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Plasma gamma glutamyltransferase levels during rifampicin therapy for tuberculosis

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Abstract. A possible effect of rifampicin enzyme induction on microsomally derived plasma gamma glutamyltransferase (γGT) during treatment for tuberculosis patients with spinal bone disease and pulmonary or lymph node involvement was studied. Of 10 patients with bone disease 5 had raised levels prior to therapy (> 60 IU/l) and none were alcohol consumers. γGT is not known to be present in bone and this probably represents an indirect effect on the liver. Changes in γGT in the first 2 months of rifampicin/isoniazid treatment were variable and will not serve as an index of response to therapy. Of 69 patients with lung or lymph node disease 15 had raised levels during treatment and 9 had a high alcohol intake, when the alcohol group were excluded there was no significant difference from controls who had completed treatment ($p > 0.1$). We conclude that plasma γGT, a standard clinical estimation of liver dysfunction, is a useful index of suspicion for alcoholics among the tuberculous group but the disease itself can produce similar levels. It did not reflect the known hepatic microsomal inducing properties of rifampicin and thus differs from the anticonvulsant model. Clinical value would be enhanced if specific liver isoenzymes in plasma were identified which separated tissue injury, enzyme induction and the effect of extrahepatic infection on the liver.

Key words: rifampicin – enzyme induction – gamma glutamyltransferase – tuberculosis

Introduction

Plasma γGT was raised in a minority of patients undergoing tuberculous treatment and several factors may be responsible [Perry et al. 1978]. Tissue injury due to the disease itself may make a contribution as well as the toxic effect of extrahepatic infection on liver enzymes [Neale et al. 1966]. In one study nearly half the patients were alcoholics [Thompson 1976] and γGT can be a useful index of high alcohol intake due to microsomal injury or enzyme induction [Rosakli and Rau 1972]. Short term studies in volunteers and long term treatment in patients have not shown the expected rifampicin inducing effect seen with other microsomal indices [Breimer et al. 1977, Ohnhaus et al. 1979, Perry and Stamp 1984] but this has not excluded a rise in individually susceptible patients or a potentiation of rifampicin induction by alcohol.

γGT is not known to be present in bone [Rosalki 1975] but when some patients with spinal disease, who were to be followed serially, were found to have raised levels prior to therapy they were also studied, using the index as a reponse to treatment, as there is no satisfactory test of bone healing [Perry 1979]. In the second part, patients with lung or lymph node disease were evaluated to separate the factors of drug-mediated enzyme induction, tissue injury and toxic effects of tuberculosis and alcohol.

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Patients and methods

Ten hospitalized patients with spinal tuberculosis, 8 of whom were Indians, had blood drawn for γGT before and during a 2 month period while receiving rifampicin 450/600 mg and streptomycin 0.75/Ig i.m. daily with isoniazid 300 mg daily replacing streptomycin at 28 days (Figure 1). They were taking no other drugs and were non-smokers and non-drinkers, renal function and alanine transaminase levels prior to therapy were normal. Measurement of γGT was made in 69 patients (45 Indians and 24 Europeans) with pulmonary or lymph node disease who were attending a chest clinic and were clinically well after 3 months rifampicin 450/600 mg and isoniazid 300 mg daily. Twenty-seven patients who had recently completed treatment were used as controls and 10 patients receiving prophylactic isoniazid 300 mg daily formed a non-rifampicin control treatment group (Figure 2). Those with raised γGT (>60 IU/l) were interviewed for high alcohol intake defined as more than 4 oz of whisky or 4 pints of beer per day.

A sub-group of patients with normal γGT were interviewed to ensure that high alcohol consumption was absent in those with normal values. Six patients on anticonvulsants and hypnotics are

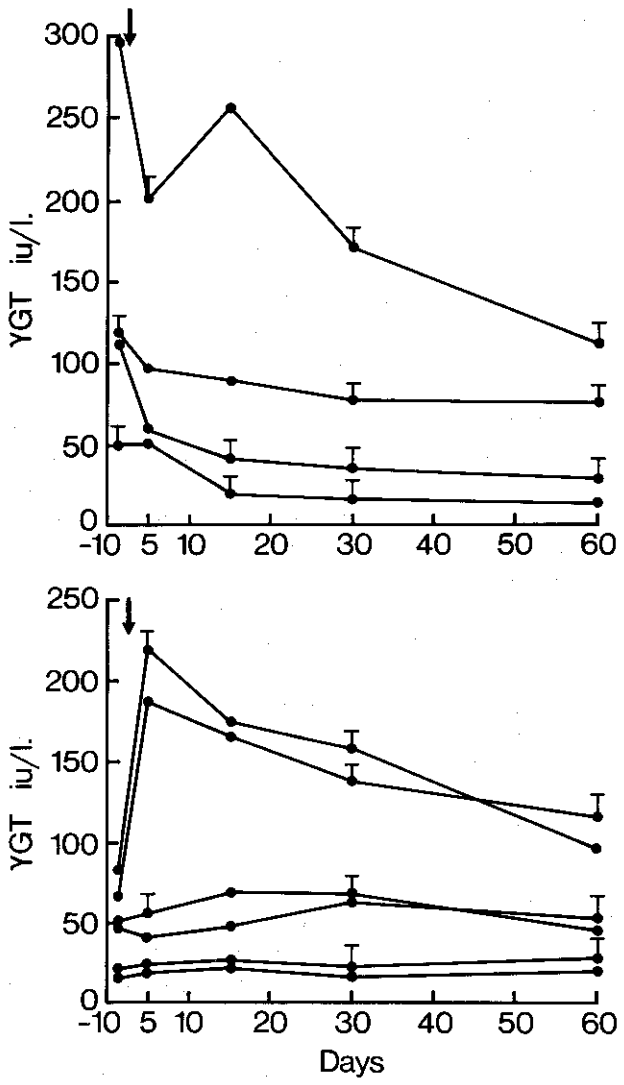

Fig. 1 Serial γGT from the start of rifampicin therapy (arrow). In the upper diagram a steady fall is seen but below 2 patients have an immediate rise and 4 were unchanged. Vertical bars denote Mean ± SEM.

shown (Figure 2) for comparison with a typical "enzyme induced group". They were receiving in descending order: primidone carbamazepine and phenytoin, butobarbitone addict, butobarbitone at night, glutethamide addiction, phenobarbitone and phenytoin, and the lowest value phenytoin alone.

γGT was measured according to the method of Rosalki et al. [1970] and the statistical analysis used was the unpaired Student's t-test and the rank sum test for abnormal distribution.

Results

In the spinal group, 5 had raised γGT prior to therapy, 3 of whom had mild increases in alanine

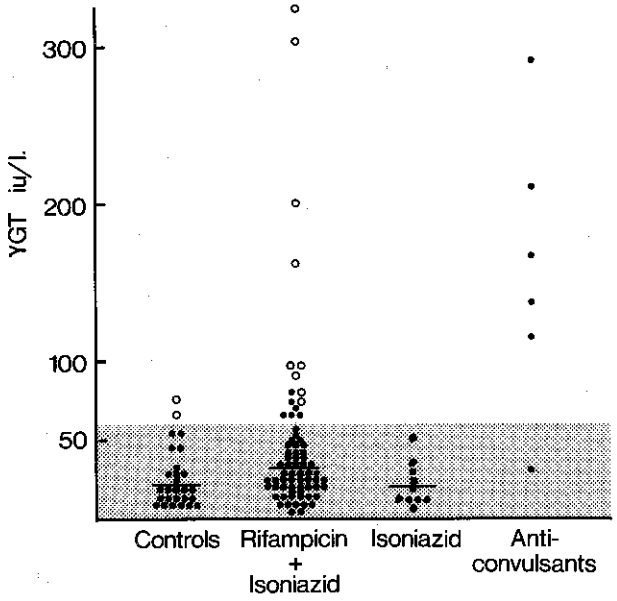

Fig. 2 Plasma γGT in 3 groups of drugs compared to controls. Note the high levels of alcoholics (open circles). Horizontal lines indicate the mean levels of non-alcoholics and the upper limit of the normal range is shown as the shaded area.

transaminase when rifampicin began. During the 2 month observation period, 4 patients showed a clear fall, 2 a clear rise and 4 were unchanged (Figure 1). At the end of this period 4 patients continued to have raised levels. Substitution of streptomycin by isoniazid did not appear to influence the trend of γGT change.

In the second group patients receiving rifampicin/isoniazid had a mean ± SD of 47.9 ± 56.1 IU/l (n = 69) and controls who had completed treatment mean ± SD of 27.1 ± 23.7 IU/l (n = 27); $p < 0.02$. However, 2 patients among the controls and 9 of 15 in the treatment group with abnormally raised values have a history of high alcohol intake. When they were excluded there was no significant difference between the control (23.5 ± 18.2 IU/l, n = 25) and treatment group (32.2 ± 19.0 IU/l, n = 60; $p > 0.1$) (Figure 2). Of 20 patients interviewed with normal γGT none had a high alcohol consumption. Those on isoniazid alone had normal γGT levels. Patients on anticonvulsants and hypnotics had increased levels and although the patient on phenytoin alone had a normal value this had doubled from baseline levels.

Discussion

The frequency of raised γGT in spinal tuberculosis prior to therapy was unexpected and the most likely explanation is an indirect toxic effect on the

liver. This was observed with other liver enzymes due to distant systemic infection [Neale et al. 1966]. Values were comparable to those with raised levels due to alcohol in the pulmonary group (Figure 2). In the upper diagram of Figure 1 patients showed a steady decline presumably as a response to treatment, in the lower diagram, 2 had an immediate rise suggesting microsomal injury by rifampicin. The 4 patients with unchanged levels provide further evidence for the absence of a rifampicin-mediated enzyme inducing effect on γGT. The variable changes in γGT preclude its use for following the healing of bone disease even if the isoenzyme does reside in bone tissue as an alternative reason for raised levels.

In patients with lung or lymph node disease those with increased alcohol intake have high levels (Figure 2) and this might characterize those who could be at risk from drug-induced hepatitis [Thompson 1976]. In patients with raised values in which alcohol intake was unlikely, a mild hepatitic effect by the drugs or a residual influence of tuberculosis appeared likely rather than as a result of rifampicin enzyme induction. We have not been able to exclude the possibility that a weak rifampicin effect was potentiated by alcohol as our control group who had completed treatment had proportionately less alcoholics, 2 out of 27 cf. 9 out of 69 in the rifampicin group. There is no evidence to strongly suggest a small sub-group who may have a genetic predisposition to rifampicin-mediated enzyme induction although this remains a possible reason for those with non-alcohol high values as mentioned above.

Until liver isoenzymes of γGT are available in the routine clinical laboratory, the correct interpretation of raised levels of this commonly used enzyme will be hampered by the competing factors discussed here.

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Relative deconvolution. An explicit method for bioavailability comparison not requiring intravenous administration

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Abstract. A method is presented which enables an explicit evaluation of the relative rate and extent of drug absorption of drug products using an oral drug solution as a reference, thereby avoiding the need for intravenous administration of the drug. The method is demonstrated using data from two sustained release phenylpropanolamine preparations and an oral solution of this drug in a human subject.

Key words: relative deconvolution – bioavailability – relative bioavailability – drug absorption – bioavailability comparison

Introduction

The procedure of deconvolution to evaluate the rate and the extent of drug input from absorption data and data from i. v. administration is the most fundamental and least assumptive method of accurately evaluating drug absorption for drugs with a linear disposition. However, the deconvolution technique has so far been limited to cases where the drug level response to a known systemic drug input (typically an i. v. bolus injection or an i. v. infusion) can be determined. This is rather limiting since in many bioavailability studies the drug is not administered i. v. either due to clinical or regulatory constraints.

The purposes of this study are: (a) to show that it is possible in some cases to circumvent this problem and perform a deconvolution in a *relative* manner on the basis of absorption data from an oral solution of the drug instead of using data from an i. v. administration; (b) to demonstrate the procedures of a proposed *relative* deconvolution method for the evaluation of the relative bioavailability of drug products, using as an example human blood level data from two sustained release phenylpropanolamine preparations and an oral solution of this drug [Dowse 1984].

Deconvolution method

Let f(t) denote the rate of absorption (amount/time) then $_0\int^\infty f(t)dt$ is the total amount of drug which gets absorbed, and $_0\int^\infty f(t)dt - _0\int^t f(t)dt$ is the amount of available drug which remains to be absorbed at time t. It is very often assumed that the absorption from an oral solution of a drug takes place in a first order manner so that the rate of absorption is proportional to the amount of available drug remaining to be absorbed, which is expressed by:

$$f(t) = k_a [_0\int^\infty f(t)dt - _0\int^t f(t)dt] \quad (1)$$

where k_a denotes the first order absorption rate constant. Differentiating (1) followed by integration and noting that $f(o) = k_aFD$, where F is the extent of bioavailability and D the dose, the above equation becomes:

$$f(t) = k_aFDe^{-k_at} \quad (2)$$

By differentiating (2) it is realized that:

$$f'(t) = -k_af(t) \quad (3)$$

where the superscript "′" denotes derivative with respect to t. If the drug has a linear disposition, whereby linear disposition is defined here in the general sense that the systemic drug level follows the superposition with respect to the rate by which the drug enters the systemic circulation, then the systemic drug level c(t), resulting from any arbitrary drug input, f(t), is given by the following convolution expression:

$$c(t) = f(t)^* c_\delta(t) = _0\int^t f(u) \cdot c_\delta(t-u)du \quad (4)$$

where $c_\delta(t)$ is the unit impulse response [Cutler 1978]. By differentiating (4) one obtains:

$$c'(t) = f(o) \cdot c_\delta(t) + f'(t)^* c_\delta(t) \quad (5)$$

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