Phenytoin-induced toxic epidermal necrolysis: Review and recommendations

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ABSTRACT

Toxic epidermal necrolysis (TEN) is a serious, life-threatening skin reaction characterized by severe exfoliation and destruction of the epidermis of the skin. In most TEN cases, drugs are believed to be the causative agent; antipsychotics, antiepileptics, and other medications such as sulfonamides are among the most common causes of drug-induced TEN. Phenytoin, a commonly prescribed medication for seizure, was found to cause TEN. Evidence-based treatment guidelines are lacking, so the best strategy is to identify and avoid potential risk factors and to provide intensive supportive care. The aim of this literature review is to focus on phenytoin-induced TEN, to explore the risk factors, and to highlight the possible treatment options once phenytoin-induced TEN is confirmed.

Key words: Adverse drug reaction, diphenylhydantoin, Lyell's syndrome, phenytoin toxicity, Stevens–Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Toxic epidermal necrolysis

In 1956, Alan Lyell described four cases of patients with an eruption resembling scalding of the skin, and he called the condition toxic epidermal necrolysis (TEN).[1] TEN, also known as Lyell's syndrome can be defined as rapidly developing extensive erythema, necrosis, and detachment of the epidermis and mucous membranes that result in severe and fatal systemic complications such as sepsis if left untreated. TEN is commonly considered a drug-induced reaction rather than a skin disease; the most common causative agents include sulfonamides, barbiturates, pyrazolones, and antiepileptics. Currently, no standard therapeutic guidelines exist for the treatment of drug-induced TEN.[2]

On the other hand, Stevens–Johnson syndrome (SJS), another dermatological reaction, is characterized by extensive mucosal necrosis, severe stomatitis, and purulent conjunctivitis. SJS and TEN are reported as related manifestations of the same pathomechanism with different grades of severity of epidermal necrosis.[3]

Cases with epidermal detachment involving <10% of body surface area (BSA) are considered SJS while those with 30% or

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more are labeled TEN. The SJS-TEN overlap is an intermediate condition where skin detachment involves 10–30% of BSA.[4]

Although TEN can be clinically diagnosed, histopathologic examination of the affected skin is necessary to confirm the diagnosis and differentiate TEN from other related skin conditions. Supportive care until epithelium regeneration is the cornerstone of TEN management. Early transfer of patients to a burn or intensive care unit (ICU) reduces infection risk, mortality rate, and length of hospital stay. SJS and TEN are severe and life-threatening conditions with mortality rates of 1–5% and 25–35%, respectively.[5]

Phenytoin

Phenytoin (or its prodrug, fosphenytoin) is a widely used medication for common types of epileptic seizures, especially when accompanied by focal brain lesions. Available in parenteral and oral forms, phenytoin is widely used. Despite the inherited risk of dose-related toxicity attributed to its zero-order pharmacokinetics, phenytoin is still considered a first-line therapy for some types of seizures.[6]

Thus, therapeutic monitoring of a patient's phenytoin serum level is crucial to assure the safety and efficacy of phenytoin therapy.

METHODS

A literature review was performed by searching science databases, in addition to the Medline database via PubMed, for relevant articles. The search included meta-analyses, systematic reviews, review articles, randomized and nonrandomized trials, and case reports. Search keywords were as follows: "Phenytoin toxicity," "toxic epidermal necrolysis," "Stevens-Johnson Syndrome," and their Medical Subject Headings terms; and then a manual search of major journals was performed for the articles located through PubMed. Related publications in the English language were reviewed, and the most relevant papers to phenytoin-induced TEN were summarized.

RESULTS

There is an evidence in medical literature indicating a causative relationship between phenytoin therapy and development of TEN. Many published case reports documenting drug-induced TEN in patients treated with phenytoin were found; these case reports described severe and life-threatening dermatological reactions.[7-10] The Naranjo adverse event probability scale was used in some of these reports to assess the correlation between phenytoin therapy and TEN. Some cases ended in patient fatalities,[8,9] one due to retreatment with phenytoin for a patient with a history of phenytoin-induced TEN 2 years before.[8] In addition, one of these case reports documented

phenytoin-induced TEN in an 8-year-old child; such a young patient is a rare occurrence.[10] Interestingly, many of these cases reported phenytoin-induced TEN in cancer patients treated with concurrent radiotherapy.[7,9]

The genetic basis of drug-induced SJS/TEN has been linked to either inherited or acquired deficiency in phase 2 detoxification enzymes or elevated cytochrome P450 (CYP450) isoform(s). A few studies have reported a relation between the human leukocyte antigen (HLA-B)*1502 and the development of phenytoin-induced SJS/TEN.[11,12]

A case–control study in France, Italy, Germany, and Portugal was performed to assess the risk of SJS and TEN during the 1st week of antiepileptic therapy. The study found that SJS and TEN are associated with short-term therapy with phenytoin.[13]

A systematic review of drug-induced SJS and TEN among Indian patients concluded that phenytoin is one of the major causative agents for SJS-TEN; it was implicated in 13.37% of the documented drug-induced SJS-TEN cases.[14]

DISCUSSION

Clinical presentation

Usually, the acute phase lasts from 8 to 12 days. Frequently, TEN and SJS are characterized initially by unspecific signs and symptoms such as fever, stinging eyes, and discomfort on swallowing. Thereafter, cutaneous manifestations start to appear a few days later; cutaneous involvement typically starts to affect the trunk, face, palms, and soles. More than 90% of cases include mucocutaneous involvement of the buccal, genital, and/or ocular mucosa.[15]

Late-phase signs and symptoms of TEN occur later in the course of the disease and include hyper- and hypo-pigmentation of the skin, nail dystrophies, and ocular complications. Fifty percent of TEN patients will develop late ocular complications including severe dry eyes, trichiasis, symblepharon, distichiasis, visual loss, entropion, ankyloblepharon, lagophthalmos, and corneal ulceration.[16,17]

Risk factors
Medications
High-risk medications implicated in drug-induced TEN represent a wide spectrum of drugs from different pharmacological groups, such as nevirapine, lamotrigine, allopurinol, sulfonamides (especially cotrimoxazole), carbamazepine, phenytoin, phenobarbital, and oxicam - nonsteroidal anti-inflammatory drugs.[18]

It is of great importance to quickly identify the culprit through a thorough medication history of the patient. Newly administered drugs, as well as nonprescribed, over-the-counter

medications, should be assessed for the risk of inducing such severe reactions. A drug causality algorithm (ALDEN) was proposed in 2010 takes into account all relevant information regarding the suspected medication including: time latency, medication use period, data on prechallenge/rechallenge and dechallenge (if available), medication type, and other possible alternative causes. This algorithm yields a numerical score that can be used to further classify the causality relationship as "very unlikely," "unlikely," "possible," "probable," or "very probable."[19]

Concomitant radiotherapy

It is noteworthy that a greater risk of phenytoin-induced TEN/SJS is reported when phenytoin is combined with whole brain radiotherapy.[9] Radiotherapy given concurrently with antiepileptic drugs (e.g., phenytoin, phenobarbital, and carbamazepine) can trigger SJS/TEN, with lesions localized predominantly at sites of radiation treatment. Research results as shown by many published reports demonstrate a strong association between combined phenytoin treatment and radiotherapy and the development of drug-induced TEN.[7,9] Patients on phenytoin therapy should be carefully monitored during radiation exposure, which might potentiate phenytoin mucocutaneous adverse drug reaction (ADR).

Albumin and phenytoin level

Therapeutic drug monitoring of phenytoin is necessary to control its therapeutic and nontoxic levels. Many factors can influence a patient's serum phenytoin level, such as hypoalbuminemia, renal failure, and interacting medications including highly protein-bound drugs (e.g., valproic acid) that cause protein binding of phenytoin. Free serum concentrations should be measured to prevent inappropriate dose modification of phenytoin.[20]

Increased risk of phenytoin-induced SJS/TEN is associated with the use of higher than recommended dose, more rapid dose escalation, and concomitant use of valproate.[21]

Genetic predisposition

The association between CYP2C9*3 and phenytoin-induced severe cutaneous adverse reactions has been shown to be statistically significant in Taiwan, Japan, and Malaysia populations according to a recently published meta-analysis. Delayed clearance of plasma phenytoin was detected in patients with severe cutaneous adverse reactions, especially CYP2C9*3 carriers. It has been concluded that CYP2C9*3, a CYP2C variant, is an important genetic factor associated with phenytoin-related severe cutaneous adverse reactions.[22]

It has been shown that severe cutaneous reactions in patients with HLA-B*1502 are not only associated with carbamazepine therapy, but also, to a lesser extent, with both phenytoin and lamotrigine.[11]

These findings indicate a genetic basis for phenytoin-induced TEN in some populations, highlighting the importance of family history and genetic association as contributing risk factors.

Patients' comorbidities

A multicenter, international case–control study was designed to elucidate the etiology of SJS and TEN, and it revealed a predisposition to TEN among patients with systemic lupus erythematosus or HIV/AIDS and recipients of bone marrow transplants.[23] Thus, caution is vital when treating those patients with phenytoin or other TEN high-risk medications.

Increased SJS/TEN risk in patient with malignancies has been reported, but the exact cause is not yet identified which may be attributed to the malignancy itself, or to the increased exposure to offending medications that given in such cases.[24]

Management
General approaches

A multidisciplinary team is essential for the proper management of TEN, including a dermatologist, burns specialists, ICU physicians, nutritionists, infectious disease specialists, pain management specialists, and well-trained nurses[25] As soon as the diagnosis of SJS or TEN has been established, the culprit drug should be stopped immediately, and the severity and prognosis of the disease should be determined to select the appropriate medical setting for further management. SCORTEN disease severity scoring system [Table 1] can be used to evaluate prognosis in patients with SJS/TEN.[26] The validated SCORTEN disease severity scoring system can be used as a risk stratification tool to assess the severity and prognosis of TEN. A SCORTEN score of 3 or more warrants patient management in an ICU if possible.[15]

In 1991, the University of Florida's treatment protocol for TEN was published.[27] These guidelines were modified later

Table 1: SCORTEN; TEN-specific severity-of-illness scoring system with respective mortality rates

SCORTEN variables
Extent of epidermal detachment - >10%
Age - ≥40 years
Heart rate - ≥120/min
Bicarbonate - <20 mmol/L
Serum urea nitrogen - >28 mg/dl
Glucose - >252 mg/dl
History of malignancy

SCORTEN value	Predicted mortality rate (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

by Fromowitz *et al.* in 2007.[28] The guidelines provide general recommendations about the management of patients with TEN as follows:

Monitor patients' fluids and electrolytes. Administer fluids and titrate based on central venous pressure and urine output; 3–4 L is usually needed in patients with 50% of the BSA affected. Parenteral or enteral nutrition provided via a soft, fine bore nasogastric tube is usually needed. It is recommended to start total parenteral nutrition in patients unable to take oral nutrition.

Plasmapheresis or hemodialysis to remove the offending medication and its metabolites or cytokines from the blood is not supported by clinical evidence and cannot be recommended due to the associated risk of sepsis.[29]

Phenytoin alternatives

Another study included 154 patients with antiepileptic-induced severe cutaneous adverse drug reactions (SCARs), including SJS/TEN, found that nonaromatic antiepileptics, e.g., valproic acid and topiramate were safe alternatives for patients with phenytoin- or carbamazepine-induced SCARs.[30] Valproic acid does not seem to have an increased risk for SJS/TEN in contrast to other antiepileptics; thus, it could be a potential alternative to phenytoin.

Drug therapy

Currently, there is no effective specific therapy for TEN. It seems difficult to enroll an adequate number of TEN patients in clinical trials owing to the rarity of the disease; thus, well-designed controlled clinical trials investigating the therapeutic options for TEN are very limited. However, several treatment modalities given in addition to supportive care approaches have been suggested and are discussed below.

Systemic steroids

Despite the lack of proven efficacy, systemic steroids were described as the mainstay treatment in controlled trials. In 2007, one retrospective study concluded that a short course "pulse" of high-dose corticosteroids (dexamethasone) might be beneficial.[5]

Later, in 2008, another retrospective case–control study conducted in France and Germany found that corticosteroids did not show a significant effect on mortality when compared to supportive care alone.[31]

Thalidomide

As a medication with known antitumor necrosis factor-alpha (TNF-a), immunomodulatory, and antiangiogenic activity, thalidomide has been suggested as a potential treatment for TEN.[32] According to a double-blinded, randomized, placebo-controlled study, thalidomide resulted in higher mortality rates compared to a placebo. The study was prematurely terminated owing to the high mortality rate in the thalidomide group, in which ten out of 12 patients died compared with three out of ten in the placebo group.[32] These results exclude thalidomide from being a safe option in the treatment of TEN.

High-dose intravenous immunoglobulins

Intravenous immunoglobulin (IVIG) use was advocated based on the hypothesis that antibodies in pooled human IVIG block the Fas-mediated necrosis of the keratinocytes *in vitro*. A literature review performed between 1992 and 2006, including all published clinical trials where IVIG was administered to treat TEN, revealed that early administration of high-dose immunoglobulin (3 g/kg total dose given over 3–4 days) should be initiated, along with supportive care for the treatment of TEN.[33]

Cyclosporine

Cyclosporine is an immunosuppressant calcineurin inhibitor used in transplantation and autoimmune diseases. A case series study of patients with TEN compared cyclosporine alone versus cyclophosphamide combined with corticosteroids. Cyclosporine was associated with significantly shorter times to complete reepithelialization, along with lower multi-organ failure and death.[34] Initial therapy with high doses of intravenous dexamethasone followed by cyclosporine halted the disease progression within 72 h in three patients diagnosed with TEN.[35] Until now, cyclosporine seems promising for TEN management, but further research is needed.

Tumor necrosis factor antagonists

As a new therapeutic strategy, targeting the proinflammatory cytokine, TNF-a has been studied in TEN patients. TEN has been treated with a single dose of the chimeric anti-TNF-a monoclonal antibody (infliximab 5 mg/kg) in one patient; disease progression stopped within 24 h, followed by complete reepithelialization within 5 days.[36] One case report of drug-induced TEN showed that administration of the TNF-a antagonist receptor Etanercept results in complete healing after 20 days, and was capable of halting epidermal detachment within 48 h after beginning Etanercept treatment.[37]

Cyclophosphamide

The preliminary beneficial effect of cyclophosphamide either as a single agent[38] or as a combination therapy with cyclosporine[34] or high-dose steroids[39] has been shown in many case series. Nevertheless, risk-benefit assessment is required to determine the therapeutic potential and the expected toxicity of this agent in the treatment of TEN.

Pentoxifylline

Pentoxifylline, a blood viscosity-reducing agent, has demonstrated potential benefits in the treatment of TEN when

administered in high doses. Despite the favorable outcomes that have been documented in two case series using high-dose pentoxifylline therapy,[40,41] once again, this therapeutic modality requires further clinical research in larger TEN populations before being recommended as a TEN treatment option.

Recommendations

Since a drug is the most common etiologic factor in TEN, rapid identification and removal of that drug are paramount. Phenytoin should be discontinued at the first sign of a rash, once drug-related TEN is suspected. If symptoms indicate drug-induced TEN, use of this drug should not be resumed, and alternative medications should be considered.[25]

Alternative drug therapy should be chosen carefully, based on the available evidence; potential options include valproic acid and topiramate.[30]

So far, all specific therapies for TEN have not been clinically proven, and clinical evidence of their efficacy is contradictory. Therefore, supportive care measures such as enteral or parenteral nutrition, skin care, pain management, and fluids/electrolyte replacement are highly recommended as the mainstay of treatment.[28]

TEN patients should receive special intensive wound care to prevent further detachment, to avoid systemic complications such as secondary infections, and to protect the exposed dermis.[25]

Since there is a genetic association between HLA-B*1502 and phenytoin-induced SJS/TEN,[11] one must keep in mind that family history of such reactions should be carefully assessed and documented by the prescribing doctor before prescribing these medicines.

Circumspection is needed when prescribing phenytoin as an alternative to carbamazepine or vice versa; a Food and Drug Administration Alert issued on November 24, 2008, regarding the association between HLA-B/1502 and phenytoin SJS/TEN stated that "health-care providers should consider avoiding phenytoin and fosphenytoin as alternatives for carbamazepine in patients who test positive for HLA-B/1502."[42]

Therapeutic drug monitoring of phenytoin is necessary to ensure effective and safe serum levels.[20]

MedicAlert warning cards need to be provided to all patients with drug-induced TEN to prevent the recurrence of this serious and life-threatening ADR. The patient should be instructed to keep this card and to show it to health-care professionals whenever needed.[25]

Supportive care for toxic epidermal necrolysis includes[25]

Adequate nutritional support

Pain management

Temperature control

Fluid balance

Antibiotics for suspected infections

Topical care including skin, eye, genital, and upper gastrointestinal tract care

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CONCLUSION

TEN is a severe, devastating, and potentially life-threatening mucocutaneous reaction associated with the use of some medications such as phenytoin. TEN may have a genetic basis, so family history is an important factor to consider. Once phenytoin-induced TEN is confirmed, early withdrawal of phenytoin and supportive care in a specialized unit are the cornerstone of any treatment plan. More research in the form of well-designed controlled clinical trials is needed to identify TEN, to understand its pathomechanisms, and to find more effective and safe drug therapies.

No specific treatment has been clinically proven to be effective for TEN, and the best therapeutic modality to date is supportive care.

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