Short report

Serum anticonvulsant concentrations and the risk of drug induced skin eruptions

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SUMMARY In two prospective studies of anticonvulsant therapy there was a high incidence of drug-induced skin reactions to phenytoin (7%) and carbamazepine (16.6%). High initial serum concentrations of these drugs appeared to be a factor influencing the occurrence of such skin reactions.

One of the commonest reasons for the early discontinuation of any drug is the development of drug induced erythematous skin reactions. This can present a particular problem with antiepileptic drugs such as phenytoin and carbamazepine where the early development of a skin eruption may prevent the long term use of what would otherwise be an effective drug.

The factors involved in the development of sensitivity to drug induced skin reactions are poorly understood. During two studies in which patients received phenytoin and carbamazepine either for the treatment of established epilepsy, or as prophylaxis following craniotomy we were impressed by the relationship of initial steady-state serum levels to the development of skin eruptions. It is the purpose of this short communication to investigate this relationship.

Methods

Patients with a recent history of two or more seizures requiring anticonvulsant therapy were randomised to phenytoin (or valproate) therapy as part of a controlled randomised comparison of these anticonvulsants.¹ Patients randomised to phenytoin were initially prescribed 300 mg daily and initial serum phenytoin concentrations determined one month after the initiation of therapy.

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Patients undergoing craniotomy for a variety of neurosurgical conditions, treatment of which has been associated with a high risk of subsequent epilepsy² were randomised to prophylactic therapy with either phenytoin or carbamazepine. In both cases anticonvulsant loading was commenced 24 hours before operation. Patients received phenytoin by intravenous infusion (15 mg/kg) over a 30 minute period with transfer to a postoperative maintenance regime of 300 mg daily. Phenytoin serum concentrations were determined one week postoperatively. Patients received carbamazepine 200 mg for three oral doses at eight hourly intervals in the 24 hours preceding surgery, and 200 mg three times daily as a maintenance dose thereafter. Serum carbamazepine concentrations were determined one week postoperatively.

Patients developing skin eruptions were either seen by one of the authors, or confirmation of the nature of the skin eruption obtained from the patient's general practitioner. Unfortunately, in a number of instances serum drug concentrations were not recorded in patients developing a rash, as their general practitioners discontinued treatment before blood could be withdrawn.

Results

Sixty patients received phenytoin for epilepsy. Exanthematous drug reactions occurred in five (8%). In one instance an exfoliative dermatitis developed which was associated with jaundice and abnormal liver function tests. Serum phenytoin levels were ascertained during the first month of treatment in three of these five patients (39.8, 21.2, and 18.4 µg/ml). One other patient who developed a skin eruption ten days after commencing phenytoin complained at that time of drowsiness and unsteady-

Table Drug concentrations in patients with and without rash

Patients				
	Mean serum phenytoin ($\mu\text{g/ml} \pm \text{SEM}$)		Mean serum carbamazepine	
With rash	21.1 $\pm$ 6.2 (5)*		8.7 $\pm$ 1.2 (6)†	
No rash	8.5 $\pm$ 0.6 (95)		6.8 $\pm$ 1.8 (34)	
	Serum phenytoin† concentration		Serum carbamazepine concentration	
	<10 $\mu\text{g/ml}$	$\geq 10 \mu\text{g/ml}$	<6 $\mu\text{g/ml}$	$\geq 6 \mu\text{g/ml}$
With rash	0	6	1	5
No rash	62	33	14	20

Differ from concentrations in patients without rash * $p < 0.001$, † $p < 0.05$.

‡Included in this table is one patient with symptoms of phenytoin intoxication and rash, in whom serum concentration was not recorded, but in whom it seems safe to assume a concentration $> 10 \mu\text{g/ml}$.

ness which cleared four or five days after phenytoin was stopped. It therefore seems likely that this patient also had high serum phenytoin levels at the time she developed her skin eruption. This patient was inadvertently restarted on phenytoin within two days of the symptoms of intoxication clearing and the skin eruption recurred within 48 hours. The drug was then stopped immediately. Fifty patients received phenytoin prophylactically because they were about to undergo a craniotomy. Three (6%) developed skin eruptions and serum levels were recorded in two of these (14, and 12 $\mu\text{g/ml}$).

Serum concentrations were obtained in 100 of the total of 110 patients receiving phenytoin. Mean phenytoin concentrations were significantly higher in patients developing a rash ($p < 0.001$ —table). The table shows a statistically significant association between the development of rash and serum phenytoin concentrations greater than 10 $\mu\text{g/ml}$ ($p = 0.005$ Fishers exact test).

Eight of 48 (16.6%) patients receiving carbamazepine prophylactically for supratentorial craniotomy developed exanthematous skin eruptions. Serum carbamazepine concentrations were recorded in six of these patients (13, 10, 9, 9, 7, and 4 $\mu\text{g/ml}$). Mean concentrations were significantly higher in patients developing skin eruptions ($p < 0.05$) (table). For carbamazepine we have investigated the association between rash and serum concentrations as greater or less than 6 $\mu\text{g/ml}$ because with this drug virtually all patients achieved serum concentrations within the accepted therapeutic range for the drug (approximately 4 to 8 $\mu\text{g/ml}$). There is no significant association between carbamazepine concentrations in the upper half of this range, or greater with the development of drug related skin eruptions ($p = 0.508$).

Discussion

The incidence of early skin eruptions due to phenytoin has been estimated at between 1 and 10%.³ The

overall incidence of 7% in this study is at the higher end of this range. It is of interest that previous reports of loading regimes for phenytoin have been associated with a high incidence of skin eruptions. Schmidt *et al*⁴ reported one skin eruption in nine patients receiving phenytoin intravenously, and Wilson *et al*⁵ reported skin eruptions in four of five children receiving oral phenytoin loading compared with five of eight patients receiving conventional initial doses of phenytoin.

Exanthemata have been reported in 7.7% of patients receiving carbamazepine.⁶ In this study a much higher incidence was experienced (16.6%). This may be due to the fact that all patients received carbamazepine loading during 24 hours prior to surgery. Carbamazepine induces its own metabolism, and thus serum levels tend to fall with the passage of time. The practical consequences of this are that many patients temporarily experience dose related side effects on commencing medication and this can be avoided by slowly increasing the dose of carbamazepine to the desired maintenance dose. In keeping with this we have found uniformly high carbamazepine levels in our patients at the end of the first week and this may in turn account for the high incidence of drug eruptions with carbamazepine. The uniformly high initial serum concentrations of carbamazepine have made it more difficult to prove an association between high initial blood levels of this drug and exanthemata, although we suspect that this exists.

One explanation for the high incidence of skin reactions in the craniotomy series of patients might be their exposure to anaesthetic agents and other drugs. Whilst we cannot exclude this possibility, there is no difference for the incidence of rash with phenytoin between surgical and non-surgical patients.

The explanation for the association between high initial levels of phenytoin and carbamazepine and the development of skin eruptions is unclear. It seems unlikely to be a direct effect of phenytoin or

carbamazepine since chronic toxicity is not associated with rashes. The major metabolites of phenytoin (parahydroxyphenytoin) and carbamazepine (10, 11 epoxide) could not be expected to be present in particularly high concentration during the initiation of therapy and would anyway tend to increase during chronic administration due to autoinduction. However, it is possible that early toxicity is due to the formation of a minor metabolite whose production would be less both with smaller loading doses and during chronic administration because of enzyme-induction. Such a toxic metabolite is likely to be a reactive intermediate and the epoxide precursor of phenytoin dihydrodiol would be a possible candidate.

Our findings suggest that it may be wise, wherever possible, to commence treatment with low doses of drug and to increase slowly the dose and serum level of carbamazepine and phenytoin in order to reduce the incidence of exanthematous drug eruptions. The possibility that dosage reduction, rather than drug withdrawal might be sufficient to control the exanthematous skin reaction has been suggested by others³ and might be considered in patients with less severe skin reactions.

The observations described here may also be of relevance to skin reactions related to other drugs.

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