Phenytoin Intoxication

Burden and risk factors

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ABSTRACT

Objective: The aim of the study is to determine: 1) the frequency of patients admitted for phenytoin toxicity and their economic burden; 2) the clinical symptoms and signs of intoxication; 3) the causes or risk factors of intoxication, and 4) the ways to prevent phenytoin toxicity.

Methods: Retrospective review of hospital ICD coded database between 1987 and 1998. All patients with phenytoin intoxication were reviewed.

Results: Thirty one patients were admitted 35 times for phenytoin toxicity. Phenytoin intoxication accounted for 1/ 5,000 admissions. Ataxia, confusion, dysarthria and nystagmus were the most common signs. The outcome was benign except for one patient who remained with a residual cerebellar syndrome. Unawareness of phenytoin pharmacokinetics, lack of clinic follow-up visits, infrequent serum level monitoring following drug dosage change and using wrong doses accounted for most of the cases.

Conclusion: Phenytoin intoxication rarely leaves any permanent sequelae but can be a cause of significant transient morbidity and prolonged hospitalization. As the major causes were related to poor follow-up or were iatrogenic, a better patient education and a stepwise dose increase based on serum level, together with drug level monitoring 2-4 weeks after dose change could decrease the incidence and severity of phenytoin intoxication.

Keywords: Phenytoin, intoxication, toxicity, epilepsy, pharmakokinetics.

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Phenytoin (PH) is one of the most commonly used anti-epileptic drugs (AED) worldwide. Its saturation kinetics are responsible for frequent toxicity because a linear increase in dosage may lead to an exponential increase in serum level.[1] The incidence of PH toxicity and the risks for its development are not well documented in the literature. We designed this study to determine: 1) the frequency of patients admitted with PH intoxication and their economic burden; 2) the clinical symptoms and signs of intoxication; 3) the causes or risk factors of intoxication, and 4) the possible measures to prevent intoxication.

Methods. The charts of all patients admitted to our hospital between 1987 and 1998 with the diagnosis of PH intoxication (ICD-9 code: 966.1) were reviewed. The following data were extracted from each chart: age, sex, initial disease for which PH was prescribed, circumstances and clinical symptoms and signs of the intoxication. Phenytoin serum levels at admission and during hospitalization were recorded. The cause or risk factors of the toxicity and evolution and outcome were evaluated. Patients with mild intoxication who were managed as outpatients were not included as they were difficult to trace in this retrospective study.

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Results. Over the 12 year period of the study, 31 patients, including 29 Saudi nationals, were admitted 35 times for PH intoxication. Their relative frequency was 1/5,000 admissions. They stayed in the hospital a total of 345 days with an average of 10 days (standard deviation (SD) 6 days) and a total estimated cost of 184,000 US $ (5,300 $ per hospital stay and 15,300 US $/year). Their ages varied from 2 to 84 years with a mean age of 34 years. Males (20) outnumbered females (11).

All patients except one were given PH to treat epilepsy. Sixteen were suffering from symptomatic epilepsy and 14 from cryptogenic or idiopathic one. The drug was prescribed in our hospital in 17 cases (55%) and was given from another facility in 13 cases. Twenty four patients were on PH for more than 6 months, 6 were on the drug for less than a month, and one child ingested it accidentally. The most common clinical symptoms and signs were confusion, ataxia, dysarthria and nystagmus. Their relative frequencies and the other symptoms and signs are outlined on Table 1. No patient had cardiac arrhythmia or significant hypotension. Phenytoin serum level on admission varied between 81 and 298 µmol/l (average 160 with a SD of 48 µmol/l) while the therapeutic range in our hospital is 40-79 µmol/l. The level normalized in 1 to 15 days (average 5 days) after stopping the drug. All patients recovered except one who remained severely ataxic 2 months after level normalization (Case 1). The most common cause of intoxication was from patients not showing up regularly in the clinics and continuing their drug without surveillance. This accounted for about half of the cases. In about another 40% of the cases, the physician prescribed an unusually high dose or did not order a blood level in the 2 weeks following a change in the dose. A loading dose of PH after a single seizure was given in some patients already on therapy. Suicidal attempt was the cause in only 3 cases. In one case, the intoxication was maintained intentionally by the family, probably in order to keep the patient in hospital for the longest possible time (Case 2). The list of causes/risk factors is outlined on Table 2. Some patients had more than a single cause.

Table 1 - Symptoms and signs of phenytoin intoxication (35 admissions).

Symptoms/Signs	Number (%)
Ataxia	34 (97)
Nystagmus	33 (94)
Dysarthria	28 (80)
Confusion	25 (71)
Stupor	8 (23)
Coma	2 (6)
Seizure exacerbation	1 (3)

% = percentage

Table 2 - Causes/risk factors of phenytoin intoxication in 35 admissions.

Cause/Risk Factors	Number (%)
Patients not coming for follow-ups, using ER to get medications	16 (46)
Loading or change in dose without follow-up or level within 2 weeks	8 (23)
Excessive dose given by physician	6 (17)
Unnecessary loading dose	5 (14)
Patient followed in anther hospital, circumstances unknown	5 (14)
Suicidal attempt	3 (9)
Dementia/Mental retardation	3 (9)
Patient mixed up instructions	2 (6)
Accidental injection (2 year child)	1 (3)
Munchausen by Proxy	1 (3)

% = percentage

Illustrative unusual cases. ***Case 1:*** A 30-year-old Indian was admitted in another hospital for seizures and brain computerized tomography (CT) was suggestive of tuberculomas. He was given 600-750 mg phenytoin daily for more than a week, together with 4 antituberculous drugs. He developed hepatic toxicity and became comatose. When he arrived to our hospital, his PH serum level was 298 µmol/l with severely disturbed liver functions. All drugs were stopped and his biological parameters returned progressively to normal within 15 days. He was then re-started on antituberculous drugs and small doses of carbamazepine. Two months later, at the time of his discharge, he remained ataxic and brain magnetic resonance imaging (MRI) showed residual cerebellar atrophy. This case was published previously to illustrate the possible residual damage after severe PH intoxication.[2]

Case 2: A 70-year-old Saudi lady was admitted for drowsiness and confusion. She was known to have atrial fibrillation, multiple strokes and post-stroke epilepsy. She was on 3 mg coumadin and 200 mg phenytoin daily for more than a year without any toxicity. At admission, she was found to have high phenytoin serum level at 108 µmol/l, and had an internationa normalized ratio (INR) at 6. The 2 drugs were stopped. After an initial drop in PH serum level, it started surprisingly to rise again and in 5 days reached the critical level of 180 µmol/l. Munchausen

syndrome by proxy was suspected with a supposed benefit to keep the patient in hospital for the longest possible time. The patient was put in isolation with a security guard at her door and PH serum level dropped again to 35 µmol/l in few days.

Discussion. Phenytoin intoxication is not uncommon. Thirty one patients were admitted to our hospital over the 12 year study period but a much larger number with less severe toxicity were managed as outpatients. The classical symptoms and signs described in PH intoxication were also found in our patients, except some rare symptoms such as choreo-athetotic or dystonic features.[1] Cerebellar signs and nystagmus were the most frequent signs as in Murphy et al's series.[1] Exacerbation of seizures was encountered in one of our cases only, as compared to 16/85 in that series with fairly similar population of idiopathic and symptomatic seizures. Outcome was generally good, except for one patient who had a cerebellar syndrome which persisted beyond 2 months after discontinuation of the drug. This type of complication has been very rarely reported, but experimental data have shown that high level of phenytoin is toxic for cerebellar cells.[3]

The cause of the intoxication was iatrogenic in more than a third of the cases. Lack of knowledge of PH phamacokinetics seemed to be the main problem. PH, unlike most other drugs, has non-linear pharmacokinetics. It is metabolized by an enzyme system that is saturable and thus capacity limited. The major pathway of metabolism of PH is parahydroxylation by the cytochrome P-450 system. Serum concentrations generally rise linearly until this enzyme is saturated. The point at which saturation occurs is unpredictable and varies among individuals.[5] Based on these particular properties, and by using computer-based simulations, Pritiviera[6] proposed the following when an increase of daily dose of PH is desired: increase by a 100 mg/d if the serum level is < 7 µg/ml (28 µmol/l), by 50 mg/d if level is between 28 and 44 µmol/l and only by 30 mg/d if the level is > 44 µmol/l. Serum levels should then be measured 2-4 weeks after any daily dose modification or even before this if any sign of toxicity is noted. Unfortunately, these rules are not well known by physicians. Another feature noted in this study is that some physicians are not aware of the usual dose of PH and have prescribed unusually high doses. In most adult patients, a daily dose of 300 mg achieves a good therapeutic serum level. Fifteen percent require a smaller dose, and in another 15%, a daily dose of 350-400 mg is necessary.[7] Doses above 400 mg/d are uncommon, need close follow-up and are potentially problematic. Another common source of intoxication was loading doses (1000 mg or more) given unnecessarily for patients presenting to the Emergency Department (ED) after a single seizure, and usually in a postictal state. This occurred in five (14%) of our cases. In Murphy et al series[1], excessive IV PH loading was responsible for the intoxication in 11 cases on 85 (13%). None of these patients was in status. Moreover, some of these patients had already therapeutic serum levels before the extra dose of PH.

Patient-related factors were responsible for the intoxication in about two-thirds of the cases. In about half of the cases, follow-up visits were very erratic with patients coming only to the ED when they have a seizure or to get a refill of their drugs. In other cases, the patients were not reliable (mentally deficient or having difficulties understanding instructions) or having psychiatric disorders (suicidal attempts). In Murphy's et al series[1], 13/85 patients were mentally subnormal and 7 took PH intentionally as a suicidal attempt.

In conclusion, PH intoxication is not uncommon and has a significant economic burden on the health systems. Its clinical symptoms and signs are easy to recognize. It does not lead to significant consequences unless serum levels are extremely high. At least one third of the cases could be prevented if physicians are aware of PH phamacokinetics and dosage pitfalls. A significant number of intoxications could also be prevented by better patient education.

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