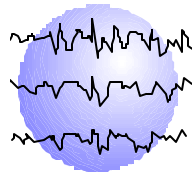


# **GAMMA GLUTAMYL TRANSFERASE IN THE ERA OF NEW ANTIEPILEPTIC MEDICATIONS**

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## REVISED ABSTRACT

**RATIONALE:** It has become standard practice to attribute elevated gamma glutamyl transferase (GGT) to antiepileptic medications (AEM) enzyme induction as a result of studies performed from the 1970s to the 1990s. This study examines the frequency of elevated GGT in children to determine how it has changed over the last 10 years.

**METHODS:** AST, ALT and GGT were obtained prospectively on 125 consecutive admissions to our pediatric inpatient epilepsy unit. These were evaluated with respect to age, sex, number and type of AEMs.

**RESULTS:** These 125 patients were on a total of 15 different AEMs. 19 (16.8%) had elevated GGT. GGT was elevated in 75% of patients treated with PHT, 57% treated with PB. Only 8% of patients treated with other AEMs had an elevated serum concentration of GGT.

**CONCLUSION:** We found that 16.8%, vs. the previously reported 50-80%, increased in GGT. Most of our patients on PB and PHT had an elevated serum concentration of GGT, which is consistent with previous reports. AST and ALT were not elevated in 2/3 of these patients and therefore suggest the increase GGT was due to enzyme induction. Elevation of GGT needs to be considered differently in light of the use of new antiepileptic medications.

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## **Introduction:**

From 1970 to 1990's elevated serum concentrations of GGT were reported in 50% to 80% of patients treated with AEM<sup>1-5</sup>. It has become standard practice to attribute elevated GGT to AEM enzyme induction and not to hepatotoxicity. These studies were performed primarily on patients treated with phenobarbital, phenytoin, and primidone. Since 1993, the 8 new AEM available in the US are associated with minimal or no liver enzyme induction. We intermittently receive inquiries regarding elevated GGT from primary care physicians who have obtained a "liver panel" on patients taking AEM. The current study reexamines the frequency of elevated GGT in light of the use of newer AEM.

## **Methods:**

After receiving a request to evaluate a 6 year old boy with Lennox-Gastaut syndrome (LGS) who had a GGT 125 times the upper limit of normal, we initiated a prospective study to evaluate GGT. It is our standard practice to obtain a metabolic panel, which includes AST and ALT, on patients the morning following admission to the inpatient epilepsy unit. We requested a GGT be added to this metabolic panel. Serum concentrations of GGT, ALT, and AST were obtained prospectively on 125 consecutive admissions. These liver enzyme concentrations were evaluated with respect to patient age, sex, number and type of AEM. Liver enzyme concentrations were evaluated using laboratory standards for age and sex.

## **Results**

There were 58 boys and 67 girls, mean age 8.6 years (range 1month to 20 years), 44 on monotherapy, 81 polytherapy with AEM, 9 on the ketogenic diet with AEM. 19/125 = 16.8% had an elevated GGT serum concentration. 10/16 = 63% of patients whose treatment included PHT, PB, or PRM had elevated GGT. 9/109 = 8.2% of patients on other AEMs had an elevated GGT concentration. 8/19 = 42% of the patients with elevated GGT concentrations also had elevated AST/ALT. In monotherapy elevated GGT serum concentrations were seen in 3 patients on PHT, 1 OXC, 1 CBZ. Table 1 shows the treatments associated with elevated GGT concentrations. Note that elevations of GGT serum concentrations were seen in 6/8 = 75% of patients on PHT, 4/7 = 57% on PB, 1/1 on PRM. The first 8 patients in the table also had elevated AST/ALT concentrations. Table 2 shows the number of patients exposed to each medication with an elevated GGT and the total number. Because many patients were on polytherapy, determination of relationship of medication to elevated GGT requires assumptions.

## **Discussion**

Our primary case that initiated the study was a 6-year-old boy with LGS and a GGT over 11,000, 125 times the upper limit of normal. The ALT and AST were also elevated, but 2 and 2.5 times normal. He was treated with FBM and had VPA added to his treatment. When the VPA was discontinued, the GGT returned to normal. Despite full evaluation for other causes of elevated liver enzymes, none was found.

## **Conclusions:**

Our prospective survey demonstrates that elevated GGT serum concentrations are not common with the newer AEMs. If GGT is elevated consideration should be given to possible hepatotoxicity.

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Table 1

Medications Associated with Elevated GGT  
(1-8 also had elevated ALT/AST)

<b>Patient</b>	<b>AEM's</b>	<b>GGT*</b>
1	PHT	324
2	PHT+LEV+TPM+CLP	237
3	PB+LTG+VPA	297
4	PB+FBM	114
5	PB+OXC+KD	293
6	FBM+LEV+TPM+ivlgG	68
7	FBM+VPA	84
8	FBM+LEV+CZP	1064
9	CBZ	57
10	CBZ+LEV+VPA	127
11	FBM+LTG+VPA	57
12	PXC+LTG+CZP	102
13	OXC	259
14	OXC+LEV+ZNS	102
15	PB+PHT+LTG	180
16	PHT	197
17	PHT+TPM	106
18	PHT	295
19	PRM+FBM+LTG	239
* Normal GGT    1-55 female    1-85 male		

Table 2

## Elevated GGT/Exposure to AEM

CBZ	2/10
CLP	1/1
CZP	2/5
ESM	0/1
FBM	6/28
GBP	0/4
LEV	5/39
LTG	6/31
OXC	5/25
PB	4/7
PHT	6/8
PRM	1/1
TPM	3/24
VPA	4/33
ZNS	1/18