

HEPATIC ENZYMES' LEVEL DURING CHRONIC USE OF ANTICONVULSANT DRUGS

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SUMMARY - We studied retrospectively 894 adult epileptic patients treated during the period from 1983 to 1992. Hepatic enzymes abnormal values were seen in 49%(n=438). In 22.3%(n=200), at least 2 enzyme levels in different moments were altered. They were divided in three groups: GI with alterations at transaminases (3%, n=6), GII with alterations at GGT and AP enzymes (72%,n=144) and GIII with alterations in both groups (25%, n=50). No patient developed clinical symptoms of liver disease. The increase of gamma-glutamyl-transferase (GGT) and alkaline phosphatase (AP) levels is frequent and not necessarily pathological. Slight increase of transaminases can occur with no clinical correlation. The routine screening of hepatic enzymes level during the chronic use of anticonvulsant drugs in adults has a questionable value.

KEY WORDS: hepatic enzymes, epilepsy, anticonvulsant drugs.

Dosagens de enzimas hepáticas em pacientes em uso crônico de drogas antiepiléticas

RESUMO - Oitocentos e noventa e quatro pacientes epiléticos adultos tratados no período de 1983 a 1992 foram estudados retrospectivamente. Valores anormais de enzimas hepáticas foram detectados em 49% (n=438) dos casos. Em 200 pacientes (22,3%), ao menos duas dosagens obtidas em momentos diferentes estavam alteradas. Estes últimos foram divididos em 3 grupos : GI, com alterações de transaminases (3%, n=6); GII com alterações de gama-glutamyl-transferase (GGT) e fosfatase alcalina (AP) (72%, n=144) e GIII com alterações nos dois grupos de enzimas (25%, n=50). Nenhum paciente desenvolveu sinais ou sintomas de doença hepática. O aumento de GGT e AP em pacientes em uso de drogas antiepiléticas é frequente e pode não ter significado patológico. Pequenos aumentos de transaminases também podem ocorrer sem correlação clínica.

PALAVRAS-CHAVE : enzimas hepáticas, epilepsia, drogas antiepiléticas.

The use of anticonvulsant drugs includes a risk of hepatotoxicity with associated mortality and morbidity rates. Such reactions are frequently idiosyncratic, due to hypersensitivity or abnormal metabolism. De Vries⁵ suggested, in 1965, that such reactions could be preceded by an asymptomatic phase, detectable by routine screening, allowing a precocious stop in the use of the drug. However, the routine laboratory monitoring had not proved to be beneficial and is of doubtful value.

This study discusses the results of repetitive hepatic enzymes blood tests during the follow-up of epileptic patients.

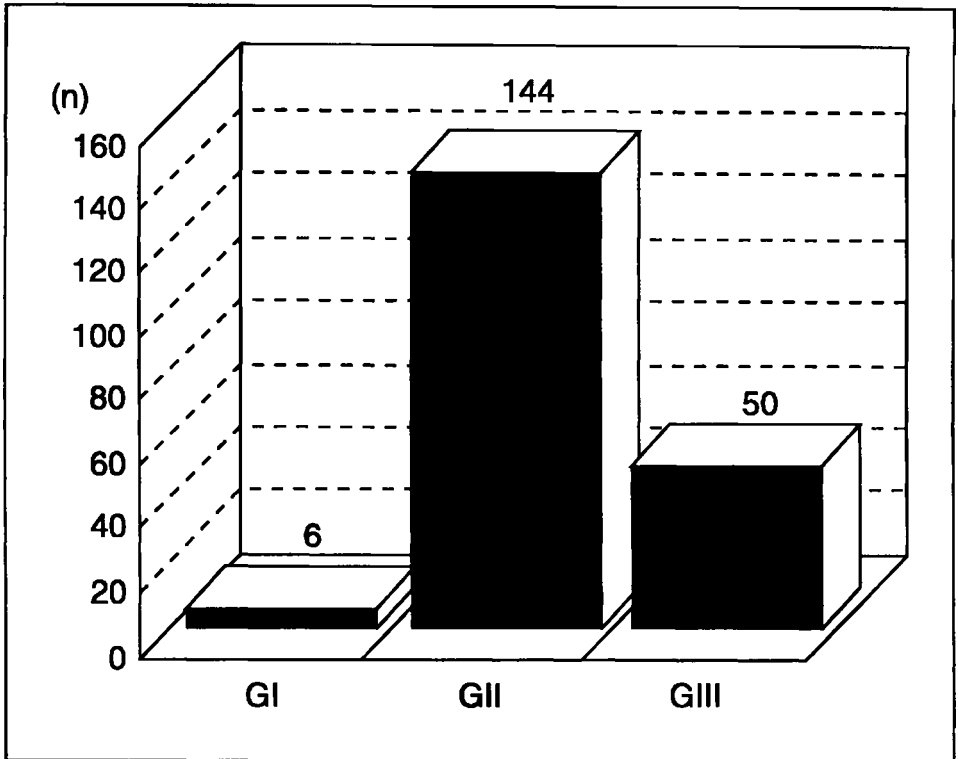


Fig 1. Distribution of the patients with at least two abnormal enzyme levels within GI, GII and GIII.

METHODS

We studied retrospectively 894 epileptic patients older than 12 years old with partial epilepsy followed at our out-patient service from January 1983 to November 1992. Repetitive routine screening of hepatic enzymes was carried out. Values of aspartate aminotransferase (AST/TGO) >20 U/l, alanine aminotransferase (ALT/TGP) >20 U/l, gamma-glutamyl transferase (GGT) >30 U/l and alkaline phosphatase (AP) >200 U/l were considered abnormal. The patients whose results were abnormal at least twice were selected and divided in 3 groups: Group I (GI) with altered transaminases; Group II (GII) with altered GGT and AP and Group III (GIII) for those patients with both transaminases and GGT/AP elevated.

RESULTS

The average follow-up time was 34.5 months. All patients studied had partial epilepsy and the most common drugs prescribed were carbamazepine (CBZ) and phenytoin (DPH). Few patients received valproate (VPA).

Hepatic enzymes' abnormal values were seen in 49% of the patients (n=438).

In 22.4% (n=200), at least 2 enzyme levels in different moments were altered; from them, 52% (n=104) were in monotherapy and 48% (n=96) were in polytherapy. These patients were further investigated.

The patients with 2 altered enzyme levels were distributed as follows: Group I (GI) only with alterations at transaminases (AST/ALT) (3%, n=6); Group II (GII) only with alterations at GGT and/or AP (72%, n=144) and Group III (GIII) when both were altered (25%, n=50) (Fig 1).

The transaminases level alterations were mild: 72.5% of AST's and 80.9% of ALT's elevations did not exceed twice the normal values (Fig 2).

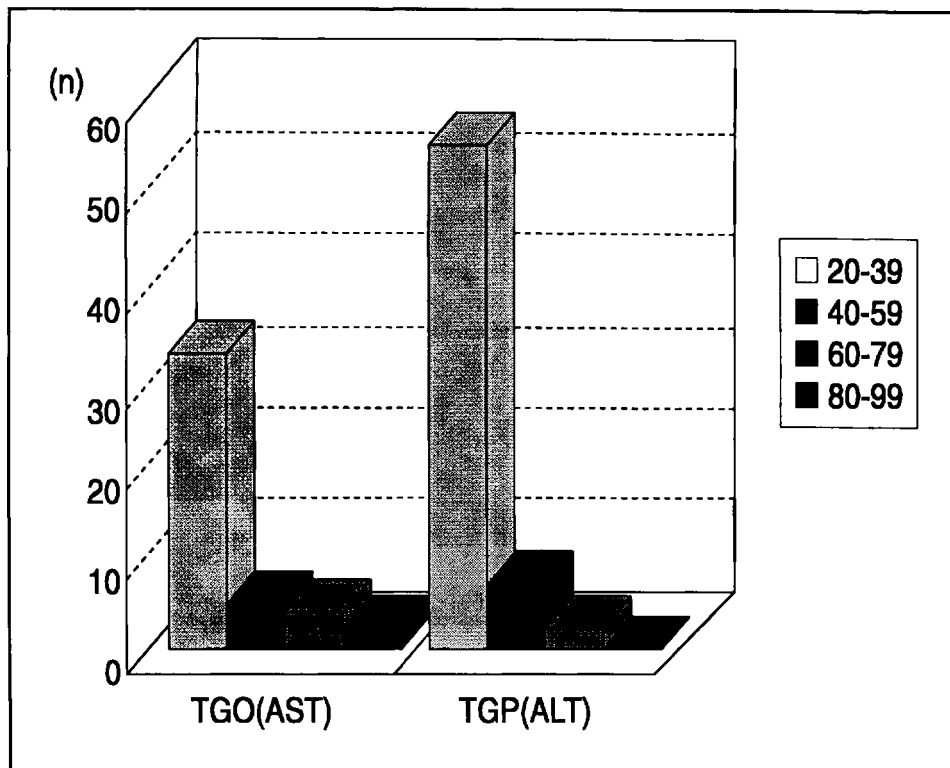


Fig 2. Distribution of the patients with increased transaminases according to the enzyme's level. Normal values: AST/ALT < 20 U/l; AP < 200 U/l; GGT < 30 U/l.

In the monotherapy group, 34.6% (n=36) received DPH, with 1 case belonging to GI (2.7%), 19 to GII (53%) and 16 to GIII (44%); 33.6% (n=35) of the cases used CBZ; 28 cases belonged to GII (80%) and 7 to GIII (20%). There were 27.9% of the patients (n=29) using phenobarbital (PB) monotherapy: 2 in GI (6.9%), 20 in GII (69%) and 7 in GIII (24%). Two cases were in GII and using primidone (PRM) and clobazam (CLB), respectively. Two patients were using VPA and were in Group II (Table 1).

Table 1. Distribution of the patients using monotherapy in GI, GII and GIII.

	GI	II	GIII	Total
CBZ	0	28	7	35
PB	2	20	7	29
VPA	0	2	0	2
DPH	1	19	16	36
PRM	0	1	0	1
CLB	0	1	0	1
Total	3	71	30	104

CBZ, carbamazepine; PB, phenobarbital; VPA, valproic acid; DPH, phenytoin; PRM, primidone; CLB, clobazam.

In the polytherapy group (n=96), 3 (3.1%) belonged to GI, 74 (77%) to GII and 19 (20%) to GIII. No patient developed symptoms or signs of liver disease.

COMMENTS

In our study we found a high proportion of altered hepatic enzymes (48.9%), mainly GGT and AP. Transaminases were increased less than twice the normal value in approximately 80% of the cases.

Although the actual incidence of hepatic lesions due to DPH has not yet been determined, some authors found it to be infrequent^{17,28} predominating in black adults with an interval from 1 to 6 weeks from drug initiation to the onset of symptoms. Immuneallergic mechanisms are probably involved at pathogenesis, leading to symptoms like fever, cutaneous alterations, lymphadenopathy²⁷ and eosinophilia. Mortality rates are between 10 and 38%⁵.

The most susceptible patients receiving CBZ are adults²⁰. The initial symptoms of hepatic failure resemble those of biliary tract infection with pruritus, fever, jaundice, chills and upper right quadrant tenderness⁸, from 3 to 4 weeks after beginning of the drug. The mortality rate is around 25%¹³. Hypersensitivity reactions or toxic metabolites can be involved.

Dreifuss et al.^{7,9} verified that the risk factors for VPA induced hepatic failure are children younger than 2 years old and receiving polytherapy. The onset symptoms include nausea, vomiting, anorexia, lethargy, edema and loss of seizure control, occurring during the first 6 months of treatment. It is followed by jaundice with or without ascites, coma, renal failure and death. The histologic features are microvesicular steatosis and necrosis²⁹. Idiosyncratic drug reactions by metabolic abnormalities are the most probable mechanisms of toxicity^{4,19} (4-pentenoic acid²², 4-en metabolite¹⁵, fatty acid beta-oxidation²³, hypocarnitinemia, deficiencies in free radical scavenging enzymes, alpha-1-antitripsin deficiency¹¹ and elevated ammonia levels²³). VPA users have been reported to have elevated hepatic enzyme levels in 7 to 44%^{26,29}, but only 0,01% develop fatal hepatotoxicity⁷. The small number of patients in monotherapy with VPA (n=2) in this series compromises the evaluation of our results in relation to this drug.

Almost half of our patients had abnormal enzyme levels, but there were no clinical correlations and no prognostic value.

The transaminases' elevations were independent from the studied drug; this is in contrast to other findings showing a differential elevation of transaminases linked to some anticonvulsants²⁴.

GGT was the most frequently altered enzyme. GGT values increment has been described in 90% of anticonvulsants users, mainly DPH, due to liver enzyme induction^{1,10,12,14,16,18,21,25}. However, Detusch et al considered an elevated GGT level an early indicator of hepatic disease⁶.

Due to the ubiquity and inespecificity of the GGT and AP enzymes alterations, the value of routine laboratory monitoring is questionable. Asymptomatic increases in hepatic enzyme concentrations are often seen with no clinical significance. There are difficulties in interpretation, frequent need for repetition of the test (6% of all tests), no use in predicting acute idiosyncratic reactions and occasionally inappropriate drug interruption due to unspecific findings^{2,3}. Clinical monitoring, on the other hand, is also limited due to late detection of hepatic failure^{2,3,25}.

Hepatic enzymes (GGT and AP) elevations are frequent and do not have necessarily a pathological meaning. Mild alterations of transaminases can also occur with no clinical significance. These findings suggest that repetitive laboratory tests for ambulatorial epileptic patients have a questionable value.

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