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The Influence of Long-term Anticonvulsant Therapy with Diphenylhydantoin and Carbamazepine on Serum Gamma-glutamyltransferase, Aspartate Aminotransferase, Alanine Aminotransferase and Alkaline Phosphatase

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Summary. In 110 patients receiving long-term anticonvulsant monotherapy with diphenylhydantoin (DPH) and carbamazepine (CBZ) the serum activities of gamma-glutamyltransferase (γ-GT), aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (AP) were examined retrospectively. Elevated serum levels of γ-GT and AP were seen in 91% and 39% of patients receiving DPH therapy compared to 64% and 14% of those receiving CBZ treatment. With all enzymes evaluated increases were more frequent and higher with DPH treatment than with CBZ. Frequency and extent of increased activity of γ-GT were highly related to daily dosage in both preparations. The proportion of pathological enzyme levels was associated with age in DPH and CBZ therapies but not found to be significant. Sex differences in the frequency of increased enzyme activities could not be demonstrated. The results are discussed in the context of induction of the cytochrome P-450 system.

Key words: Cytochrome P-450 system – Enzyme induction – Diphenylhydantoin – Carbamazepine – Hepatotoxicity

Introduction

In antiepileptic therapy diphenylhydantoin (DPH) and carbamazepine (CBZ) have a largely identical spectrum of action. Both preparations are considered highly suitable for the treatment of simple and complex-partial seizures with or without secondary generalization as well as for primary generalized tonic-clonic grand mal [31]. With 80% of previously untreated patients suffering from these types of seizures further seizures can be prevented by means of a DPH or CBZ monotherapy [3, 29, 32, 33].

With regard to potential side effects both DPH and CBZ can lead to allergic reactions and hematopoeotic disorders independently of dosage; rare cases of aplastic anemia may also occur. Dose-related side effects comprise among others vertigo, ataxia, diplopia, nausea, somnolence, and agitation [2, 31]. Unlike DPH, CBZ does not cause gingival hyperplasia or hypertrichosis. Furthermore, the incidence of polyneuropathy and osteomalacia appears to be lower so that, in light of the similar efficacy, some authors prefer initial therapy using CBZ [2, 10, 11, 31]. However, the decision as to which product to use in a given case should be based on the particulars of the individual.

A certain advantage of CBZ as compared to DPH is the positive linear pharmacokinetics, due to which a doubling of the serum concentration can be expected upon doubling the quotidian dosage. This holds true for DPH only in low concentrations; starting at an individually different level the serum concentration rises exponentially to the increase in dosage. A disadvantage of CBZ is its relatively short half-life, on account of which the daily dose has to be split up into three, or, in the retard variant, two portions, whereas the entire DPH dosage can be administered at once.

Like almost all anticonvulsants DPH and CBZ lead to an increase in serum levels of certain hepatic enzymes. In descending order of frequency increased levels of gamma-glutamyltransferase (γ-GT), alkaline phosphatase (AP), leucine aminopeptidase (LAP), aspartate aminotransferase (ALT), lactate dehydrogenase (LDH), and alanine aminotransferase (AST) were detected [31]. Depending on the respective preparation and the therapeutic régime – monotherapy or combinational therapy – up to 90% of

epilepsy patients treated had increased serum levels of γ-GT, which could cause concern regarding possible toxic hepatic damage [1, 5, 7, 8, 11, 30]. This concern seems groundless so long as the other hepatic enzymes remain within the range of reference and there are no clinical or laboratory chemical indications of liver damage. Isolated increases in γ-GT levels are considered largely insignificant, and the therapy should not be changed on their account. They are attributed to microsomal enzyme induction, respective to an increase in the dissimilation of γ-GT inhibitors in the liver [1, 5, 8, 29, 30].

Increased serum activities of AP were observed principally in adolescent patients [8, 18]. Numerous anticonvulsants – primarily DPH but also CBZ and others – directly inhibit intestinal calcium resorption and, due to dissimilation of osteal calcium, lead to a manifest vitamin D-sensitive osteopathia antiepileptica [18, 26]. Children who have been hospitalized for many years and adults suffering from age-related osteoporosis are especially predisposed to this [18]. In this context regular checks of serum AP levels are regarded the most sensitive procedure for detecting the beginning of rachitis or osteomalacia [18, 25].

The decision as to whether it is a matter of clinically insignificant adaptation of the liver or the beginning of hepatic damage becomes more difficult if, in addition to an increase in γ-GT levels, there is also increased activity of transaminases. Toxic liver diseases occur in less than 1% of patients treated [12]. They are observed somewhat more frequently with DPH than with CBZ and, as a rule, develop independently of dosage within the first 10 weeks, showing symptoms of allergic reaction such as fever, lymphadenopathy, exanthema, eosinophilia, and hepatosplenomegaly [15, 19, 21, 23, 27, 36]. Approximately one-third of the patients die of acute liver failure, the rest regain a trouble-free state a few weeks after stopping the preparation [31]. The incidence of lethality seems slightly higher with DPH than with CBZ [12]. In most cases there is no association with the hepatic enzyme data in the sense of a registration of the presymptomatic phase [4, 7]. Only during the course of the illness will ALT and AP levels rise almost inevitably, less frequently there is also an increase in AST and LDH [17]. With regards to possible hepatotoxicity it is recommended that the preparations should be stopped if repeated analyses indicate transaminase levels more than five times higher than normal [6].

The investigation presented focused on the following aspects:

1. Is there a difference between long-term anticonvulsant monotherapy with DPH and CBZ regarding frequency and extent of increased activity of γ-GT, transaminases, and AP?
2. Can sex-, age-, and dose-related differences in variability and degree of changes in serum levels of these enzymes be demonstrated?

Patients and Methods

In 110 unselected patients (54 males, average age 44.3 years; 56 females, average age 48.3 years) who received inpatient treatment at our hospital between 1986 and the first half of 1987 the serum activities of γ-GT, transaminases, and AP were evaluated retrospectively. The patients received DPH or CBZ monotherapy and had been pretreated accordingly for between 2 months and 8 years. The indication was seizure prophylaxis after brain surgery and symptomatic and idiopathic grand mal and focal seizures.

The hepatic enzymes were determined according to the usual standard methods. The normal range for γ-GT was defined as up to 28 units/l in males and 18 units/l in females, for ALT 22 units/l (males) and 15 units/l (females), and for AST 18 units/l (males) and 15 units/l (females). Independent of sex, the assumed upper limit for AP was 170 units/l.

The data were statistically evaluated by means of the χ^2 four-field test and the nonparametric Wilcoxon U-test.

Results

There were 54 patients treated with DPH, receiving an average daily dosage of 281 mg, and 56 patients received CBZ at an average quotidian dosage of 629 mg. Elevations in γ-GT were seen in 91% of patients receiving DPH treatment; the individual levels varied from 14 to 283 units/l in male, and 14 to 218 units/l in female patients. In 39% of the cases there was a moderate increase in AP with levels of between 83 and 289 units/l in men and 106 to 226 units/l in women. An increase in ALT was observed in 28% of the patients, with values between 5 and 48 units/l in male and 5 and 81 units/l in female patients. An increase in ALT in women was observed in only 1 case, reaching levels up to five times the upper norm. Finally, there was a marginal increase in AST in 11% of the cases; the levels detected ranged from 5 to 21 units/l in males and 5 to 25 units/l in females.

Treatment with CBZ led to γ-GT elevations in 64% of the cases, ranging from 9 to 87 units/l in men and 9 to 178 units/l in women. The levels of AP were increased in 14% of patients, with males showing serum levels of between 71 and 216 units/l, and females from 77 to 175 units/l. Pathological increases in ALT occurred in 9% of the cases with a variation of individual levels from 14 to 32 units/l in men and 4 to 20 units/l in women. Only in 1 case was there an increase in AST with individual data ranging from 4 to 25 units/l in males and from 4 to 14 units/l in females. A detailed analysis of the results is shown in Tables 1–4.

Table 1. Frequency of enzyme elevations

	n	γ-GT	AP	ALT	AST
DPH	54	90.7% *	38.9% **	27.7% *	11.1% **
CBZ	56	64.3%	14.3%	8.9%	1.8%

χ^2 four-field test * $P < 0.001$ ** $P < 0.01$
γ-GT, gamma-glutamyltransferase; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DPH, diphenylhydantoin; CBZ, carbamazepine

Table 2. Average level and SD of enzymes examined (units/l)

	n	γ-GT	AP	ALT	AST
DPH	54	75.9 ± 54.7 *	164.0 ± 51.9 **	17.4 ± 13.7 **	10.3 ± 4.8 **
CBZ	56	35.9 ± 27.3	126.3 ± 42.2	11.4 ± 6.0	8.0 ± 3.2

Wilcoxon U-test * $P < 0.001$ ** $P < 0.025$

Table 3. Daily dosages of DPH and CBZ and frequency of increased serum levels of enzymes

	n	γ-GT	AP	ALT	AST
DPH					
< 300 mg/day	15	73.3% *	33.3% NS	26.7% NS	6.7% NS
≥ 300 mg/day	39	97.4%	41.0%	28.2%	12.8%
DBZ					
< 600 mg/day	16	43.8% *	12.5% NS	12.5% NS	0% NS
≥ 600 mg/day	40	72.5%	15.0%	7.5%	2.5%

χ^2 four-field test * $P < 0.01$

Table 4. Average level and SD of enzymes examined and daily dosage of DPH and CBZ

	n	γ-GT	AP	ALT	AST
DPH					
< 300 mg/day	15	60.3 ± 49.3 *	182.3 ± 62.4 NS	16.0 ± 11.2 NS	8.9 ± 4.0 NS
≥ 300 mg/day	39	81.9 ± 56.8	169.9 ± 49.7	17.9 ± 14.5	9.8 ± 5.0
CBZ					
< 600 mg/day	16	24.8 ± 16.9 **	118.6 ± 38.3 NS	11.6 ± 6.2 NS	7.3 ± 3.0 NS
≥ 600 mg/day	40	39.9 ± 29.4	130.8 ± 48.9	11.3 ± 5.9	8.3 ± 3.0

Wilcoxon U-test * $P < 0.01$ ** $P < 0.025$

Discussion

In the majority of patients long-term treatment with DPH or CBZ led to increases in γ-GT levels, in rare cases increases, usually slight, in transaminases, and moderately increased AP levels also occurred (Tables 1 and 2). Relevant sex- and age-related differences in frequency and extent of enzyme elevations could not be demonstrated for either preparation. Nonetheless, in general increased enzyme levels were observed in older patients which may be due to the fact that in advanced age the protein binding is lower on account of the partially reduced plasma albumin concentrations so that the free portion of the preparation is increased and the rate of biotransformation rises [35]. Only with γ-GT was an association between daily dosage and the extent of increased enzyme levels detected: DPH dosages of less than 300 mg/day and CBZ dosages of less than 600 mg/day led to a significantly more rare and lower increase in γ-GT than higher dosages of these preparations (Tables 3 and 4).

The obvious trend from our data agrees with the results of other authors. What is remarkable, however, was the almost inevitable increase in γ-GT levels with DPH therapy, and, contrary to most reports, the percentage of increased activity of γ-GT in the case of monotherapy with CBZ was relatively high [5, 8, 10, 11, 30]. In a recent investigation regarding CBZ monotherapy in adult patients with seizures the average levels of γ-GT and AP remained within the normal range [22]. Other authors have never found increased levels of ALT and AST with CBZ monotherapy, whereas AP was increased in 7%, and γ-GT in 40% to 43% of the cases studied [9, 16, 17]. Moreover, the sex- and age-related differences occasionally described were not confirmed [10, 11, 14].

Increased serum levels of γ-GT with DPH or CBZ monotherapy must be rated as a manifestation of an adaptational proliferation of the smooth endoplasmatic reticulum with an induction of the cytochrome P-450 system. Pretratment of rats with 50–150 mg/kg of phenytoin caused a modest increase in liver weight, an increase in microsomal protein content per gram of liver and a 30%–50% increase in cytochrome P-450 concentration per milligram of microsomal protein. This suggests that DPH is a potent hepatic enzyme inducer [18a].

Biopsies of the liver of patients treated with DPH and CBZ, who had increased γ-GT and transaminase levels, only showed hyperplasia of the hepatocytes without inflammatory changes or signs of cellular necrosis or fibrosis when examined under a light microscope; under an electron microscope a proliferation of the smooth endoplasmatic reticulum could be de-

tected [1, 24]. This would indicate that increased serum levels of γ-GT and slight, usually passing increases in transaminases do not reflect hepatotoxicity and do not constitute an indication for a change of therapy or for invasive diagnostic measures.

Due to hyperplasia of the hepatocytes, proliferation of the smooth endoplasmatic reticulum, and increases in cellular protein concentrations, enzyme inducers such as DPH and CBZ – of which DPH can be considered a more potent inducer than CBZ – frequently lead to hepatomegaly and increased blood supply [13, 28]. Furthermore, they induce structural and functional changes in hepatocellular membranes [20]. The enzyme induction primarily stimulates novosynthesis of microsomally bound γ-GT in the cells' marginal surfaces. Increased plasma levels of γ-GT could therefore result from established structural and functional changes in membranes due to increased permeability of hepatocellular membranes. An increased permeability of hepatocellular membranes might also serve to explain the slight elevation of transaminases and AP. Regarding AST one must take into account that it is a bilocalized enzyme, 60% of which is located in the mitochondria, 40% in the cytosol. The difference in localization of the enzymes might explain the relatively rare and moderate increase in AST activity as this enzyme is released in larger quantities only in the case of more severe liver damage [34]. At the same time this would mean that of the enzymes studied a stronger and persistent increase in AST would be most likely to indicate the beginning of necrotic liver cell damage.

The constellation of the fetal and adult forms of γ-GT should be taken into consideration as an hitherto unexamined aspect regarding early detection of hepatotoxic side effects of anticonvulsants, as it is known that in the case of alcoholic fatty liver the proportion of the fetal form is remarkably higher than normal, whereas in alcoholic liver cirrhosis this ratio is inverted [34]. Whether or not analyses of the fetal and adult variants of γ-GT are diagnostically useful for early detection of hepatotoxic adverse effects of anticonvulsants remains to be examined in further investigations.

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