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Brief Communication

Risk factors of early adverse drug reactions with phenytoin: A prospective inpatient cohort

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ABSTRACT

Introduction: Phenytoin (PHT) is an effective and inexpensive antiepileptic drug (AED). However, its use has been limited for fear of adverse drug reactions (ADRs) and is being replaced by newer AED, increasing the costs and causing major budget problems, particularly for developing countries.
Objective: The objective of this study was to determine ADR frequency, explore, and establish related risk factors.
Methods: Prospective data were collected from a cohort of inpatients using PHT for the first time. Pharmacovigilance was performed during hospitalization and after one month from the discharge. Clinical variables, plasma levels, and concomitant medications were collected and their association with the occurrence of different ADRs was explored.
Results: One hundred patients were included: 59 were women, and mean age was 59 ± 21 years. Thirty-three patients presented ADR, all moderate and idiosyncratic. The most frequent were rash (17%), fever (10%), and elevated transaminases (10%). Female gender (85% vs 52%, $p = 0.029$), younger age (mean age: 49 vs 62 years, $p = 0.032$), and higher PHT plasmatic levels after IV-PO load (mean plasmatic levels: 18.6 vs 13.9 μg/mL, $p = 0.040$) were found to be associated with rash. A higher number of concomitant medications were also found to be associated with the risk for developing any ADR. The multivariate analysis revealed an association between rash and younger age (cut-off: 35 years old; relative risk (RR) = 11.7; $p = 0.026$), and higher PHT plasmatic levels (cut-off: 16 μg/mL; RR = 12.5; $p = 0.021$); and increased risk of elevated transaminases with use of PHT inductors (RR = 18; $p = 0.006$). A longer hospital stay was found in patients who developed fever (mean: 43 days, $p < 0.0001$) and elevated transaminases (mean: 26 days, $p = 0.041$) compared with patients without ADR (mean: 17 days).
Conclusions: Phenytoin is a widely used AED associated with easily detectable ADR through structured pharmacovigilance. The development of ADR is associated with longer hospital stays. Recognition of local risk factors may lead to ADR prevention in a near future. Larger studies are needed to better define PHT-related ADR risk profile and to individualize treatment regimens.

1. Introduction

Phenytoin (PHT) is a well-known, inexpensive, and very versatile antiepileptic drug (AED), given its different administration routes and proven efficacy in a variety of epileptic syndromes, seizure prophylaxis, and status epilepticus, which has been compared with other AED, such as carbamazepine, valproic acid, or levetiracetam [1]. However, its usage as first-line treatment has been dramatically reduced, mainly because of fear of developing adverse drug reactions (ADRs). This has led to the prescription of newer AED, increasing health costs [2,3], especially problematic in developing countries [4].

Therefore, a more structured way for selecting and using AED should be recognizing their potential risk factors for developing ADR, avoiding their presentation or reducing their severity through pharmacovigilance [5]. The most described risk factors for developing ADR include female gender, administration route, polypharmacy, comorbidities such as infectious (e.g., HIV, herpes virus) or immunologic disorders (e.g., systemic lupus erythematous), organ failure (e.g., renal, hepatic), and genetic polymorphisms. Nonetheless, all of these factors may vary among different populations, warranting their identification in local studies [6].

Antiepileptic drugs like PHT, have specific drug hypersensitivity syndromes caused by non-IgE immune mechanisms, including rash, fever, hepatitis, and lymphadenopathy, among others. These ADRs can be clinically monitored, and their early recognition through pharmacovigilance will lead to prompt suspension avoiding unwanted and severe consequences [7].

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We conducted a prospective study in a cohort of consecutively recruited inpatients who started PHT therapy for the first time throughout the course of a year. We registered the occurrence of different ADRs, and explored possible risk factors for their development.

2. Methods

2.1. Patients' characteristics

We collected prospective data during a period of 12 months from patients consecutively hospitalized in the Neurology Service including basic and critical patient units at the Clinical Hospital of the Pontifical Catholic University of Chile. The protocol was approved by the local Ethics Committee, and a signed informed consent was obtained from patients or their authorized caregivers.

Inclusion criteria were as follows: (1) age ≥ 15 years old, (2) diagnosis of an acute brain or systemic illness, and (3) PHT prescription by the treating neurologist. Exclusion criteria comprise patients who were previously exposed to PHT, patients with previous ADR history to other medications, and patients with prescription of PHT without neurologic consultation.

Demographics data included gender, age, comorbidities, concomitant medications (number, type, PHT interaction classified in inductors, inhibitors, and neutral or variable effect on enzymatic metabolism, and PHT plasmatic levels), PHT administration route, season, and days of hospitalization.

Three administration protocols were identified: intravenous (IV) load, peroral (PO) load, and initial maintenance dose (MD). Loading doses were calculated using 15–20 mg/kg; IV load was administered in 1 h with a mean rate of 10–20 mg/min, PO was administered 1/3 of the dose every 1 h for three times, and MD was usually 300 mg/day administered every 12 h (e.g., 100 mg a.m. and 200 mg p.m.). Phenytoin plasmatic levels, adjusted by albumin, were monitored 1 h after IV load, 6 h after PO load, and at 5–7 days after PHT initiation in MD patients.

2.2. Adverse drug reaction assessment

Daily pharmacotherapeutic evaluation was performed in order to monitor drug reactions. We registered infusion-related reactions (bradycardia, phlebitis), presence of cutaneous signs (maculopapular rash, erythroderma, exfoliative dermatitis, fixed drug reactions) not attributed to infusion of other medications or contact with substances, fever (axillary body temperature > 37 °C) not explained by an infection (determined jointly with an infectology consultation), elevated transaminases (mild: <5× normal value, moderate: 5–15×, severe: >15×), performed as needed, or every 2 weeks during hospitalization and 1 month after discharge. Other ADRs referred by the patient or the treating physician considered to be related to PHT were also recorded.

Data were obtained from clinical registries during hospital stay (intrahospital) and until one month after being discharged (ambulatory), supplemented with information provided by the treating physician. An ad hoc pharmacotherapeutic questionnaire was designed using the Dader method, based on patient-oriented health and pharmacotherapeutic problems, and by the establishment of health state evaluation guidelines [8]. Treating physician was informed of any unnoticed ADR for the assessment of an eventual PHT suspension. The drug reaction frequencies were calculated in each group, and a *Probability of Causality* analysis was applied using both the Naranjo [9] and the WHO (WHO Collaborating Centre for International Drug Monitoring) algorithms [10].

2.3. Statistical analysis

Two groups were compared according to ADR occurrence: (1) ADR group (rash, fever, elevated transaminases, and any adverse effect) and (2) group without any ADR. Differences in qualitative variables between the groups were established using Fisher exact test. For quantitative variables, Mann–Whitney U test was used, because of the nonnormal distribution of the data, and for significant differences, a Receiver Operating Characteristic (ROC) curve was created to calculate the cut-off values according to Youden's J index. Further, relative risk (RR) and 95% confidence interval (95% CI) were obtained using a univariate and multivariate analysis with binomial logistic regression.

The results were reported using mean ± standard deviation, median, range, and percentages. Differences were considered significant at $p < 0.05$. For statistical analysis IBM SPSS Statistics 21 was used.

3. Results

3.1. Clinical characteristics

One hundred patients were included in the study. Mean age was 59 ± 21 years and females represented the 59%. Fifty-one different comorbidities were registered in previous medical history, or were newly diagnosed during the hospital stay (supplementary table 1). The most common was epilepsy (45%), arterial hypertension (26%), brain tumor (18%), status epilepticus (17%), and hemorrhagic stroke (16%). From the 17 patients that were hospitalized with status epilepticus, one had previous diagnosis of epilepsy, and the other 16 patients were newly diagnosed.

Mean hospital stay was 20 ± 24 days (Table 1). Patients received a mean of 8 ± 5 (range: 0–25) concomitant medications from a list of 116 drugs, divided in inductors or capable of decreasing PHT plasmatic levels (n = 4), inhibitory or that increased PHT plasmatic levels (n = 15), and with variable or neutral effects (n = 97) (supplementary table 2).

3.2. Phenytoin treatment regimen

Forty-four patients received IV load, 35 PO load, and 21 MD. Phenytoin loading (IV or PO) was used as treatment of recent seizure or status epilepticus in 47 patients (59.5%) and as prophylaxis in 32 patients (40.5%). Seasons of PHT onset were autumn (36 patients), winter (33), spring (18), and summer (13). Mean plasmatic levels achieved from IV/PO load was 14.4 ± 7.0 and 14.6 ± 7.4 in MD patients. Overdose (plasmatic levels: >20 μg/mL) occurred in 23% (18/79) and 24% (5/21) of the patients with IV-PO load and MD respectively (Table 1).

3.3. Phenytoin ADRs

A total of 33 patients developed ADR to PHT. These appeared in mean 12 ± 9 days (median: 10 days) after the initiation of PHT (range: 1–30 days). The most frequent were mild skin rash (n = 15), transient fever (n = 4), and mild–moderate elevated transaminases (n = 4). Seven patients developed 2 simultaneous ADRs: association of fever/elevated transaminases (n = 5), rash/elevated transaminases (n = 1), and fever/rash (n = 1). Infusion-related ADR was only present in 1 patient (mild bradycardia), and no phlebitis were observed. Other ADRs reported were: 1 patient with confusion and 1 with walking instability (Table 1).

3.4. Risk factors for developing ADR

When creating groups according to ADR occurrence, the univariate analysis for developing rash found a greater proportion of females (85% vs 52%, p = 0.029), younger age (mean age: 49 vs 62 years, p = 0.032), higher PHT plasmatic levels after IV-PO load (mean plasmatic levels: 18.6 vs 13.9 μg/mL, p = 0.040), and higher number of concomitant medications (mean: 10 vs 7, p = 0.043) (Table 2). Every comorbidity and comedication that was statistically significant more frequent in patients who developed rash is described in supplementary tables 3 and 4. The RR and 95% CI obtained from univariate analysis are showed

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