Lamotrigine Augmentation in Delirium Tremens

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SUMMARY

Introduction Delirium tremens (DT) is most severe neurological complication of alcohol withdrawal with high mortality rate. DT is related to an altered balance of excitatory and inhibitory amino-acid neurotransmitters, which is basically due to upregulation of glutaminergic neurotransmission induced by chronic ethanol exposure. Lamotrigine (LTG) is believed to act by reducing excitatory glutamate release due to inhibition of Na (+) channels.

Objective The aim of this study was to investigate efficiency of the LTG therapy in the treatment of delirium tremens.

Methods This prospective clinical study included 240 patients with ICD-10 criteria for DT, who were randomly divided into control and experimental group. The patients were observed within 28 days at the Intensive Care Unit of the Centre for Urgent Psychiatric disorders, according to a specific protocol, which included CIWA- Ar and MDAS clinical scales. Control and experimental group were treated according to the NIAAA protocol for 2004, and experimental group with adding of LTG according to a specific program.

Results CIWA and MDAS scores in the experimental and control group has statistical significant differences after the third day ($p>0.1$), and especially after the fifth day (ECIWA5/KCIWA5=8.36±6.782/32±5.562; EMDAS5/KMDAS5=4.89±3.408/26.33±1.497) ($p>0.5$).

Conclusion LTG is significantly efficient in the treatment of delirium tremens, but it does not decrease mortality rate.

Keywords: delirium tremens; lamotrigine; glutamate; alcohol withdrawal

INTRODUCTION

Alcohol withdrawal syndrome appears in people who stopped drinking after a long-term excessive alcohol abuse. The long-term alcohol abuse leads to addiction, caused by changes in specific neurotransmitter systems, namely excitatory transmitters which in turn categorize alcoholism in the family of glutamate related disorders. Delirium tremens represents the most severe neurological complication related to alcohol withdrawal syndrome, with a world population mortality rate up to 20% [1, 2, 3].

Clinical diagnosis is in accordance with ICD 10 criteria, describing DT symptoms such as severe confusion, disorientation, hallucinations (most commonly visual, audio or tactile), agitation, convulsions, extreme sympathic hyperactivity with cardiovascular complications and other possible somatic complications. Due to the listed symptoms, DT patients are hospitalized in the intensive care units [4-10]. The neurobiochemical base of delirium tremens is the regulation of glutamine neurotransmission caused by chronic alcoholism [11-17].

Lamotrigine (LTG) is believed to reduce glutamate release by inhibiting the Na+ channels. During the 21 day trial period, the acute and chronic influences were examined, namely the influences on amino acid neurotransmitters asparate, glutamate, taurine and GABA. The observations showed that by the fourth day of use, LTG significantly inhibited veratridine induced glutamate release. LTGs effect on other amino acids was significantly lower [18]. LTG is a drug with good biological availability and minimal side effects, that are within safe medical reach and can be administered (in somewhat lower dosage) to people with severe liver and kidney damage [19].

OBJECTIVE

The aim of this study was to examine the efficiency of LTG therapy in the treatment of delirium tremens.

METHODS

Study design

The study was intended to be clinical in nature. The research was done at the Centre for Urgent Psychiatric Disorders of the Special Hospital for Mental Disorders "Dr. Laza Lazarević", Belgrade, from May 2004 to May 2006. All the participants and their families gave their oral consent. Upon completion of the study the participants were monitored on monthly basis.

Participants and procedure

The study included all the DT patients, according to ICD10 criteria for DT (previously subjected to psychiatric, neurological and general

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exams), over the age of 18 years, hospitalized at the Centre for Urgent Psychiatric Disorders during the above stated time period (totalling 240 patients) [20]. Due to the specific needs of the study, a unique protocol was developed for clinical tracing and objective scoring of the patients and included the following data: Clinical Institute Withdrawal Assessment Scale (CIWA-Ar score) (appendix 1), the Memorial Delirium Assessment Scale (MDAS score) (appendix 2) for objective assessment of clinical symptoms [21, 22], general condition and superimposed medical complications, therapy, side effects and mortality rate. The protocol was conducted for each individual patient on 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 10th, 14th, 17th, 21st, and 28th day of their hospital stay. The patients were randomly placed in either control or experimental groups. The only reason anyone would be disqualified was disobeying the therapy protocol.

Medication

The control group was treated according to the standard NIAA (National Institute on Alcohol Abuse and Alcoholism) protocol [4]. The experimental group was treated the same way with LTG in accordance with the needs of the study (appendix 3). Control group participants experiencing convulsions were treated with anti-convulsive drugs according to the NIAAA protocol. The experimental group participants experiencing convulsions were not given other anti-convulsive drugs than LTG [4, 5, 7, 10, 23-26].

Statistical analysis of the results was conducted using SPSS 12.0 program for Windows.

RESULTS

The experimental group participants were 52.70±13.27 years of age and the control group participants were 56.50±12.02 years of age. In both groups, the subjects were predominantly male with average drinking habit of 25.79±10.54 years (experimental group) and 25.19±12.02 (control group).

Of the participants in the experimental group, 91.2% were diagnosed with DT for the first time, for 6.1% it was a second occurrence, and for 2.7% it was a third occurrence (only documented occurrences that resulted in treatment of DT were taken into account).

Similar results occurred for the control group participants; 93.9% were diagnosed with DT for the first time, 5.4% were diagnosed the second time and 0.7% were diagnosed with DT for the third time.

Upon admittance, 100% of the patients were diagnosed with varying degrees of liver damage (increased transaminase, increased serum bilirubin, etc.), without any major changes in clinical and laboratory results during the study.

36.1% of the experimental group participants and 33.3% of the control group participants had convulsions upon admittance, and 54.4% of the experimental group participants and 50.3% of the control group participants had cardiac problems (hypertension, arrhythmia, myocardial infarction). During the observations 29.9% of the experimental group participants and 27.9% of the control group participants experienced other somatic complications (bronchopneumonia, acute lung oedema, hypertension, heart rhythm irregularities, and stroke). Furthermore, 36.1% of the experimental group participants and 34.7% of the control group participants developed late neurological complications of alcohol withdrawal syndrome with Sy Wernicke Korsakoff.

None of the patients from either groups experienced side effects of the therapy.

Death occurred in 3.4% of the experimental group participants and 4.1% of the control group participants, but mortality rate difference between the experimental and control groups had no statistical significance (p>0.01) (Table 1). An average CIWA score on the first

Table 1. Subjects' general information

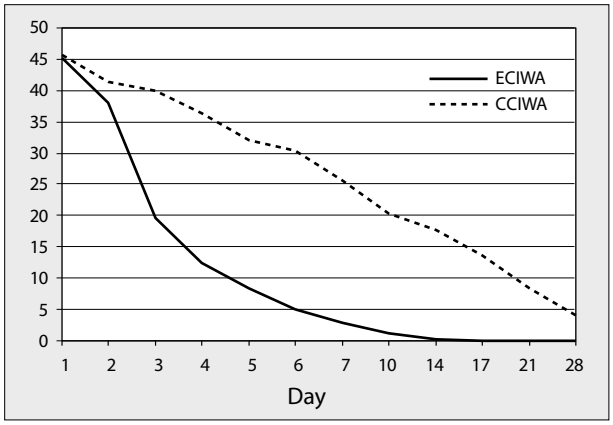
Parameter		Experimental group	Control group
Age (years)		52.70±13.27	56.50±12.02
Gender (male)		99.3%	99.3%
Drinking habit		25.79±10.54	25.19±10.38
Order of delirium tremens	First	91.2%	93.9%
	Second	6.1%	5.4%
	Third	2.7%	0.7%
Liver lesion		100%	100%
Convulsion		36.1%	33.3%
Cardial complications		54.4%	50.3%
Other somatic complications		29.9%	27.9%
Sy Wernicke–Korsakoff		36.1%	34.7%
Side effects		0%	0%
Exitus letalis		3.4%	4.1% (p>0.01)

Table 2. CIWA-Ar score in experimental and control group

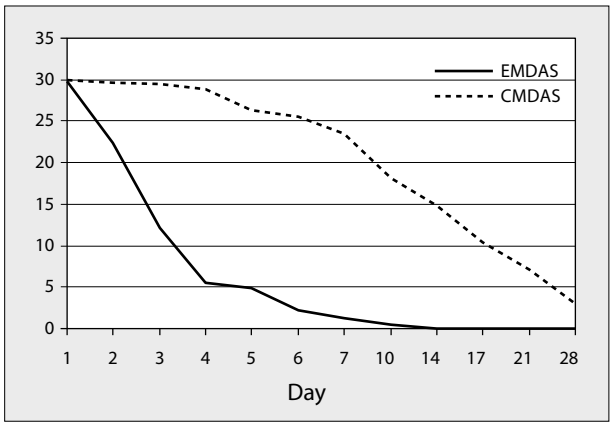
Day	ECIWA	CCIWA	p
1	45.11±6.577	45.67±1.707	>0.01
2	38.08±10.291	41.33±5.522	>0.01
3	19.52±5.825	40±5.187	<0.01
4	12.35±4.762	36.33±5.111	<0.01
5	8.36±6.782	32±5.562	<0.01
6	4.84±6.061	30.33±6.073	<0.01
7	2.88±4.693	25.67±4.977	<0.01
10	1.12±2.129	20.33±6.603	<0.01
14	0.14±0.513	17.67±6.183	<0.01
17	0.00±0.000	13.67±4.248	<0.01
21	0.00±0.000	8.33±2.761	<0.01
28	0.00±0.000	4±3.280	<0.01

Table 3. MDAS score in experimental and control group

Day	EMDAS	CMDAS	p
1	29.85±0.358	30±0.987	>0.01
2	22.45±5.189	29.67±0.749	>0.01
3	12.10±3.585	29.50±0.767	<0.01
4	5.47±3.390	28.83±0.690	<0.01
5	4.89±3.408	26.33±1.497	<0.01
6	2.11±2.271	25.50±1.901	<0.01
7	1.19±1.656	23.50±2.943	<0.01
10	0.42±0.727	18.17±4.545	<0.01
14	0.07±0.257	14.83±3.499	<0.01
17	0.00±0.000	10.33±1.707	<0.01
21	0.00±0.000	7.17±1.959	<0.01
28	0.00±0.000	3±1.640	<0.01



Graph 1. CIWA-Ar score differences between experimental and control group



Graph 2. MDAS score differences between experimental and control group

day of DT for both groups was around 45 (ECIWA1/KCIWA1=45.11±6.577/45.67±1.707), which corresponded to severe DT. The findings were also supported by MDAS score (EMDAS1/KMDAS1=29.85±0.358/30±0.000). Statistically significant differences among the experimental and control groups began to show after the third day of therapy ($p<0.01$) (ECIWA3/KCIWA3=19.52±5.825/40±5.187; EMDAS3/KMDAS3=12.10±3.585/29.50±0.767), and to become more apparently significant after the fifth day of treatment (ECIWA5/KCIWA5=8.36±6.782/32±5.562; EMDAS5/KMDAS5=4.89±3.408/26.33±1.497) (Table 2; Graph 1; Table 3; Graph 2).

DISCUSSION

Alcohol withdrawal syndrome appears in persons who stopped drinking after a long-term excessive alcohol abuse. Alcoholism is understood to mean a daily intake of 1-3 liters of beer or 1-2 dl of short drinks, every day of the week, or drinking on occasion done to replace every day life routine over a long time period. Alcohol withdrawal syndrome usually occurs in middle age people, but is know to occur in children, teenagers and elderly. The alcohol withdrawal syndrome usually occurs from 5-10 hours to 7-10 days from the last alcoholic intake [1, 7, 10]. The severity of the withdrawal symptoms depends on the "chemical addiction" to alcohol. According to the most recent research the addiction can be attributed to genetic variations, for example connectivity of the R1 genetic variety and NMDA receptors, A9 variety of the DAT gene with DT, or GRIN 1 locus with epileptic seizures with delirium tremens [27, 28, 29].

Numerous evidence indicate that ethanol selectively inhibits NMDA receptors, thus its continual intake brings about compensatory regulation of NMDA receptor functions responsible for tolerance development and alcohol addiction. Delirium tremens represents one the most severe neurological complication related to alcohol withdrawal syndrome, with a world population mortality rate up to 20% [1, 2, 3].

Clinical diagnosis is in accordance with ICD 10 criteria, describing DT symptoms such as severe confusion, disorientation, hallucinations (most commonly visual, audio or tactile), agitation, convulsions, extreme sympathic hyperactivity with cardiovascular complications and other possible somatic complications [4, 7]. When DT starts, it is impossible to stop it with any therapy currently available in the world. Heart attacks, heart rhythm abnormalities, acute heart malfunction, strokes, etc are all possible complications of DT with a potentially deadly outcome. Due to these factors, DT patients are treated in the intensive care units [4-10]. Neurobiochemical base of DT is caused by an altered balance of excitatory and inhibitory neurotransmitters in charge of regulating the glutaminergic neurotransmission induced by chronic alcoholism. The first 36 hours of withdrawal syndrome are characterized by increase in density, by 49%-94%, of receptor sites of NMDA and AMPA receptors, especially in the frontal cortex, hippocampus, and central amygdales. This is clear evidence of the involvement of the above mentioned receptors in brain hyperactivity during delirium tremens. Additionally, delirium tremens subjects have significantly lower serum levels of GABA, glicine and glutamate decarboxilase (GAD), and increased levels of glutamate and aspartate [11-17].

According to the NIAAA protocol, the treatment of DT involves administration of sedatives; diazepam for severe forms of DT without any other complications for speed and efficiency (10 mg IV, then 5 mg IV every 5 minutes until the patient is calm, while at the same time keeping the patient awake). Lorazepam is a more adequate solution for patients with liver damage, ulcus, or other severe medical conditions (4 mg every hour intramuscularly up to a dose of 10-12 mg every 4 hours for total of 3 days, and then somewhat smaller intramuscular doses and adequate peroral doses). Due to present liver lesions in all the patients (both experimental and control groups), and common cardio and other somatic complications we administered lorazepam intramuscularly [4, 5, 7, 10, 24, 25, 26].

Even though LTG is known for its anticonvulsive and stabilizing effect, the goal of this specific study was to establish LTGs potential effect on the basic pathophysiological mechanisms of delirium tremens, namely the dominance of the excitatory neurotransmission. LTG is believed to reduce glutamate release by inhibiting the Na+ channels. During the 21 day trial period, acute and chronic influences were examined, namely the influences on amino acid

neurotransmitters asparate, glutamate, taurine and GABA. The observations showed that by the fourth day of use, LTG significantly inhibited veratridine induced glutamate release. LTGs effect on other amino acids was significantly lower [18]. LTG is a drug with good biological availability and minimal side effects, that are within safe medical reach and can be administered (in somewhat lower dosage) to people with severe liver and kidney damage. For all these reasons, and due to urgency for treating DT, we changed the protocol of introducing LTG to achieve efficient concentrations of LTG that will secure the inhibition of excessive release of glutamate (table 4). The maximum dose never exceeded 200mg/24 hours due to liver damage in all the patients; additionally the total period of time during which the therapy was administered never exceeded 21 days in order to avoid a potential development of Stevens-Johnson syndrome [19].

The participants were in the same age range, predominantly male, with an average drinking habit of 25 years. Majority of the participants were diagnosed with DT for the first time and exhibited numerous complications caused by a long-term alcoholism; examples include liver damage, heart problems and over 30% of the participants experienced DT related convulsions. One third of the participants from both groups developed other somatic complications during DT, and almost 35% participants developed later neurological complications like Sy Wernicke Korsakoff. No participants had unwanted therapy side effects. Mortality rate difference between the experimental and control group had no statistically significance, thus we could not claim that the LTG therapy increased the chances of survival, which was the anticipated result, since most common causes of death in DT patients were due to somatic complications (heart attack, acute heart failure, etc) [4, 6, 10].

From all the information stated above we can conclude that all the participants from both experimental and control groups have similar characteristics and similar severity level of DT. This was confirmed using objective scales for scoring DT, whose accuracy is 95%-100%. An average CIWA score on the first day of DT (before starting the therapy) for both groups was around 45 (limit for DT is CIWA score>15), which corresponds to severe DT. The findings are also supported by MDAS score, which was around 30 on the first day (the limit for severe delirium is MDAS score>13). Statistically significant differences among the experimental and control groups began to show after the third day of therapy, when an average CIWA3 score begans to drop in the experimental group, while the control group was still experiencing high scores. The differences in objective scores became more apparently significant after the fifth day of treatment, when the experimental group begans to show CIWA3 score equal to that of persons with a mild/moderate DT, while the control group still exhibited rather high scores. In clinical terms, the participants in the experimental group were not in the life threatening condition, while the control group participants still were [21, 22]. Finally, after the tenth day, the experimental group participants did not exhibit a single symptom of alcohol withdrawal syndrome, while this was the time when the control group participants just began to be out of life threatening danger. The time period described as crucial for being out of DT for the experimental group was 3-5 days, which is the same time period necessary (under experimental conditions) for LTG to induce the inhibition of glutamate release [18], which in turn explains the LTG efficiency in treating the DT.

CONCLUSION

LTG significantly expedites the recovery process of participants with delirium tremens, which is not only of medical but also of socio-economic significance; however, it does not decrease the mortality rate. The time period described as crucial for being out of DT for the experimental group was 3-5 days, which is the same time period necessary (under experimental conditions) for LTG to induce the inhibition of glutamate release.

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Примена ламотригина у лечењу особа са делиријум тременсом

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КРАТАК САДРЖАЈ

Увод Делиријум тременс (ДТ) је најтежа неуролошка компликација алкохолног апстиненцијалног синдрома с високом стопом смртности. Неуробиохемијску базу ДТ чини дисбаланс између ексцитаторних и инхибиторних неуротрансмитера у чијој се основи налази усходна регулација глутаминергичке неуротрансмисије узроковане хроничним алкохолизмом. Ламотригин, како се сматра, делује преко редукције ослобађања глутамата инхибицијом натријумовог канала.

Циљ рада Циљ студије је био да се утврди ефикасност терапије ламотригином у лечењу особа са ДТ.

Методе рада Клиничка проспективна студија је обухватила 240 испитаника са ДТ којима је дијагноза постављена према критеријумима Десете ревизије Међународне класификације болести. Они су методом случајног избора сврстани у контролну и експерименталну групу. Клинички су праћени 28 дана у Центру за ургентну психијатрију, у Јединици интензивне неге, према посебно дизајнираном протоколу, уз објективизацију клиничке слике путем *CIWA-Ar* и *MDAS* скале. Испитаници обе групе су лечени према протоколу *NIAAA* за терапију ДТ из 2004. године, с тим да су испитаници експерименталне групе примали и ламотригин према посебној схеми. Резултати скорова *CIWA* и *MDAS* у експерименталној и контролној групи су се разликовали од трећег дана са статистичком значајношћу од $p>0,1$, а од петог дана са значајношћу од $p>0,5$ (*ECIWA5/KCIWA5*=8,36±6,782/32±5,562; *EMDAS5/KMDAS5*=4,89±3,408/26,33±1,497).

Закључак Ламотригин значајно убрзава опоравак испитаника са ДТ, али не смањује стопу смртности од ове компликације.

Кључне речи: делиријум тременс; ламотригин; глутамат; алкохолни апстиненцијални синдром