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Allergic Reactions to Phenytoin in a General Hospital in Singapore

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SUMMARY **Phenytoin is used for the treatment and prevention of fits. We investigated all patients reported to have phenytoin allergy in our hospital and found 42 confirmed cases. Sixty-nine percent were female and 83.3% were Chinese. The mean age of the patients was 46.5 years. The reactions reported were maculopapular rash (71.4%), Stevens-Johnson syndrome (14.3%), fever (4.8%), generalized exfoliative dermatitis (2.4%), toxic epidermal necrolysis (2.4%), vasculitis (2.4%) and agranulocytosis (2.4%). In conclusion, the majority of reported allergic reactions to phenytoin were cutaneous (92.9%) and one fifth of these were potentially life-threatening.**

Anticonvulsants tend to be prescribed for long periods of time, which allows for the development of reactions that may not be apparent in drugs given only briefly. In our hospital, phenytoin is the first-line drug for the treatment of generalised fits and also for preventing seizures in "high-risk" patients, such as those with serious head injuries or post-craniotomy.

Our hospital handles general cases and is also a tertiary center for neurological and neurosurgical referrals. We recently encountered several patients with serious allergic reactions to phenytoin and therefore decided to do a retrospective study of this problem.

MATERIALS AND METHODS

Study design

All cases of phenytoin allergy detected by our hospital reports to the National Patient Medical Information (NPMI) were retrospectively investigated. Case-records were retrieved from the Medical Record Office (MRO) and information entered using a standardised protocol. Predefined criteria were used to determine eligibility for inclusion.

Patient selection and case definition

The following selection criteria were used:

a) Paediatric or adult patients had to receive either oral or intravenous phenytoin and then developed a reaction.

b) The reaction must have been proven or thought to be allergic and must have been temporally consistent with the administration of phenytoin.

c) Hospital records must describe the reaction adequately and document the duration between starting phenytoin and the onset of the reaction.

d) Patients were excluded if there were possible non-allergic aetiologies for the reaction or if they had received another drug to which they had a known allergy.

RESULTS

Demographic and clinical features

72 patients were identified by the NPMI. However, records from 8 patients were not available and 22 cases were excluded. Of these, 13 were not included because

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of poor documentation, 2 because of idiopathic urticaria, 2 because of non-specific pruritus, 2 because of a lack of appropriate temporal association with use of the drug, 1 because of proven seborrhoeic dermatitis, 1 because of a non-specific rash and 1 because of misclassification. The demographic features of the 42 remaining patients who met eligibility criteria are shown in Table 1. None of the 42 patients were previously exposed to phenytoin and none had a history of atopy. Seven patients had known drug allergies:- 3 to ampicillin, 1 to aspirin, 1 to carbamazepine, 1 to both ampicillin and cotrimoxazole, and one to both valproate and carbamazepine. Table 2 shows the indications for the use of phenytoin.

Table 1. Characteristics of the 42 patients with phenytoin allergy.

Age when reaction occurred (years)	46.5 ±20.1
Sex (% females)	69.0
Race (% Chinese)	83.3
Number with history of additional allergy to other drugs	7
Duration of phenytoin before reaction (days)	26.9 ±16.3

Table 2. Indications for phenytoin use.

	Number	%
Therapeutic		
Epilepsy	13	31.0
Intracranial tumour	4	9.5
Cerebral infarct	3	7.1
Intracranial bleed	2	4.8
Brain abscess	1	2.4
Fulminant hepatitis	1	2.4
Prophylactic		
Intracranial tumour	11	22.6
Intracranial bleed	6	14.3
Head injury	1	2.4

Types and severity of allergic reactions

Table 3 shows the types of reactions that occurred in our patients. Although the majority of the reactions were cutaneous, 9 patients had potentially life threatening syndromes (Stevens-Johnson syndrome, generalised exfoliative dermatitis, toxic epidermal necrolysis and agranulocytosis).

Table 3. Types of reactions to phenytoin in 42 patients.

Reactions	Number	%
Maculopapular rash	30	71.4
Stevens-Johnson syndrome	6	14.3
Fever	2	4.8
Generalised exfoliative dermatitis	1	2.4
Toxic epidermal necrolysis	1	2.4
Vasculitis	1	2.4
Agranulocytosis	1	2.4

One of our cases illustrates the potential severity of phenytoin allergy. A 37-year old woman was given phenytoin prophylactically following craniotomy for a ruptured right occipital arteriovenous malformation. She was re-admitted for agranulocytosis and anaemia 44 days later. The haemoglobin was 9.7 g/dl, total white blood cell count 600 per mm^3, with a differential of neutrophils 5%, lymphocytes 79%, monocytes 8% eosinophils 8%, and basophils 0%, and platelet count 277,000 per mm^3. Bone marrow biopsy showed suppression of the granulocytic cell lines. The white cell count had normalized nine days after discontinuing phenytoin and after the administration of a 4 days

course of subcutaneous granulocyte colony-stimulating factor.

All patients recovered from the adverse reactions. Standard management was to discontinue phenytoin immediately upon discovering the reaction and to begin another anticonvulsant after the reaction had resolved. No patients had increased frequency of fits or status epilepticus on discontinuation of phenytoin.

DISCUSSION

Our finding that most reactions were cutaneous is consistent with results from other studies.[1,2] The mean duration of treatment prior to the reaction was 26.7 days and ranged from 7 to 70 days. In a report of allergic rashes in paediatric patients, the mean duration between starting phenytoin and the development of a reaction was 12 days with a range of one to 47 days.[3] Tone *et al.*[4] reported that the histological findings of different types of skin eruptions due to phenytoin are surprisingly similar, suggesting that a common pathogenesis mechanism may be responsible. These features include adhesion of infiltrated cells to the basal layer of the epidermis, cell infiltration into and dyskeratotic cells in the epidermis and vacuolation of basal cells in the epidermis.

Stevens-Johnson syndrome is a serious skin condition that is called toxic epidermal necrosis (TEN) when skin detachment is extensive:- there were six cases of Stevens-Johnson syndrome and one of TEN in our series. Patterson and colleagues recently reported a series of 41 case of Stevens-Johnson syndrome:- phenytoin was the putative cause in 13.[5] These investigators argued that clinical, histological, and cytochemical evidence supports an immunological pathogenesis in Stevens-Johnson syndrome. Phenytoin was implicated in eight of 245 patients with Stevens-Johnson syndrome or TEN; the multivariate relative risk was calculated to be 8.3.[6] The increased risk was largely confined to the first two months of treatment. If the patient survives the initial episode of TEN, re-exposure to the drug is often fatal.[7]

Agranulocytosis is a rare side-effect of phenytoin. We found less than 10 cases in a literature review.[8-14] In one case, phagocytic histiocytes were seen in the bone marrow biopsy. However, this finding was not seen by other investigators or during our study. Anti-granulocyte antibody has been reported by some investigators,[9] but not others.[10-11] There is a single report of a non-complement dependent antibody that suppresses granulopoiesis and mediates peripheral destruction of polymorphonuclear leucocytes.[10] Experience with growth factors in the management of these cases has been reported[12] and the case in our series responded well to G-CSF. In one report, granulocytopaenia followed treatment with phenytoin and cimetidine,[13] but cimetidine alone has not been proven to cause neutropaenia.[14-15]

The risk-to-benefit ratio of prophylaxis with phenytoin may be greater than previously thought. Several influential studies carried out in the seventies and early eighties demonstrated that phenytoin reduced the incidence of fits in patients with severe head injuries and craniotomy, both acutely and long term.[16-18] This led to its routine use but these studies did not focus on adverse reactions. However, recent studies and editorials suggest that prophylactic phenytoin may be of less benefit than previously thought.[19-21] Temkin *et al.*[19] reported that in a placebo-controlled double-blind study of 404 patients with serious head injury analysed on an intention-to-treat basis, phenytoin was useful for reducing seizures in the first week only.[19] In the two-year follow-up period, the frequency of fits was the same in both group. Another study compared the efficacy of phenytoin or carbamazepine and concluded that there was little evidence to support the routine use of prophylactic anticonvulsant.[21] The occurrence of potentially dangerous side-effects mandates that the prophylactic role of phenytoin be re-examined. It should probably be given for the first week in head injury, and omitted in craniotomy cases.

There are several limitations of our study. First, there was selection bias of the types of reaction we saw because of the nature of the reporting system. Serious, idiosyncratic or easily observed reactions are more likely to be reported by the attending doctors. Secondly, the use of only one source to trace patients leads to underestimation of the true number of cases, particularly non-hospitalized patients. Finally our database is recent and thus cases occurring before it was installed would not have been detected.

We conclude that:

1) The majority of the reported reactions to phenytoin in our hospital are cutaneous and a fifth are potentially life-threatening

2) The use of phenytoin for treatment or prophylaxis should be accompanied by close monitoring for adverse reactions. The routine use of the drug as a prophylactic must be re-examined.

3) Cases of suspected drug reactions should be evaluated by an allergist to ensure accurate reporting, standardised data-collection, complete work-up of the patient and relevant counselling. We are currently working on a project with our hospital's Pharmacy and MRO to address these problems.

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