THE CLINICAL CONSEQUENCES OF CHRONIC HEPATIC ENZYME INDUCTION BY ANTICONVULSANT DRUGS

The phenomenon of hepatic microsomal enzyme induction by drugs such as the barbiturates has attracted the increasing attention of biochemical pharmacologists, but, in comparison, the clinician has only just begun to appreciate the many consequences of this altered metabolic state. Immediate effects on the metabolism of other drugs are now widely recognized, although many physicians are still unaware that, for example, combining barbiturate sedation with warfarin anticoagulation exposes the patient to a risk of severe haemorrhage should the barbiturate be inadvertently stopped without adjustment of the dose of warfarin (MacDonald & Robinson, 1968).

The long-term consequences of living with chronically induced hepatic enzymes have only just begun to be appreciated. The epileptic patient may take large doses of several drugs for many years, and these drugs are among the most potent of known enzyme inducers. Unexpected effects can occur, for the enzymes which are induced are often not specific for one metabolic pathway, but may bring about a common chemical change (e.g. hydroxylation) in a number of widely differing substances, both endogenous and exogenous.

It is likely that 'anticonvulsant osteomalacia' is the result of such an effect (Dent, Richens, Rowe & Stamp, 1970; Richens & Rowe, 1970; Lancet, 1972a). This syndrome has excited considerable interest from those concerned with recent advances in vitamin D metabolism and metabolic bone disease, for its description coincided with a flurry of advances in our knowledge of the transformation of the vitamin into its biologically active form. Cholecalciferol (vitamin D₃) requires hydroxylation in the liver to produce the circulating hormonal form of the vitamin, 25-hydroxycholecalciferol (Blunt, De Luca & Schnoes, 1968), and this substance is then further hydroxylated in the kidneys to produce the biologically active metabolite, 1,25-dihydroxycholecalciferol (Fraser & Kodicek, 1970). Anticonvulsant drugs disturb the hepatic hydroxylation, possibly by inducing enzymes in collateral pathways, leading to the formation of inactive metabolites (Dent *et al.*, 1970; Hahn, Birge, Scharp & Avioli, 1972; Silver, Neal, Davies, Breckenridge & Thompson, 1972). The concentration of circulating 25-hydroxycholecalciferol is low in epileptic patients (Stamp,

Round, Rowe & Haddad, 1972) and although frank osteomalacia is rare, subclinical disease is common (Christiansen, Rødbro & Lund, 1973). Although it will respond to treatment with oral vitamin D, the dose required is higher than in patients who have a simple dietary deficiency (Stamp *et al.*, 1972; Borgstedt, Dryson, Young & Forbes, 1972). It has been suggested that prophylactic vitamin D should be given to all patients on anticonvulsant drugs (Hahn, Hendin, Scharp & Haddad, 1972).

Another vitamin, folic acid, is also frequently deficient in these patients, as evidenced by subnormal serum and red cell folate concentrations (Reynolds, 1972). Although this abnormality has been recognized for more than 20 years, the mechanism is still uncertain. The evidence for malabsorption of folic acid is conflicting (Reynolds, 1972), and the suggestion has been made that it is yet another example of an abnormality caused by enzyme induction (Richens & Waters, 1971; Maxwell, Hunter, Stewart, Ardeman & Williams, 1972). An increase in its turnover might lead to deficiency when the supply of dietary folate, like that of vitamin D, is limited. Whether the deficiency has pathological consequences is disputed. Certainly macrocytosis and, rarely, megaloblastic anaemia can occur (Klipstein, 1964), but the claim that the mental deterioration sometimes seen in chronic epileptics is caused by folate deficiency (Reynolds, 1968) is questionable. There are other equally plausible explanations, such as repeated brain injury by fits and falls, and the possible damaging effect of toxic levels of anticonvulsant drugs. Furthermore, a number of controlled trials of folic acid supplementation in epileptic patients have failed to show a beneficial effect on mental state (e.g. Ralston, Snaith & Hinley, 1970; Mattson, Gallagher, Reynolds & Glass, 1973).

Induction of hydroxylase enzymes in the liver is responsible for the greatly increased urinary excretion of 6- β -hydroxycortisol in epileptic patients, and measurement of this substance has been used as an index of induction (Werk, MacGee & Sholiton, 1964). This increase in elimination does not matter if the pituitary-adrenal axis is intact, because the adrenal cortex increases its secretion rate in compensation (Werk, Thrasher,

Sholiton, Olinger & Choi, 1971). However, a patient who has both epilepsy and hypopituitarism from, say, meningitis is likely to require a higher maintenance dose of cortisol. Therapeutic use has been made of this effect by administering phenytoin to patients with Cushing's disease, but the beneficial effect is small (Choi, Werk & Sholiton, 1970). Dexamethasone metabolism is similarly affected, as has been shown in asthmatic patients who were given phenobarbitone in addition for sedative purposes (Brooks, Werk, Ackerman, Sullivan & Thrasher, 1972). The metabolism of other steroid compounds such as androgens and oestrogens is also induced (Kuntzman, 1969), and this may be the reason why epileptic patients develop acne, coarse facies and hirsuties. It has even been suggested that Dupuytren's contracture, which occurs frequently in epileptic patients, may be the result of a hormonal disturbance caused by hepatic enzyme induction (Lancet, 1972b).

D-glucuronic acid is an end product of D-glucuronic acid metabolism in the liver, and is excreted normally in the urine (Levy & Conchie, 1966). Anticonvulsant drugs can increase the excretion of this substance 100-fold or more (Latham, Millbank, Richens & Rowe, 1973) and this is presumed to be by induction of enzymes on the D-glucuronic acid pathway (Hunter, Maxwell, Carrella, Stewart & Williams, 1971). Measurement of urinary D-glucuronic acid has thus become an alternative method of assessing enzyme induction in man. A related pathway, bilirubin conjugation, is also induced and this effect has been used for treating patients with Gilbert's disease and neonatal hyperbilirubinaemia (Black & Sherlock, 1970; Yeung, Tam, Chan & Lee, 1971). Epileptic patients have low serum bilirubin levels (Thomp-

son, Eddleston & Williams, 1969). They also have elevated levels of some serum enzymes of liver origin, e.g. γ -glutamyl-transpeptidase, and this is considered to be a result of induction of their synthesis (Whitfield, Moss, Neale, Orme & Breckenridge, 1973).

How much the hepatic metabolism of other drugs is accelerated by anticonvulsant therapy is in many cases not known, but if antipyrine and quinine are typical examples, the effect is likely to be considerable, for the half-lives of these two compounds in epileptic patients can be reduced to about 25% of the value in normal subjects (Ballinger, Browning, O'Malley & Stevenson, 1972; Padgham & Richens, unpublished observations). Acceleration of griseofulvin, warfarin, phenylbutazone, diazepam, digitoxin, metyrapone and DDT metabolism have been reported (Burns & Conney, 1965; Kuntzman, 1969; Ballinger *et al.*, 1972) but studies of other drugs frequently used in epileptic patients are needed.

Phenobarbitone has traditionally been used for studying hepatic microsomal enzyme induction in animal experiments. In man, however, it seems that phenytoin and primidone are equal, if not greater, in effect, and the less used anticonvulsant, pheneturide, may be more potent than any of these (Latham *et al.*, 1973). Further studies of this compound would be interesting, and assessment of its value as a bilirubin conjugase inducing drug in hyperbilirubinaemia would be of interest.

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References

- BALLINGER, B., BROWNING, M., O'MALLEY, K. & STEVENSON, I.H. (1972). Drug-metabolizing capacity in states of drug dependence and withdrawal. *Br. J. Pharmacol.*, **45**, 638-643.
- BLACK, M. & SHERLOCK, S. (1970). Treatment of Gilbert's syndrome with phenobarbitone. *Lancet*, *i*, 1359-1361.
- BLUNT, J.W., De LUCA, H.F. & SCHNOES, H.K. (1968). 25-hydroxycholecalciferol. A biologically active metabolite of vitamin D₃. *Biochemistry*, **7**, 3317-3322.
- BORGSTEDT, A.D., DRYSON, M.F., YOUNG, L.W. & FORBES, G.B. (1972). Long-term administration of antiepileptic drugs and the development of rickets. *J. Pediatr.*, **81**, 9-15.
- BROOKS, S.M., WERK, E.E., ACKERMAN, S.J., SULLIVAN, I. & THRASHER, K. (1972). Adverse effect of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *New Eng. J. Med.*, **286**, 1125-1128.
- BURNS, J.J. & CONNEY, A.H. (1965). Enzyme stimulation and inhibition in the metabolism of drugs. *Proc. Roy. Soc. Med.*, **58**, 955-960.
- CHOI, Y., WERK, E.E. & SHOLITON, L.J. (1970). Cushing's syndrome and dual pituitary-adrenal control. *Arch. Intern. Med.*, **125**, 1045-1049.
- CHRISTIANSEN, C., RØDBRO, P. & LUND, M. (1973). Effect of vitamin D on bone mineral mass in normal subjects and in epileptic patients on anticonvulsants: a controlled therapeutic trial. *Br. med. J.*, **2**, 208-209.
- DENT, C.E., RICHENS, A., ROWE, D.J.F. & STAMP, T.C.B. (1970). Osteomalacia with long-term anticonvulsant therapy in epilepsy. *Br. med. J.*, **4**, 69-72.

- FRASER, D.R. & KODICEK, E. (1970). Unique biosynthesis by kidney of a biologically active vitamin D metabolite. *Nature, Lond.*, **228**, 764-766.
- HAHN, T.J., BIRGE, S.J., SCHARP, C.R. & AVIOLI, L.V. (1972). Phenobarbital-induced alterations in vitamin D metabolism. *J. Clin. Invest.*, **51**, 741-748.
- HAHN, T.J., HENDIN, B.A., SCHARP, C.R. & HADDAD, J.G. (1972). Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. *New Eng. J. Med.*, **287**, 900-904.
- HUNTER, J., MAXWELL, J.D., CARRELLA, M., STEWART, D.A. & WILLIAMS, R. (1971). Urinary D-glucaric acid excretion as a test for hepatic enzyme induction in man. *Lancet*, **i**, 572-575.
- KLIPSTEIN, F.A. (1964). Subnormal serum folate and macrocytosis associated with anticonvulsant drug therapy. *Blood*, **23**, 68-86.
- KUNTZMAN, R. (1969). Drugs and enzyme induction. *Ann. Rev. Pharmac.*, **9**, 21-36.
- LANCET. (1972a). Anticonvulsant osteomalacia. *Lancet*, **ii**, 805.
- LANCET. (1972b). The puzzle of Dupuytren's contracture. *Lancet*, **ii**, 170.
- LATHAM, A.N., MILLBANK, L., RICHENS, A. & ROWE, D.J.F. (1973). Liver enzyme induction by anticonvulsant drugs, and its relationship to disturbed calcium and folate metabolism. *J. Clin. Pharmac.*, **13**, 337-342.
- LEVY, G.A. & CONCHIE, J. (1966). β -Glucuronidase and the hydrolysis of glucuronides. In: *Glucuronic Acid*, ed. Dutton, G.J., pp. 301-364. New York: Academic Press.
- MACDONALD, M.G. & ROBINSON, D.S. (1968). Clinical observations of possible barbiturate interference with anticoagulation. *J. Am. med. Ass.*, **204**, 97-100.
- MATTSON, R.H., GALLAGHER, B.B., REYNOLDS, E.H. & GLASS, D. (1973). Folate therapy in epilepsy. A controlled study. *Arch. Neurol.*, **29**, 78-81.
- MAXWELL, J.D., HUNTER, J., STEWART, D.A., ARDEMAN, S. & WILLIAMS, R. (1972). Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? *Br. med. J.*, **1**, 297-299.
- RALSTON, A.J., SNAITH, R.P. & HINLEY, J.B. (1970). Effects of folic acid on fit-frequency and behaviour in epileptics on anticonvulsants. *Lancet*, **i**, 867-868.
- REYNOLDS, E.H. (1968). Mental effects of anticonvulsants and folic acid metabolism. *Brain*, **91**, 197-214.
- REYNOLDS, E.H. (1972). Diphenylhydantoin: Haematologic aspects of toxicity. In: *Antiepileptic Drugs*, eds. Woodbury, D.M., Penry, J.K. & Schmidt, R.P., pp. 247-262. New York: Raven Press.
- RICHENS, A. & ROWE, D.J.F. (1970). Disturbance of calcium metabolism by anticonvulsant drugs. *Br. med. J.*, **4**, 73-76.
- RICHENS, A. & WATERS, A.H. (1971). Acute effect of phenytoin on serum folate. *Br. J. Pharmac.*, **41**, 414P-415P.
- SILVER, J., NEAL, G., DAVIES, D., BRECKENRIDGE, A. & THOMPSON, G.R. (1972). The effect of phenobarbitone induction on vitamin D metabolism. *Clin. Sci.*, **42**, 12P.
- STAMP, T.C.B., ROUND, J.M., ROWE, D.J.F. & HADDAD, J.G. (1972). Plasma levels and therapeutic effect of 25-hydroxycholecalciferol in epileptic patients taking anticonvulsant drugs. *Br. med. J.*, **4**, 9-12.
- THOMPSON, R.P.H., EDDLESTON, A.L.W.F. & WILLIAMS, R. (1969). Low plasma bilirubin in epileptics on phenobarbitone. *Lancet*, **i**, 21-22.
- WERK, E.E., MACGEE, J. & SHOLITON, L.F. (1964). Effect of diphenylhydantoin on cortisol metabolism in man. *J. Clin. Invest.*, **43**, 1824-1835.
- WERK, E.E., THRASHER, K., SHOLITON, L.J., OLINGER, C. & CHOI, Y. (1971). Cortisol production in epileptic patients treated with diphenylhydantoin. *Clin. Pharmac. Ther.*, **12**, 698-703.
- WHITFIELD, J.B., MOSS, D.W., NEALE, G., ORME, M. & BRECKENRIDGE, A. (1973). Changes in plasma γ -glutamyl-transpeptidase activity associated with alterations in drug metabolism in man. *Br. med. J.*, **1**, 316-318.
- YEUNG, C.Y., TAM, L.S., CHAN, A. & LEE, K.H. (1971). Phenobarbitone prophylaxis for neonatal hyperbilirubinaemia. *Pediatrics*, **48**, 372-376.