

# Valproic Acid and Essential Metals

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## ABSTRACT

The effect of Valproic Acid on the serum concentration of copper, zinc, calcium, and magnesium was examined in this study. Twenty-five epileptic patients treated with Valproic Acid as mono-therapy were selected randomly. Another 50 drug-free healthy volunteers were used as a control group. Ten ml of blood was extracted from each individual for elemental measurement on atomic absorption spectrometry and for the estimation of the drug level on TDX/FLX. The patients had mean serum values of 103.97  $\mu\text{g/dl}$ , 113.68  $\mu\text{g/dl}$ , 9.14 mg/dl, and 2.16 mg/dl for Cu, Zn, Ca, and Mg respectively. In the control group the mean serum levels for Cu, Zn, Ca, and Mg were 104.50  $\mu\text{g/dl}$ , 115.04  $\mu\text{g/dl}$ , 9.22 mg/dl, and 2.21 mg/dl respectively. It was concluded that Valproic Acid had no significant effect ( $P < 0.05$ ) on the mean serum concentrations of the essential metals.

(Key Words: blood serum, copper, zinc, calcium, magnesium, epilepsy)

## INTRODUCTION

Several metals play important roles in biological processes and as such can be categorized as essential. Sodium, potassium, calcium, and magnesium exist in millimolar amounts in body fluids or tissues, and thus are not considered trace metals (Savory 1992). Those known to be essential components of nutrients are iron, copper, manganese, zinc, cobalt, molybdenum, selenium, and chromium. Essentiality also has been indicated for arsenic, cadmium, lead, lithium, nickel, tin, and vanadium, all of which fall into the ultra-trace category (Hambidge 1986).

Many of the anticonvulsant drugs are potent enzyme inducers or inhibitors, and significant drug interactions occur when they are co-administered with other medications (Stan 1996). Side effects of treatment with the anti-epileptic drugs suggested the possibility of alteration of trace metal status in humans and experimental animals (Suzuki 1992). The available literature regarding the effect of Valproic Acid on essential metals is limited and contradictory, so this study was conducted to acquire a deeper understanding of these effects.

## MATERIALS AND METHODS

Fifty healthy drug-free cases (male = 35, female = 15) age ranged between 6 months to 81 years were taken as normal control. Twenty-five registered patients (male = 13, female = 12)

age ranged 3 1/2 - 62 treated with Valproic Acid were randomly selected from Riyadh Medical Complex, Riyadh, Saudi Arabia. They were divided into six groups: Group A (All members, n= 25), Group B (Males, n= 13), Group C (Females, n= 12), Group D (Age 4-18 years, n= 13), Group E (Age 19-60 years, n= 9), and Group F (Age >60 years, n= 3). From each patient, 10 ml of blood was collected in a plain tube and serum was separated to measure the levels of essential elements and Valproic Acid levels. For elemental analysis, atomic absorption spectrometry (flame method) was selected. A TDX/FLX automated machine based on Fluorescence Polarization Immunoassay was used for the estimation of Valproic Acid level.

The mean serum concentrations of the essential elements in Valproic Acid group were recorded and compared with the mean serum concentrations of these elements in the control group. Student T Test was applied with a standard of significance equated to a P value of less than 0.05.

## RESULTS

Group A had a serum copper range of  $103.97 \pm 25.24 \mu\text{g/dl}$ ; the mean serum copper of  $102.62 \pm 25.22 \mu\text{g/dl}$  for Group B was; and it was  $105.33 \pm 26.31 \mu\text{g/dl}$  in Group C. For Group D, Group E, and Group F, the serum copper ranges were  $97.17 \pm 18.87 \mu\text{g/dl}$ ,  $122.00 \pm 35.46 \mu\text{g/dl}$ , and  $117.10 \pm 31.72 \mu\text{g/dl}$  respectively.

The zinc ranges were  $113.68 \pm 14.04 \mu\text{g/dl}$  for Group A;  $114.23 \pm 13.95 \mu\text{g/dl}$  for Group B; and  $113.08 \pm 14.74 \mu\text{g/dl}$  for Group C. The ranges for serum zinc in Group D, Group E, and Group F were  $112.44 \pm 13.81 \mu\text{g/dl}$ ,  $115.17 \pm 15.96 \mu\text{g/dl}$ , and  $127.08 \pm 15.43 \mu\text{g/dl}$  respectively.

Serum calcium ranges in Group A were  $9.14 \pm 1.20 \text{mg/dl}$ , but in Group B the range was  $9.58 \pm 0.80 \text{mg/dl}$  and in Group C a range of  $8.66 \pm 1.44 \text{mg/dl}$  was found. In Group D the range of serum calcium was  $9.30 \pm 1.08 \text{mg/dl}$ , in Group E it was  $8.62 \pm 1.60 \text{mg/dl}$ , and it was  $9.62 \pm 1.54 \text{mg/dl}$  in Group F.

Serum magnesium levels in Group A were  $2.16 \pm 0.44 \text{mg/dl}$ ; in Group B they were  $2.14 \pm 0.41 \text{mg/dl}$ ; and in Group C levels were  $2.16 \pm 0.51 \text{mg/dl}$ . In Group D, the mean serum magnesium range was  $2.24 \pm 0.34 \text{mg/dl}$  and for Group E it was  $1.90 \pm 0.32 \text{mg/dl}$ , however, Group F had a range of  $2.19 \pm 0.39 \text{mg/dl}$ . The ranges of essential elements in Valproic Acid Groups are summarized in Table 1. Ranges of essential elements in the similar categories of the control group are given in Table 2.

Table 1: Ranges for Essential Elements in Valproic Acid Subgroup.

Group	Copper Range ( $\mu\text{g/dl}$ )	Zinc Range ( $\mu\text{g/dl}$ )	Calcium Range ( $\text{mg/dl}$ )	Magnesium Range ( $\text{mg/dl}$ )
A	$103.97 \pm 25.24$	$113.68 \pm 14.04$	$9.14 \pm 1.20$	$2.16 \pm 0.44$

B	102.62 ± 25.22	114.23 ± 13.95	9.58 ± 0.80	2.14 ± 0.41
C	105.33 ± 26.31	113.08 ± 14.74	8.66 ± 1.44	2.16 ± 0.51
D	97.17 ± 18.87	112.44 ± 13.81	9.30 ± 1.08	2.24 ± 0.34
E	122.00 ± 35.46	115.17 ± 15.96	8.62 ± 1.60	1.90 ± 0.32
F	117.10 ± 31.72	127.08 ± 15.43	9.62 ± 1.54	2.19 ± 0.39

Table 2: Ranges for Essential Elements in Control Group.

Group	Copper Range (µg/dl)	Zinc Range (µg/dl)	Calcium Range (mg/dl)	Magnesium Range (mg/dl)
A	104.05 ± 21.12	115.04 ± 15.93	9.22 ± 1.32	2.21 ± 0.36
B	105.10 ± 21.12	115.00 ± 15.80	9.38 ± 1.20	2.19 ± 0.34
C	103.06 ± 21.63	115.10 ± 16.53	9.02 ± 1.48	2.24 ± 0.44
D	105.46 ± 23.92	114.65 ± 15.43	8.80 ± 1.40	2.24 ± 0.39
E	102.52 ± 16.94	115.45 ± 16.77	9.62 ± 1.08	2.16 ± 0.36
F	137.10 ± 19.34	106.03 ± 16.81	9.06 ± 1.27	2.67 ± 0.43

The mean serum level of copper in the control and Valproic Acid groups were 104.50µg/dl, and 103.97µg/dl respectively. Zinc had a respective mean level of 115.04µg/dl, and 113.68µg/dl in control and patient groups. In the control, the mean serum level of calcium was 9.22mg/dl and in Valproic Acid group it was 9.14 mg/dl. The respective levels of magnesium in control and Valproic Acid were 2.21 mg/dl and 2.16 mg/dl. The mean serum levels of the essential elements in patient group and in the control group are given in Table 3.

Table 3: The Mean Serum Level of Each Element in the Control and Valproic Acid Groups.

Group	Copper Mean (µg/dl)	Zinc Mean (µg/dl)	Calcium Mean (mg/dl)	Magnesium Mean (mg/dl)
Control Group	104.50	115.04	9.22	2.21
Valproic Acid	103.97	113.68	9.14	2.16

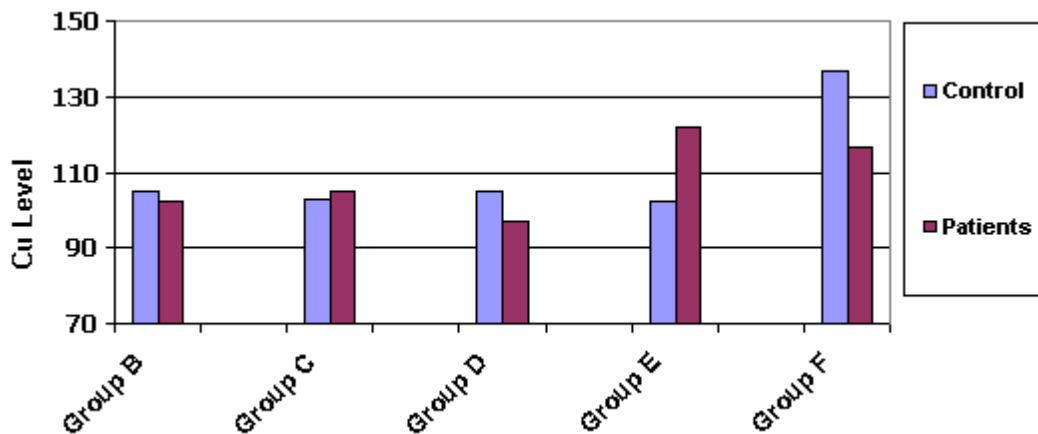
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## DISCUSSION

Our study showed that the mean serum levels of Cu, Zn, Ca, and Mg in patients were not statistically different from those of the control subjects and the P values were not significant (Table 2). The level of serum Valproic Acid weakly correlated with the mean serum concentrations of the essential elements, and this finding agreed with the previous studies of Kuzuya et al. 1993.

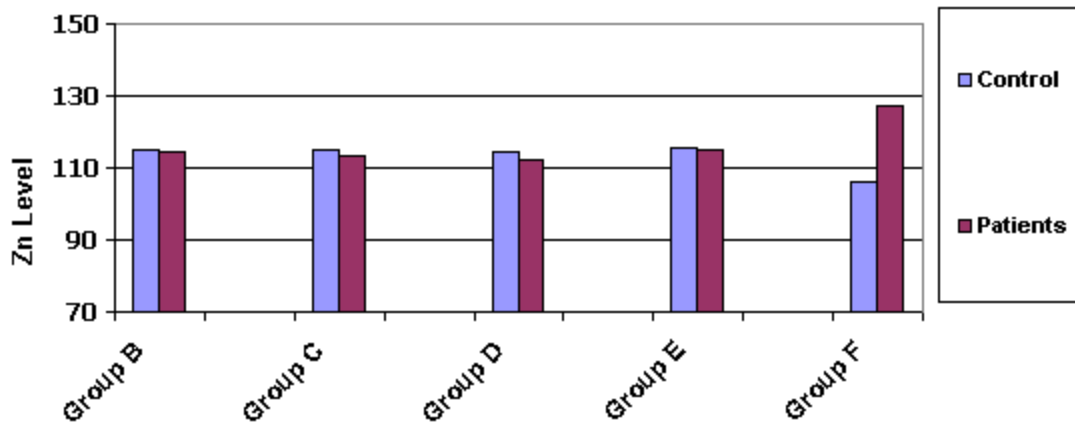
Only in Group E, was the increase significant ( $P < 0.05$ ) for serum copper while in the remaining age groups; serum copper levels were the same as those for the control set (Figure 1). However, the decrease in the mean serum copper in adults could also be contributed to some other factors (e.g., hormonal and/or dietary changes).

Figure 1: Mean Serum Copper Level in Valproic Acid Subgroups.



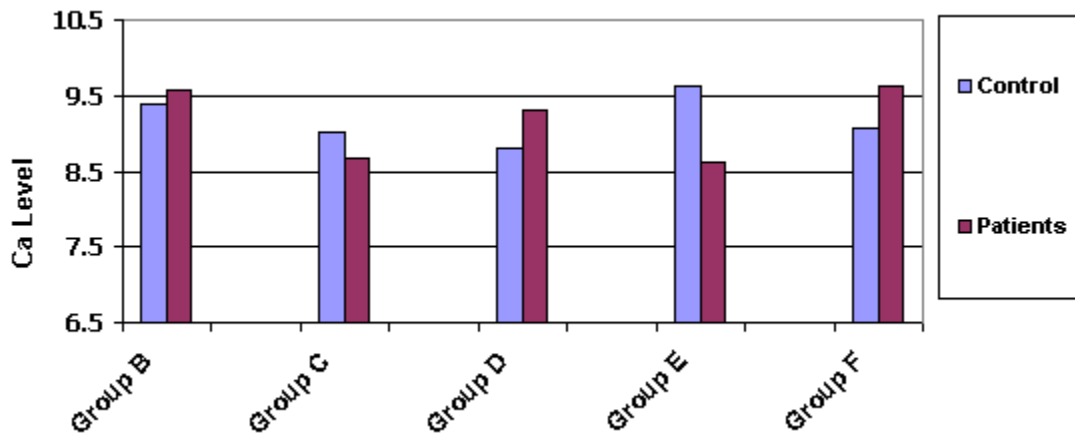
There was no significant difference in the mean serum zinc among the different groups and control groups, however, the elderly (Group F) showed increased levels of serum zinc when compared with the elderly of the control group (Figure 2). The increased level of serum zinc in the elderly could be contributed to a variety of disease and non-disease factors (dietary) rather than to Valproic Acid effect.

Figure 2: Mean Serum Zinc Level in Valproic Acid Subgroups.



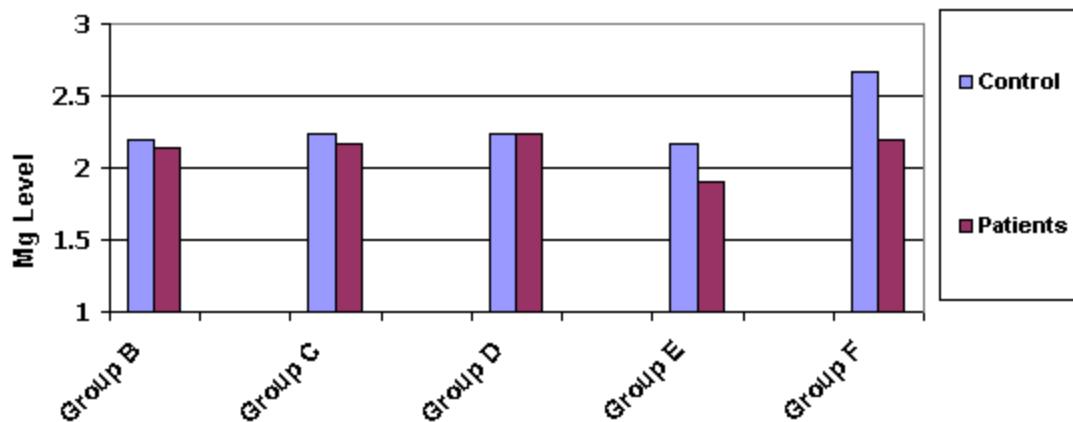
Except the significant decrease of mean serum calcium in Group E, the mean serum calcium levels in Valproic Acid Groups were approximately the same as those for the control groups. In Valproic Acid groups, Group B on comparison with Group C had a significant increase in the mean serum calcium (Figure 3). We suggested that the variation in serum calcium between males and females could be due to hormonal effects.

Figure 3: Mean Serum Calcium Level in Valproic Acid Subgroups.



Serum magnesium in Valproic Acid Groups showed no significant changes except in Group F, which had a significant decrease. This may indicate that the elderly are more vulnerable to adverse effects of Valproic Acid (Figure 4).

Figure 4: Mean Serum Magnesium Level in Valproic Acid Subgroups.



## CONCLUSION

Our study showed that Valproic Acid had no significant effect on the mean serum concentrations of the essential elements and the level of serum Valproic Acid weakly correlated with the mean serum concentrations of the essential elements. It is still recommended that the dosage and administration of this drug be carefully monitored to ensure that levels are properly adjusted to be in the therapeutic range to achieve maximum benefit. It must be remembered that changes in serum essential element levels did not necessarily reflect true aberrations in metabolism, since several conditions (disease and non-disease) can influence the indices of these elements.

This study demonstrated that levels of essential elements in patients treated with Valproic Acid mono-therapy differed somewhat from the control levels, but remained within the normal range, indicating that there is no need to adjust serum concentration of these elements in order to treat diseases related to them, unless the symptoms of deficiency or toxicity appear.

In the light of the present findings we recommend that the study concerning the effect of anti-epileptic drugs on the essential elements must continue. Further, we suggest that the study should expand to include other biological materials like cells and tissues, because the concentration of essential metals in these tissues reflects the exact status of their store in the body.

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