

November 2003

Severe skin reactions in patients receiving cranial radiotherapy while using phenytoin.

Introduction

Phenytoin has been used in the Netherlands since 1940. At this moment phenytoin is available in two brands, Diphantoine[®] and Epanutin[®]. Phenytoin is indicated for the *treatment of various kinds of epilepsy and for the treatment of cardiac arrhythmias, especially those induced by digitalis* [1,2]. Its anticonvulsive effect is probably based on voltage dependent blockade of membrane sodium channels. Commonly observed ADRs of phenytoin are mild gastro-intestinal complaints and reactions concerning the central nervous system, like ataxia, nystagmus, tremor and confusion. In rare cases severe skin toxicity can occur, expressing as erythema multiforme, toxic epidermal necrolysis or Stevens Johnson syndrome [1,2].

The view on the criteria for differentiation between Stevens Johnson syndrome, erythema multiforme and toxic epidermal necrolysis is a matter of debate. Stevens-Johnson syndrome is considered to be a serious bullous variant of erythema multiforme and is therefore synonym with erythema multiforme major (EMM). Others see Stevens-Johnson syndrome and erythema multiforme major as two different skin eruptions, because they differ in expression and in causing factors. The symptoms of Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are also largely similar, including extensive necrosis of the epidermic layers and erosion of mucosa, although TEN is not characterized by preceding bulla formation. SJS and TEN are both in most cases drug-induced, in contrast with EMM, that can be caused by (viral) infections as well as by drugs [3,4].

Reports

Lareb recently received a report concerning Stevens-Johnson syndrome in a patient using phenytoin and receiving cranial radiotherapy. A 73 year old male was using phenytoin (100 mg once daily) for epilepsy due to cerebral non-Hodgkin's lymphoma for one month. He used dexamethasone and prednisone as concomitant medication. On the day he received his first cranial radiotherapy session, he experienced the first symptoms of a skin reaction with lesions on the skin of his shoulders and oromucosal lesions. The skin reaction was progressive and was diagnosed by a dermatologist to be Stevens Johnson syndrome. Radiotherapy course lasting for 5 days was completed, but phenytoin was discontinued immediately and symptoms gradually resolved.

The time to onset strongly suggests the Stevens Johnson Syndrome to be provoked by the radiotherapy. The improvement of symptoms soon after discontinuation of phenytoin and before end of the radiotherapy suggests a causal relationship with phenytoin. According to the reporter the use of corticosteroids could have attributed to the event.

Other sources of information

Literature

In the literature several cases of Stevens Johnson syndrome or erythema multiforma major were reported after phenytoin was combined with radiotherapy. The cases are briefly presented in table 1.

Table 1. Overview of literature reports of Stevens-Johnson syndrome and similar skin reactions related to the combined exposure to phenytoin and radiotherapy

Sex, age	Suspected ADR	Time to onset after phenytoin	Time to onset after cranial irradiation	Concomitant cortico-steroids	Outcome	Ref
M,47	EMM	35 days	29 days	yes	recovered	[5]
F,61	EMM	35 days	35 days	yes	Recovered	[6]
M,53	TEN	> 30 days	30 days	yes	Recovered	[7]
M,48	TEN	>30 days	>30 days	yes	Recovered	[7]
M,44	TEN	unknown	25 days	yes	Recovered	[7]
M,45	SJS	32 days	30 days	yes	Recovered	[7]
F,41	TEN	66 days	31 days	yes	Recovered	[8]
M,30	SJS	30 days	15 days	yes	Recovered	[9]
M,43	SJS	28 days	20 days	yes	Recovered	[9]
F,35	SJS	28 days	21 days	no	Recovered	[9]
F,67	EM	30 days	21 days	yes	Recovered	[9]
M,55	EM	26 days	24 days	yes	Recovered	[9]
F,36	EM	24 days	21 days	no	Recovered	[9]
F,59	EM	35 days	30 days	yes	Recovered	[9]
F,26	EM	35 days	28 days	yes	Recovered	[9]
F,28	SJS	Not specified	not specified	no	Recovered	[10]
M,22	TEN/SJS	57 days	25 days	yes	Fatal	[11]
F,56	TEN/SJS	42 days	16 days	no	Recovered	[11]
F,41	SJS	36 days	29 days	no	Recovered	[11]
F,45	SJS	30 days	21 days	no	Recovered	[11]
F,72	TEN	45 days	unclear	yes	Fatal	[12]
M,62	TEN	28 days	unclear	no	Recovered	[13]

EM: erythema multiforme; EMM: erythema multiforme major; TEN: toxic epidermal necrolysis; SJS: Stevens -Johnson syndrome

In all cases phenytoin was discontinued immediately after diagnosing the skin lesions, in most cases leading to gradual improvement of the lesions. In two cases the reaction was progressive and fatal due to sepsis and shock. In some cases radiation therapy was resumed after discontinuation of phenytoin and recovery of the skin lesions, with no evidence of recurrence. Another patient had radiation therapy before starting phenytoin with no reaction [9]. In many cases the time to onset of the skin lesions was probably related to corticosteroid tapering, leading to decreased immune suppression.

Databases

The Lareb database contains one other report of Stevens Johnson syndrome during phenytoin treatment. In this report, no radiotherapy was involved. The WHO database does not allow a search on a combination with radiotherapy.

Mechanism

The pathogenesis of SJS induced by phenytoin-radiation therapy as described in the literature is not fully understood. SJS is believed to be an immunologic reaction to certain drugs or its toxic metabolites. Irradiation is believed to enhance an immunologic response, for example when administered shortly after an immunization. Probably irradiation enhances also the immunologic response to phenytoin, resulting in increased risk of severe skin reactions on combined exposure to phenytoin and irradiation [5,11,12]. Although this reaction is only described upon cranial

irradiation, we are not aware of any mechanism that prevents this reaction to occur on other types of irradiation.

Conclusion

Stevens-Johnson syndrome is a severe and sometimes fatal skin reaction, that can rarely be induced by phenytoin. The Netherlands Pharmacovigilance Centre received a report of Stevens-Johnson syndrome possibly related to the combined exposure to phenytoin and cranial irradiation. A literature search revealed twenty-two similar cases, indicating that cranial irradiation can provoke Stevens-Johnson syndrome and similar severe skin reactions, like erythema multiforme (major) and toxic epidermal necrolysis during treatment with phenytoin.

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