from the
DRUG DESK
A Drug Information Update from the B.C. Drug and Poison Information Centre

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Patient is a 50-year-old male with epilepsy. He has been taking phenytoin 400 mg daily for 4 years and has been seizure-free for 4 years. Physician measured his LFTs last week; ALT/AST were normal but GGT was around 140. Patient states he is not experiencing any new symptoms and he is not on any other medications. He does not drink at all and is physically active. Pharmacist wants to know if intervention is necessary and if not, at what GGT level would an intervention be necessary?

Gamma-glutamyl transpeptidase (GGT) is a biliary excretion enzyme.[1] Normal serum levels range from 1-94 units/L. Elevations of this enzyme may be due to a wide variety of causes such as alcohol abuse, alcoholic liver disease, pancreatic disease, myocardial infarction, severe chronic obstructive pulmonary disease, renal diseases, systemic lupus erythematosus, hyperthyroidism, cancer, rheumatoid arthritis, diabetes mellitus and even after ingesting a few drinks of alcohol. Drugs such as phenytoin may also elevate levels of this enzyme.

Phenytoin may cause hepatoxicity (e.g. hepatitis, necrosis) at therapeutic doses.[2] However, occurence of chronic hepatitis induced by phenytoin is rare.[3] The signs of hepatotoxicity occur shortly after initiating therapy (e.g. 1-8 weeks) in acute cases, but in chronic cases may not be evident until therapy has been continued for years. Hepatitis is associated with signs and symptoms such as fever, rash, lymphadenopathy, and splenomegaly (in acute cases) and more rarely: sore throat, malaise, chills, myalgia, pruritis.

One study measured serum GGT at 6, 12, and 24 months post-phenytoin initation for seizure disorders in 58 patients.[4] Baseline GGT was 45.2 units/L. At 6 months, mean GGT was 135.8 units/L, at 12 months it was 111.9 and at 24 months it was 116.8. Eight patients experienced an increase to over 200 units/L. Higher doses of phenytoin (>300 mg daily) and concomitant alcohol use correlated with larger GGT increases. Overall, they concluded that 90% of their patient population experienced elevated GGT on phenytoin. This study did not report if there were any associated signs or symptoms or whether there was any

evidence of liver damage. The authors concluded that GGT elevation was an expected effect of long-term phenytoin therapy and is not grounds for further investigation.

Another study compared the effects of primidone, phenytoin, valproic acid, and phenobarbital on GGT, ALT, and AST levels.[5] Phenytoin was associated with a statistically significant elevation in GGT and ALT. However, the authors did not specify the time frame for this elevation.

Summary and Recommendations

Advise physician to obtain an ALP level because an elevation in ALP would be an indication for further liver investigation. The patient should be monitored for other signs and symptoms of hepatoxicity (e.g. jaundice, fever, rash, elevation of other LFTs, INR) on a regular basis. A high GGT in the presence of phenytoin therapy, in the absence of an elevation of ALP or any other signs and symptoms of hepatic dysfunction, does not appear to justify discontinuation of therapy.

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References available upon request.