Phenytoin-Induced Severe Cutaneous Drug Reactions: Suspected Interactions with Corticosteroids and H_2-Blockers

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Abstract

Background: Cutaneous drug reactions are attributed usually to one culprit drug, however, some CDRs[1] may be associated with drug interactions.

Objectives: To present a case series of four patients with phenytoin-induced severe CDRs, including toxic epidermal necrolysis (2 patients), exanthematous eruption (1 patient) and hypersensitivity syndrome (1 patient). In all patients the reactions appeared following the combined intake of phenytoin, corticosteroids and H_2-blockers.

Conclusions: Our case series may imply the role of drug interactions between phenytoin, corticosteroids and H_2-blockers in the induction of severe CDRs.

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A variety of cutaneous drug reactions may be induced by phenytoin. These include exanthematous eruptions, Stevens-Johnson syndrome, and toxic epidermal necrolysis, as well as a hypersensitivity syndrome that consists of fever, cutaneous eruption and internal organ involvement [1–3]. Previous reports focused on the role of cranial irradiation in the pathogenesis of anticonvulsant hypersensitivity reactions [4,5]. However, little emphasis has been given to drug interactions with corticosteroids and H_2-blockers in the pathogenesis of phenytoin-induced CDRs.

We present a case series of four patients with severe CDRs induced by phenytoin, associated with the simultaneous use of corticosteroids and H_2-blockers.

Case Descriptions

Case 1

A 38-year-old woman underwent brain surgery to remove a meningioma. The patient was treated with phenytoin (dose range 300–400 mg daily), cimetidine (800–1,000 mg daily) and dexamethasone (36 mg daily).

Three weeks after administration of these drugs a macular erythematous rash associated with fever (38^0C) was noted by the patient. Skin examination revealed a widespread erythematous macular rash, associated with large erosions on the face and trunk, with involvement of the lips but sparing the eyes and genitalia. Nikolsky's sign was positive within the erythematous areas. A biopsy specimen was consistent with toxic epidermal necrolysis [Table 1]. Routine laboratory test results were within normal limits, except for mild anemia (hemoglobin 10.1 g/dl), leukocytosis (white blood cell count 15,240/mm^3), and elevation in transaminase level (alanine aminotransferase 77 units/L).

Phenytoin was suspected as the culprit drug and was replaced by primidone. Cimetidine therapy was not withdrawn, dexamethasone dose was increased to 100 mg daily, and topical treatment with wet dressings was applied. A complete resolution was noted a month later.

Case 2

A 62-year-old man underwent brain surgery to remove a malignant astrocytoma. The patient was treated with phenytoin (dose range 300–400 mg daily), cimetidine (800–1,000 mg daily) and dexamethasone (16–20 mg daily). During the postoperative course a surgical wound infection was treated with penicillin.

Five weeks after the phenytoin administration a rash appeared. The rash was diagnosed clinically and histologically as toxic epidermal necrolysis [Table 1]. Phenytoin was withdrawn and replaced by carbamazepine. The cimetidine therapy was unchanged, the dexamethasone dose was increased, and topical treatment was instituted, followed by a complete recovery.

Case 3

A 24-year-old woman underwent a craniotomy to remove glioblastoma multiforme. Packed red blood cells were infused during the postoperative period. The patient was given phenytoin (dose range 100–300 mg daily), dexamethasone (4–32 mg daily), cimetidine (800 mg daily) and ranitidine (300 mg daily). The patient occasionally also took paracetamol and dypirone tablets.

Three weeks later a rash appeared associated with pruritus. General physical examination was unremarkable except for a low grade fever (37.6^0 C). Skin examination revealed a widespread exanthematous rash on the face, neck, trunk and extremities, but sparing the palms and soles and the mucous membranes [Table 1]. A biopsy was not performed. Routine laboratory tests were normal except for hematuria (25–30 red blood cells per high power

[1]CDRs = cutaneous drug reactions

Table 1. Characteristics of phenytoin-induced severe CDRs, associated with corticosteroids and H_2-blockers consumption

	Case 1	Case 2	Case 3	Case 4
Sex /Age (yr)	F/38	M/62	F/26	M/52
Cutaneous reaction	TEN	TEN	Exanthematous eruption	Hypersensitivity syndrome
Brain neoplasm	Meningioma	Astrocytoma	Glioblastome multiforme	Meningioma
Culprit drug — latent period (wk)				
Phenytoin	3	5	3	2
Dexamethasone	3	5	3	4
Cimetidine/Ranitidine	3	5	3	2

field) and elevated blood sedimentation rate (65 in the first hour).

Phenytoin was withdrawn and replaced by carbamazepine, and dexamethasone and ranitidine doses were unchanged. The treatment regimen also included a topical corticosteroidal cream and an oral antihistamine preparation, which led to resolution of the rash.

Case 4

A 52-year-old man underwent brain surgery for removal of a meningioma. The patient's history was positive for hay fever, allergic rhinitis and arthralgia. The patient's mother was known to suffer from pemphigus vulgaris. The patient reported being treated postsurgery with valproic acid and corticosteroids in another hospital, whereafter treatment was changed to phenytoin (300 mg daily), ranitidine (300 mg daily) and dexamethasone (8–16 mg daily). In addition, the patient took paracetamol, brotizolam and nitrazepam tablets.

Two weeks after the institution of phenytoin, ranitidine and dexamethasone, a rash appeared that gradually worsened. General physical examination was unremarkable except for fever (38^0C). Skin examination revealed erythema multiforme-like rash located on the head, trunk, body folds, palms and soles, composed of erythematous papules and patches with a purpural component and target-like lesions. Erosions were noted in the mouth and the conjunctivas. Histologic findings were consistent with erythema multiforme of mixed epidermal/dermal type [Table 1]. Laboratory tests revealed mild hematuria (red blood cell trace), elevated blood sedimentation rate (50 in the first hour), leukopenia (white blood cells 3,500/mm^3) with eosinophilia (12% esosinphils) and thrombocytopenia (platelets 45,000/mm^3). The hemoglobin level was slightly decreased (11.6 g/dl). Kidney and liver function tests were normal. The clinical and laboratory findings suggested a diagnosis of hypersensitivity syndrome.

Phenytoin was withdrawn and replaced by phenobarbital. Ranitidine and dexamethasone therapy was unchanged. Treatment with a topical corticosteroidal cream and oral antihistamine preparations was instituted. During the following 2 weeks the rash, fever and hematuria disappeared and blood cell counts returned to normal limits.

Discussion

The pathogenic mechanisms underlying CDRs involve immune and non-immune mechanisms. Recently, reports have focused on the role of risk modifiers such as immune [6], infectious [7], metabolic [8,9] and other factors in the etiology of CDRs. Although many patients with CDRs report the consumption of multiple medications, CDRs are usually attributed to intake of one drug and little attention is drawn to drug interactions. In the four patients described here, the phenytoin-induced severe CDRs included toxic epidermal necrolysis, exanthematous eruption and hypersensitivity syndrome. In all four patients the reactions appeared following the combined intake of phenytoin, dexamethasone and H_2-blockers.

According to published guide tables and the latent time period between drug intake and the appearance of the CDRs, it is suggested that the offending drug in our patients was phenytoin. The major role of phenytoin in the etiology of these CDRs is further supported by resolution of the reactions following withdrawal of phenytoin. Our data are in accord with the literature indicating that phenytoin therapy is frequently associated with exantemathous reactions, whereas Stevens-Johnson's syndrome, toxic epidermal necrolysis and hypersensitivity syndrome are accepted as major but rare side effects of phenytoin [1–3]. Moreover, the possible role of interactions with other co-medications consumed by our patients may be of importance in the pathogenesis of the phenytoin-induced CDRs.

All four patients took corticosteroids before the appearance of the CDRs. Although corticosteroids — which are used in the therapy of CDRs [10] — are not usually conceived as an etiologic factor for CDRs, corticosteroid-induced CDRs have been reported [11]. Furthermore, a controlled study by Roujeau et al. [2] indicated a high risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during the first 2 months of corticosteroid administration. Phenytoin usually increases the clearance of dexamethasone [12], however Lawson et al. [13] demonstrated that dexamethasone may increase phenytoin serum levels, thus contributing to phenytoin toxicity.

Both cimetidine and ranitidine therapy increase phenytoin serum levels [14,15] and phenytoin toxicity [16]. In addition, both drugs were reported previously to be the culprit drug in CDRs, including Steven-Johnson syndrome and toxic epidermal necrolysis [17–19].

Given that the first 2 months of valproic acid administration are associated with increased risk for toxic epidermal necrolysis or Stevens-Johnson syndrome [2], valproic acid might have predisposed our patient 4 to phenytoin-induced hypersensitivity syndrome. The possible association between valproic acid and phenytoin in the induction of a CDR is supported by an *in vitro* observation that valproic acid administration increased irreversible binding of phenytoin to rat liver microsomes, contributing to phenytoin toxicity [20].

It is also possible that additional medications consumed by our patients, such as penicillin, paracetamol or dypirone, might also have interacted with phenytoin, cimetidine and dexamethasone.

With regard to the possible role of cranial irradiation in the pathogenesis of phenytoin-induced CDRs, as suggested previously by Delattre et al [4], this should not be considered since our patients did not receive cranial irradiation.

Our case series of phenytoin-induced severe CDRs after resection of a brain neoplasm implies that drug interactions between phenytoin, corticosteroids and H_2-blockers may be associated with an increased risk for severe CDRs. Additional prospective studies are necessary to elucidate this matter.

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Capsule

Hepatitis C in the USA

Because many persons with chronic hepatitis C virus (HCV) infection are asymptomatic, population-based serologic studies are needed to estimate the prevalence of the infection and develop and evaluate prevention efforts.

A study by a group from the CDC led by M. Alter performed tests for antibody to HCV (anti-HCV) on serum samples from 21,241 persons aged 6 years old or older who participated in the third National Health and Nutrition Examination Survey conducted during 1988 through 1994. Prevalence of HCV RNA was determined by means of nucleic acid amplification and the genotype by means of sequencing. The results showed that the overall prevalence of anti-HCV was 1.8%, corresponding to an estimated 3.9 million persons nationwide (95% confidence interval, 3.1 to 4.8 million) with HCV infection. Of those with HCV infection 65% were 30–49 years old. Seventy-four percent were positive for HCV RNA, indicating that an estimated 2.7 million persons in the United States (95% CI, 2.4–3.0 million) were chronically infected, of whom 73.7% were infected with genotype 1 (56.7% with genotype la, and 17.0% with genotype lb). Among subjects 17 to 59 years of age, the strongest factors independently associated with HCV infection were illegal drug use and high risk sexual behavior. Other factors independently associated with infection included poverty, 12 or fewer years of education, and having been divorced or separated. Neither sex nor racial-ethnic group was independently associated with HCV infection.

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