How the rate of titration of lamotrigine influence to its tolerability and frequency of side effect and is it really optimal?

Andriy. E. Dubenko, Institute of neurology, psychiatry and narcology NAMS of Ukraine, Kharkiv, Ukraine.

Purpose

The main advantage of the drug lamotrigine is a good tolerance. However, it has side effects that limit its use. The greatest danger is the appearance of the rash, which in most cases is not dangerous, but may be the initial symptom of the development of such severe syndromes, syndrome Stevens–Johnson, syndrome Layla, syndrome hypersensitivity to anticonvulsants, and therefore requires discontinuation of the drug. The need for longterm titration of lamotrigine causes is the reason that the therapeutic dosages of lamotrigine is only possible after 2 to 3 months after the start of treatment, which complicates its use in patients with epilepsy due to the preservation of seizures during the titration, the complexity of early assessment of efficacy and, as a result of a significant deterioration in compliance and reduction of the final effectiveness of the drug.

In the available literature there is no clear explanation of such a rate titration of lamotrigine. Clearly it is proved that the appointment of the drug without titration significantly increases the risk of side effects, primarily skin rash, which is the most frequent reason for early discontinuation of the drug, as in the titration of lamotrigine decreases the risk of dizziness, nausea, vomiting and sleep disturbances .

Methods and results

Great experience with the drug lamotrigine in clinical practice suggests the possibility of more rapid titration of the drug. We propose the following scheme titration of lamotrigine. For patients who are not taking valproic acid start of titration from 25 mg 2 times a day, then increase dose by 25 mg every 5 days, starting from the morning hours. The dose that was planned to be achieved by titration, was 200 mg / day (100 mg 2 times a day). The titration scheme was presented in table 1.

Table 1

Regime titration of lamotrigine in patients studied, which not received valproic acid

Morning dose (mg)	Evening dose (mg)	Duration of prescription
25	25	5 days
50	25	5 days
50	50	5 days
75	50	5 days
75	75	5 days
100	75	5 days
100	100	

Thus, the period of dose titration is 30 days.

For patients taking valproic acid proposed mode titration, starting at 25 mg daily with subsequent increase daily dose by 25 mg 1 time per 5 days. The purpose of the titration was to achieve a daily dose of 200 mg of lamotrigine a day (some patients a maintenance dose was 150 mg per day (75 mg 2 times a day) as a result of high doses of valproic acid (more than 1500 mg per day) – 6 patients.

The titration scheme presented in table 2.

Table 2

Mode titration of lamotrigine in patients studied, which received valproic acid

Morning dose (mg)	Evening dose (mg)	Duration of prescription
12,5	12,5	5 days
25	25	5 days
50	25	5 days
50	50	5 days
75	50	5 days
75	75	5 days*
100	75	5 days
100	100	

*in 6 patients achieve the dose of lamotrigine 150 mg per day – explanations in the text.

Thus, the period of titration of lamotrigine to a selected therapeutic dose was 30 to 40 days.

Under observation there were 186 patients The age of the patients was 18-54 years. All patients received lamictal (56 patients) or generic drugs lamotrigine, which had bioequivalence to the brand. Before starting treatment all patients were familiarized with the instructions to the drug and agreed to a more rapid dose titration of lamotrigine and signed inform consent. Patients with a history of skin rash associated with the use of drugs or other allergic reactions associated with the medication in the study were not included. Each patient was seen monthly for 12 weeks after you start taking lamotrigine. The clinic visits were performed 1 times in 4 weeks. Patients had the opportunity over the phone to report side effects. Patients which had no contacts with site during the first three weeks of treatment start was lost in the study were not included. Observed all side effects of lamotrigine, but for further analysis took into account the frequency of the following side effects – skin rash, dizziness, nausea, vomiting, sleep disturbance. These adverse reactions were chosen because they are most often found in the application of lamotrigine are the cause of its abolition as a result of side effects. The incidence of side effects compared with data from multicentre clinical trials [9-38]. We selected studies where the mode of the titration corresponds to that presented in the instructions. Comparisons were performed between the data of all study patients and data analysis of all studies, as well as separate groups of patients with first monotherapy, patients whose lamotrigine was added to valproic acid and patients with a combination of lamotrigine with other AEDs. Results to compare the averaged data presented in the results of relevant clinical studies.

Analysis of the results of the study to disseminate the major side effects of lamotrigine showed the following data. (Table 3,4)

Table 3

The prevalence of major side effects in the studied patients who took lamotrigine.

	rash		nausea		vomiting		dizziness		sleep disturbances	
	patients	%	patients	%	patients	%	patients	%	patients	%
All patients - 186	18	9,7 %	23	12,4%	11	5,9%	22	11,8%	9	4,8%
Monotherapy - 27 patients	2	7,4%	4	14,8%	2	7,4%	4	14,8%	1	3,7%
Polytherapy without VPA - 106 patients	10	9,4%	11	10,4%	5	4,7%	9	8,5%	5	4,7%
Polytherapy with VPA - 43 patients	6	13,9%	10	23,2%	2	4,7%	9	20,9%	3	7%

Table 4

The number of patients studied, which was cancelled lamotrigine because of the development of major side effects

	rash		nausea		vomiting		dizziness		sleep disturbances	
	patients	%	patients	%	patients	%	patients	%	patients	%
All patients – 186	16	8,6%	1	0,5%	3	1,6%	4	2,2%	1	0,5%
Monotherapy – 27 patients	1	3,7%	0	0%	0	0%	0	0%	0	0%
Polytherapy without VPA – 106 patients	9	8,5%	0	0%	2	1,9%	1	0,9%	0	0%
Polytherapy with VPA – 43 patients	6	13,9%	1	2,3%	1	2,3%	3	6,9%	1	2,3%

Comparative evaluation of the frequency of side effects was performed with the averaged data obtained in the data analysis of 24 clinical study of various designs and 6 meta-analysis and reviews that evaluated the tolerability and side effects of lamotrigine in various clinical situations [9–38]. Follow to note that data on the prevalence of the most common side effects in different studies vary greatly; therefore, we considered the average and the minimum and maximum prevalence rates of one or another side effect on the median estimates in various studies, and information about withdrawal as a result of development of this or that side effect. Data were analyzed for all patients and was compared with the total performance of all studied patients, and data were analyzed separately tolerability of lamotrigine in combination with valproic acid, in the appointment of lamotrigine as monotherapy epilepsy (usually newly diagnosed), and when adding lamotrigine to other AEDs. Among these clinical trials, meta-analysis and reviews were selected those in which the titration of lamotrigine was produced similarly as proposed in the instructions to the various lamotrigine.

Comparing this data with data in various clinical studies, follow to note that the estimated prevalence of adverse reactions in different studies varies considerably. Rash was observed at 2.3% –17% percent of all patients who received lamotrigine in monotherapy and in combination with other AEDs. The reason for the cancellation of lamotrigine skin rash was 2,1%–11,5% of all patients receiving lamotrigine. To calculate the average percentage incidence of rash (as well as other estimated side effects) was not possible due to the different number of patients in the studies, the presence of placebo groups in which the same was observed rashes and other side effects. The prevalence of the syndrome Stephen Jones ranged from 0,5%–2,1%. (Table 6). Also evaluated the frequency of occurrence of the studied adverse reactions in different groups of patients studied. It was divided into 3 groups. Patients treated with lamotrigine as monotherapy, patients receiving lamotrigine in combination with other AEDs (except valproic acid) ,and a group of patients that lamotrigine was added and valproic acid. In this group of patients mode titration of lamotrigine was different from the first two groups of patients (table 2). The quantitative composition of the groups was 27,106 and 43 patients, respectively. The data presented in tables 5,6.

Table 5

A study comparing the incidence of side effects in patients studied with the data of the conducted analysis

	rash		nausea		vomiting		dizziness		sleep disturbances	
	our dates	literature	our dates.	literature	our dates.	literature	our dates	literature	our dates	literature
All patients -	9,7%	2,3–17%	12,4%	5-31%	5,9%	1–8,5%	11,8%	10–38%	4,8%	1,4–12%
Monotherapy -	7,4%	2,3–13%	14,8%	6–14,3%	7,4%	1–3,3%	14,8%	10–29,5%	3,7%	1,4–8%
Polytherapy without VPA -	9,4%	3,1–16,5%	10,4%	7,4–23%	4,7%	1,91–4,2%	8,5%	12–38%	4,7%	1,6–4%
Polytherapy with VPA	13,9%	4,3–17%	23,2%	12–31%	4,7%	2,7–8,5%	20,9%	15–26,3%	70%	4–12%

Table 6

Comparison of frequency of discontinuation of lamotrigine for the development of side effects in patients studied with data analysis conducted

	rash		nausea		vomiting		dizziness		sleep disturbances	
	our dates	literature	our dates.	literature	our dates.	literature	our dates	our dates.	our dates	literature
All patients -	8,6%	6,4–9,2%	0,5%	0,5–4,3%	1,6%	0,3–2,1%	2,2%	0,5–3%	0,5%	0–2,1%
Monotherapy -	3,7%	1,7–3,9%	0%	0,5–2,3%	0	0,3–0,6%	0	0,5–1%	0	0–1,2%
Polytherapy without VPA -	8,5%	3,1–10,3%	0%	0,8–3,8%	1,9%	0,3–0,8%	0,9%	1–2,5%	0	0–1,8%
Polytherapy with VPA	13,9%	4,3–15,5%	2,3%	0,9–4,3%	2,3%	1,1–2,1%	6,9%	1–3%	2,3%	0,5–2,1%

Conclusions

The safety profile and tolerability of lamotrigine is determined by gradual titration of the dose until necessary for a particular patient, however, the need for a long period of dose titration is often a significant obstacle for prescribing this medication. Clearly proved that the appointment of therapeutic doses of lamotrigine without titration significantly increases the risk of side effects that lead to drug discontinuation [30,33], but the question about the optimal rate of titration of lamotrigine, in our opinion, require further study. Certainly it is extremely difficult to draw a convincing comparative statistical analysis of our data with data from heterogeneous studies and meta analyses that have been selected for comparative evaluation of the obtained data. The comparison of obtained data with literature sources showed that the increase in the rate of titration of lamotrigine in 2 times does not increase the incidence of major side effects and does not increase the percentage of patients requiring drug discontinuation because of their development as all patients who were prescribed lamotrigine, and separate groups of patients. The highest risk of developing side effects of lamotrigine was in patients in whom the drug was added to valproic acid, which is compared with literature data and in this group most often had the need for discontinuation of lamotrigine. However, the small observations quality does not allow to draw definitive conclusions. Certainly the study cannot be the basis for an unambiguous conclusion about the possibility of a more rapid dose titration of lamotrigine, however, the continuation of such studies appears to be a promising, because the very slow titration significantly complicates the use of lamotrigine in antiepileptic practice. The search for optimal speed titration of lamotrigine, in our opinion should be continued, which will allow more widely to assign the probe without additional side effects.

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