

# Efficacy Of Monotherapy With Carbamazepine And Valproic Acid In Patients With Bronchial Asthma: Is Asthma A Neurological Disease?

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## Abstract

Antiasthmatic activity of carbamazepine and sodium valproate was investigated in 28 patients (open-label trial) with moderate and severe bronchial asthma. Stable and complete remission was achieved in 10 patients of the carbamazepine group (n=14), and in 11 patients of the sodium valproate group (n=14). A follow-up study showed high and stable antiasthmatic efficacy of carbamazepine or sodium valproate monotherapy. Based on the high efficacy of these anticonvulsants in patients with bronchial asthma we suppose that bronchial asthma can be considered as mainly neurogenic paroxysmal and inflammatory disease.

## INTRODUCTION

Bronchial asthma is widely recognized as a disease of civilization. The study of bronchial asthma etiopathogenesis is limited mainly to investigation of mediators of airways chronic inflammation on cellular or tissue level<sub>1</sub>

Respectively, the treatment of bronchial asthma is aimed on the pharmacological effect on these mediators. Significant attention is paid to the investigation of immune mechanisms of bronchial asthma. But bronchial asthma also is a disease with paroxysmal clinical picture and it seems interesting to investigate antiasthmatic activity of anticonvulsive medicines in patients with asthma.

We performed small open-lable trial of carbamazepine and valproate sodium in patients with bronchial asthma. The objective of this study was to assess effect of 3-months-long peroral administration of carbamazepine or sodium valproate on pulmonary function assessed by PEFVR and incidence of asthma attacks in patients with moderate-to-severe bronchial asthma.

## METHOD

Eligibility criteria: non-stable efficacy of conventional asthma therapy, disease duration more than 1 year, frequency of asthma exacerbations 1 or more per month and absence of stable and long-term remissions. Patients had remained on their previously prescribed antiasthmatic treatment (inhaled hormones, beta-agonists, antihistamines,

sodium cromoglycate, cholinolytics).

Exclusion criteria: presence of concomitant severe diseases, age younger than 18 years.

Study design: 28 patients eligible to participate the trial were assigned to a 12-week phase of treatment with either a carbamazepine (N=14) or sodium valproate (N=14). The number of patients without asthmatic attacks and peak-flow parameters were registered before, during and after the treatment of asthma by carbamazepine or sodium valproate. We also have registered concomitant usage of other antiasthmatic medicines before and during investigation.

The patients were allowed to abandon previously prescribed routine antiasthmatic treatment in case of high efficacy of the carbamazepine or sodium valproate, except of long-term high dose peroral or parenteral hormonal therapy, but no patient had received such a treatment in our cases.

Our study is compliant with Helsinki Declaration and GCP principles, and study was approved by Ethical Committee and subjects gave their consent to participate.

The trial was conducted in 2000.

Endpoint definition: the efficacy of carbamazepine and sodium valproate was evaluated by disappearance of any asthmatic syndrome and normalization of peak-flow rates, and also by abandoning of any other antiasthmatic therapy

except carbamazepine or sodium valproate.

Limitation of the Study: insufficient quantity of peak flow-meters drove us to register peak-flow rates of our patients weekly in the morning during 3 month when visiting their doctor, instead of every day patients' self-measurements.

## STATISTICAL ANALYSIS

The null hypothesis for patients enrolled in trial was that carbamazepine or sodium valproate does not improve symptoms of asthma when added to an existing treatment regimen. Wilcoxon signed rank test was used throughout for statistical analysis of data. For statistical analysis of data we used SPSS for Windows (Release 11.0). Data are presented as Mean ± Standard Deviation.

## RESULTS

### PATIENT POPULATION

In total, 28 patients with moderate persistent or severe asthma (14 of carbamazepine group and 14 of sodium valproate group) completed the trial and were analyzed (Table 1)

#### Figure 1

Table 1: Patient characteristics before and after the treatment by anticonvulsants.

Variable	Carbamazepine group before the treatment	Carbamazepine group after the treatment	Sodium valproate group before the treatment	Sodium valproate group after the treatment
# of patients	14 (100%)	14 (100%)	14 (100%)	14 (100%)
# of patients without asthmatic attacks	0	10 (71.4%)*	0	11 (78.6%)*
Peak-flow rates (L/min)				
Mean	302.50±83.55	432.14±103.04*	275.71±121.51	422.86±113.91*
Range	200-475	240-550	150-520	160-610
% predicted peak-flow rate				
Mean	62.00±16.24	87.50±13.81*	53.14±16.82	83.79±18.51*
Range	42-92	59-100	31-82	34-100
Number of patients which received other antiasthmatic medication.	14 (100%)	4 (28.5%)*	14 (100%)	3 (21.4%)*

\* - Difference between this and previous groups is statistically significant (p<0.05).

In 10 patients from 14 (71.4% of carbamazepine group, see table 1) and in 11 patients from 14 (78.6% of carbamazepine group, see table 1) asthmatic attacks disappeared after 7-15 days of treatment with optimal dose of carbamazepine. In other 4 patients from the carbamazepine group without efficacy and in 3 patients of the sodium valproate group without efficacy asthmatic attacks remained at pre-treatment level.

We observed appearance and significant growth of number of patients without asthmatic attacks. At the end of the treatment, 10 patients from 14 patients from the carbamazepine group and 11 patients from 14 patients from the sodium valproate group had no asthmatic attacks at all.

## PEAK-FLOW RATES

Analysis of symptoms show that with absence of asthmatic attacks after 7-15 days of the treatment in 10 patients from the carbamazepine group and in 11 patients from the sodium valproate group, we also observed quite gradual increase in morning peak-flow rates during first 4 weeks of study. On the 6th week of the treatment in 10 patients from the carbamazepine group and in 11 patients from the sodium valproate group we have registered significant increase of peak-flow rates, which gradually persisted during next weeks and almost reached calculated normal level at the end of 12th week. In other 4 patients of the carbamazepine group and in other 3 patients from the sodium valproate group peak-flow rates remained at pre-treatment level.

Concomitant treatment with routine antiasthmatic drugs

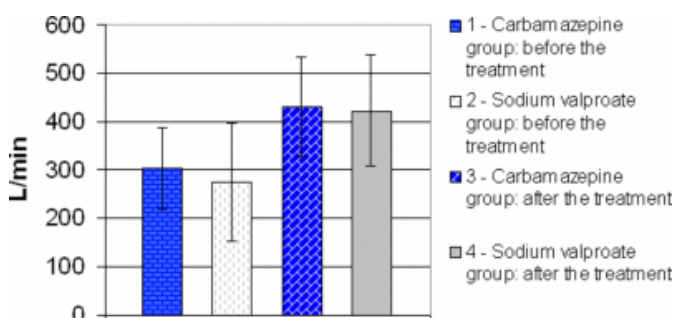
Ten patients from the carbamazepine group and 11 patients from the sodium valproate group, in which treatment by anticonvulsants was effective against bronchial asthma, after 2-8 weeks from the beginning of trial stopped any previously prescribed antiasthmatic treatment .

## STUDY FOLLOW-UP

According our data of follow-up study, all 10 responders of the carbamazepine group and 11 responders of the sodium valproate group continued treatment by our drug after the study. Peak-flow rates in all these patients remained in the normal range after more than 3 year of finishing the trial. All of the responder patients did not restore any other previously prescribed antiasthmatic treatment and they received only carbamazepine or sodium valproate during last 3 years. After more than 3 years of beginning of anticonvulsants use no one from the responder patients receives anticonvulsants or other antiasthmatic treatment, but in spite of this they have no asthma symptoms at all – they are practically healthy persons.

**Figure 2**

Figure 1: Peak-flow rates in patients before and after the treatment



## DISCUSSION

Such interesting data of antiasthmatic efficacy of anticonvulsants in our open-label study provoke us to further investigation in this field. It seems that bronchial asthma is mainly paroxysmal neurogenic disease (we like term – neurosomatic disease), and airways inflammation during asthma also is more neurogenic than immune process. The role of allergies is very important during asthma, but allergies may be only an initial trigger factor for neurogenic development of asthma as a chronic disease. Many authors support the neurogenic character of inflammation in the bronchus during bronchial asthma<sup>1</sup>, but no one underlines paroxysmal clinical picture of asthma symptoms. Antiepileptic agents are quite effective in therapy of other non-epileptic paroxysmal disorders, like trigeminal neuralgia<sup>2</sup> and migraine<sup>3</sup>. Like in asthma, neurogenic inflammation also plays a major role on pathogenesis of these diseases<sup>4, 5</sup>. Of course, asthma is not only “bronchial

seizure”, or “partial bronchial seizure” – this is very simplified vision of problem, but it seems real that neurogenic paroxysmal and inflammatory mechanisms play very important role in asthma sustaining as a chronic disease.

For supporting of anticonvulsants efficacy during bronchial asthma, it is necessary to perform double-blind randomized placebo-controlled trials with other anticonvulsants during asthma. In the future publications we are ready to show our results of such trials.

## CORRESPONDENCE TO

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