Activity of leucocyte delta-aminolaevulinic acid synthase during diphenylhydantoin anti-convulsant therapy

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Diphenylhydantoin (DPH) is one of the phenobarbitone-type group of drugs which induces the mixed function oxidase enzyme (MFO) system (Tschudy, 1974). Induction of this system is associated with an increase in the concentration of cytochrome P-450. This increased cytochrome is thought to result from the drug stimulating at a translational level the production of the cytochrome apoprotein which then combines with free haem to form cytochrome P450 (Rajamanickam, Manchanahalli, Rao & Padmanaban, 1975). The utilisation of haem results in depletion of the free haem pool and consequently by negative feedback control increased activity of the rate-controlling enzyme of haem biosynthesis delta-aminolaevulinic acid (ALA) synthase (Padmanaban, Rao-Malathi, 1973). Increased activity of this enzyme has been observed in hepatic biopsy tissue of patients on anti-convulsant therapy (Bonkowsky & Pomeroy, 1977).

We have measured the activity of ALA synthase in peripheral leucocytes of 16 patients on DPH anti-convulsant therapy. The assay was performed using 30 ml venous blood (Brodie, Thompson, Moore, Beattie & Goldberg, 1977). No correlation was found between enzyme activity and age, drug dosage or plasma drug concentration. There was a correlation between duration of therapy and leucocyte ALA synthase activity. Those on therapy for 4–10 days having marked increased enzyme activity and the remainder similar enzyme activity compared to control subjects. In a further study we monitored the activity of leucocyte ALA synthase in 6 patients newly commenced on DPH. This did not alter during the first 2 days of therapy but between the third and tenth day all showed a marked rise in activity (varying between 6 and 20 times pretreatment values) and returning to pretreatment values within 2 weeks of commencing therapy (Figure 1).

The finding that the activity of ALA synthase increased only temporarily in spite of continued drug therapy probably indicates that when the system is induced a new steady state will be reached and haem requirements return to normal. Our observations that these enzyme changes are occurring in peripheral leucocytes as well as in hepatic tissue may considerably facilitate *in vivo* human studies of drug-related enzyme induction. Monitoring the effect of drugs on the activity of leucocyte ALA synthase in non-porphyric subjects may provide a more reliable means of assessing the safety of drugs for patients with acute porphyria.

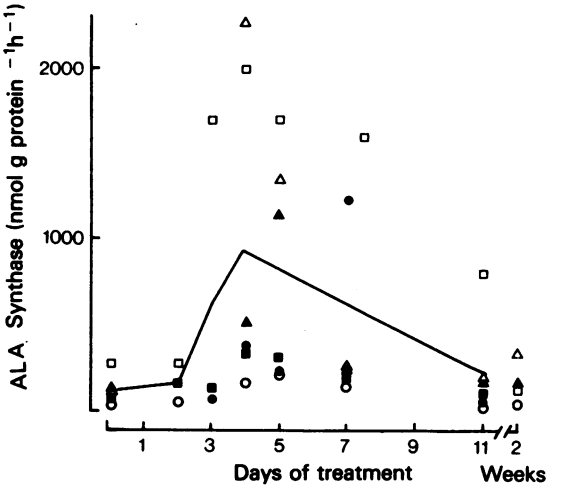

Figure 1 Activity of Leucocyte ALA synthetase during first 2 weeks of diphenylhydantoin therapy. Each patient is represented by different symbol. Continuous line indicates mean values.

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