hemolytic anemia and interstitial pulmonary infiltrates (5-7). Rhabdomyolysis and acute renal failure have been described in three patients (12,13,14). Localized or generalized lymphadenopathy is often present and this usually resolves following discontinuation of phenytoin. Laboratory evaluation in PHS has revealed leukocytosis with eosinophilia and atypical lymphocytosis, and a mild Coomb-negative hemolytic anemia.

There is no specific therapy for phenytoin hypersensitivity syndrome other than immediate discontinuation of phenytoin and supportive care. Corticosteroids have been used in many cases. Most case reports suggest a positive response to steroids when initiated early in the course of the illness (4,7,9,11). However, there have been no controlled clinical trials which have evaluated the use of corticosteroids in the PHS.

CONCLUSION:
The patient described in this report, presented to hospital with the adult respiratory distress syndrome and features of multi-system organ failure following the use of phenytoin. Such a rapidly fulminating form of PHS has not been well documented. The early recognition of this syndrome and the institution of high dose corticosteroids may have been responsible for the favorable outcome in this case.

References
10. Robinson DS, MacDonald MG, Hobin FP. Sodium diphenylhydantoin reaction with evidence of circulating antibodies. JAMA 1965; 192:171-172.
Author Information

Paul Marik, MBBCh, FRCPCH
Department of Critical Care Medicine, St Vincent Hospital; University of Massachusetts