

ALLERGIC SKIN RASH WITH LAMOTRIGINE AND CONCOMITANT VALPROATE THERAPY

EVIDENCE FOR AN INCREASED RISK

L.M. LI *, M. RUSSO **, M.F. O'DONOGHUE ***, J.S. DUNCAN ****, J.W.A.S. SANDER *****

ABSTRACT - Cutaneous rash is one of the commonest adverse events associated with lamotrigine. We assessed whether the risk is increased in patients receiving concomitant valproate therapy in a population of 103 adult patients with intractable epilepsy, who had lamotrigine added to their treatment. Of the 33 patients taking valproate, 10 (30%) developed a rash, whilst of the 70 not taking valproate, only 6 (8%) developed a rash. This suggests a significantly higher risk of cutaneous rash when starting lamotrigine in patients already taking valproate ($p < 0.02$).

KEY WORDS: allergic skin rash, antiepileptic drugs, lamotrigine, valproate.

Rash cutâneo com lamotrigina e concomitante uso de valproato: evidências de maior risco

RESUMO - Rash cutâneo é um dos efeitos adversos mais comuns associados ao início de tratamento com lamotrigina, uma nova medicação antiepiléptica. Avaliamos se esse risco é maior em pacientes medicados concomitantemente com valproato em 103 pacientes adultos com epilepsia refratária, que tiveram lamotrigina adicionada a seu tratamento. Dez dos 33 pacientes (30%) que faziam uso de valproato e 6 (8%) dos 70 pacientes que não usaram valproato desenvolveram rash. Isto sugere que existe maior risco de desenvolver rash cutâneo quando se adiciona lamotrigina em pacientes em uso de valproato ($p < 0,02$).

PALAVRAS-CHAVE: rash cutâneo, drogas antiepilépticas, lamotrigina, valproato.

Cutaneous rash is a well established adverse effect of phenytoin, carbamazepine, and has also been reported with lamotrigine (LTG) therapy. It is very rare with valproate (VPA). The overall rate of skin rash in patients receiving lamotrigine is approximately 3%¹. There have been suggestions of a higher incidence of skin rash in patients receiving LTG therapy with concomitant VPA².

To further investigate this observation, we reviewed all case records of adult inpatients with refractory epilepsy at the assessment unit of Chalfont Centre for Epilepsy, admitted between 1991 and 1993, to identify patients who had LTG added to their therapy. We noted whether side effects were recorded after its introduction.

Epilepsy Research Group, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London and The National Hospital - Chalfont Centre for Epilepsy, Gerrards Cross, United Kingdom: * MD, Research Fellow in Clinical Neurophysiology; ** MD, Major (Neurologist) U.S. Army Medical Corps; *** MRCP, Registrar in Clinical Neurology; **** DM, FRCP, Consultant and Senior Lecturer in Clinical Neurology; ***** MD, PhD, Consultant and Senior Lecturer in Clinical Neurology. Aceite: 18-outubro-1995.

J.W.A.S. Sander, MD PhD - The National Hospital / Chalfont Centre for Epilepsy - Chalfont St. Peter - Gerrards Cross, Bucks SL9 0RJ, United Kingdom. FAX 44 1 494 873991.

MATERIAL AND METHODS

Of 376 case records reviewed, 103 patients had LTG added to their antiepileptic drug (AED) therapy. There were 60 women and 43 men with mean age 35 (range 14 - 54).

RESULTS

The median starting dose of LTG was 50 mg/day (25-100 mg daily with an incremental dose of 25 to 50 mg every one of two weeks). Of 33 patients taking concomitant VPA at a median dose of 2000 mg/day (600-3000 mg), 13 (39%) developed side effects: 10 (30%) developed skin rash, 2 (6%) tremor. Of 70 patients not taking concomitant VPA, 13 (19%) developed side effects: 6 (8%) of them developed skin rash.

Statistical analysis using Chi-square test found the difference to be significant at $p < 0.02$ level when comparing these two groups for skin rash. The relative risk was 4.

One patient on VPA, and two not on VPA had florid manifestations with systemic involvement which required steroid therapy and 1 patient on VPA and carbamazepine developed a rash and died of liver failure. Only 1 patient out of 97 (1%) had a previous reported skin rash episode on VPA. The mean latency to onset of rash was 14 days (range 3-26 days). The median dose of LTG that was taken when a rash developed in patients on VPA was 100 mg/day (50-200 mg), and in patients not on VPA was 200 mg/day (100-200 mg).

There was no differential risk of developing an allergic skin rash in patients taking LTG in association with carbamazepine, phenytoin, vigabatrin or barbiturates (Table 1). No significant difference in risk for skin rash was found comparing patients who had had LTG and VPA with concomitant enzyme inducing medication (5/17) to those with LTG and VPA without concomitant enzyme inducing medication (5/16). Two patients had their LTG restarted at dose of 6.25 mg/day which was slowly increased without recurrence of skin rash.

DISCUSSION

The present results have shown significantly higher rate of developing skin rash in patients starting LTG taking concomitant VPA when compared to patients starting LTG with other concomitant AEDs. The severity of skin rash was variable; 4 of 16 patients were severely affected, requiring systemic steroids and hospitalization.

The aetiology of skin rash induction by LTG is not clear, but appears to be an allergic hypersensitivity phenomenon³. Some evidence has suggested that the mechanism of skin rash is related to the rate of dosage escalation, with the risk proportional to the initial speed of dosage rise

Table 1. Incidence of cutaneous rash in 103 patients ** starting lamotrigine.

LTG added to:	Cutaneous rash/total
Valproate	10/33 (30%)*
Vigabatrin	3/15 (20%)
Barbiturates	2/13 (15%)
Benzodiazepines	3/20 (15%)
Carbamazepine	7/55 (13%)
Phenytoin	1/14 (7%)

* Chi-square test $p < 0.02$.

** Some patients had more than one antiepileptic drug.

^{3,4}. VPA is known to inhibit LTG metabolism, increasing its serum concentration ⁵. It is possible that in patients on concomitant VPA starting LTG the higher serum concentration of LTG leads to a higher risk of skin rash.

In order to minimise the occurrence of cutaneous rash, it is suggested that LTG should be introduced at dose of 25 mg on alternate days with a gradual increase over a period of weeks in patients with concomitant VPA therapy, and started at 25 mg/day in patients not taking VPA. Skin rash is not an absolute contraindication for reinstatement of LTG, if the patient has benefitted markedly from LTG, as we observed no recurrence of skin rash in 2 patients who had LTG reintroduced very gradually. Since we have started to introduce LTG at 25 mg on alternate days dosing patients with concomitant VPA, we have noted a significant fall in rate of allergic skin rash to LTG.

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