

# Safety of expanded therapeutic range of valproic acid

R. Juvany<sup>1</sup>, E. Leiva<sup>1</sup>, M. Gasol<sup>1</sup>, M. Pineda<sup>1</sup>, A. Padullés<sup>1</sup>, J. Miró<sup>2</sup>, M. Falip<sup>2</sup>, R. Jódar<sup>1</sup>

<sup>1</sup>Pharmacy Service. IDIBELL, Hospital Universitari de Bellvitge. L'Hospitalet de Llobregat, Barcelona, Spain

<sup>2</sup>Neurology Service. IDIBELL, Hospital Universitari de Bellvitge. L'Hospitalet de Llobregat, Barcelona, Spain

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## BACKGROUND:

- ✓ Therapeutic drug monitoring (TDM) of total valproic acid (TVPA) concentrations is challenging for its variable pharmacokinetics.
- ✓ In our service the TVPA is normalized according to serum albumin (NTVPA).
- ✓ The accepted serum concentration range is 50-150 mg/L. Higher concentrations could be useful in complicated seizures such as status epilepticus (SE).
- ✓ The aim of this study was to evaluate the security of high NTVPA levels.

## MATERIAL AND METHODS:

- ✓ Retrospective observational study in patients treated with VPA included in TDM program with a minimum of two NTVPA levels over 150 mg/L separated by at least 7 days.
- ✓ NTVPA was calculated from TVPA according to serum albumin\*:

$$\text{NTVPA} = (\text{TVPA} \times \text{unbound fraction}) / 6,5$$

- ✓ Parameters recorded:

- Demographics: age, sex, admission service.
- Pharmacological treatment: VPA indication, dosage, concomitant antiepileptic therapy, serum concentration of TVPA, serum albumin, pharmacological sedation.
- Efficacy variables: seizures, electroencephalogram (EEG).
- Laboratory data: platelet count, liver enzymes (ALT)
- Adverse effects.

## RESULTS:

### ➤ Demographics

- 24 patients were included (13 men), followed for a mean of 32 days [7-156].
- Mean age was 62 years [29-86].
- 16 (67 %) patients were admitted to intensive care units.

### ➤ Pharmacological treatment

- 140 TVPA analyses (6 analyses/patient [2-13]).
- 14 (58 %) were treated for status epilepticus.
- The results of the TVPA and NTVPA, albumin serum concentrations are shown in [Table 1](#) and [Graph 1](#).

**Table 1.** Descriptive parameters: serum levels of albumin, TVPA and NTVPA

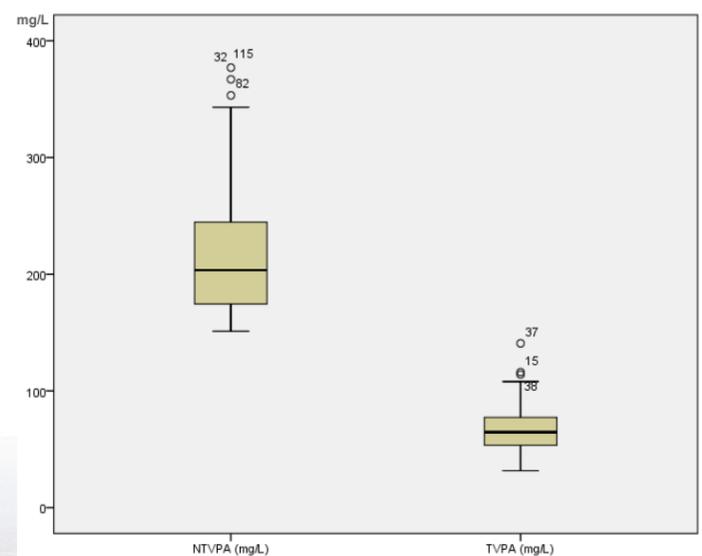
	Median	Max	Min	P25	P75
Albumin (g/L)	25	38	18	22	27
TVPA (mg/L)	64	140	32	53	77
NTVPA (mg/L)	203	377	151	174	245

- Most of the patients (n=17) received a combined therapy with one or more of the following antiepileptic drugs: phenytoin, levetiracetam, oxcarbazepine, carbamazepine, clonazepam, phenobarbital and lacosamide.

### ➤ Efficacy variables

- 2 patients had clinical seizures despite high levels of NTVPA, both confirmed by EEG.

**Graph 1.** Distribution of TVPA and NTVPA



### ➤ Side effects

- diarrhea (n=1)
- sedation (n=2); however, 15 patients were pharmacologically sedated.

### ➤ Laboratory monitoring

- 116 data of ALT and 119 of platelet count have been analyzed.
- 5 patients had ALT levels over two-fold the normal range (> 1,4 ukat/L) at baseline. At the end of the treatment, all of them had values < 1,4 ukat/L.
- 22 patients had a normal platelet count, and 2 had a platelet count < 135 x10E9/L but stabilize during the treatment.

## CONCLUSIONS:

1. Expanded therapeutic range NTVPA levels may be a save option to treat complicated seizures such as status epilepticus
2. According to our results, we could propose 245 mg/L as an upper level of therapeutic range of NTVPA with a close monitoring of platelet count and liver enzymes.

## Bibliography:

\* Hermida J, Tutor JC. A theoretical method for normalizing total serum valproic acid concentration in hypoalbuminemic patients. J Pharmacol Sci 2005; 97:489-93