Pheneturide, a more potent liver enzyme inducer in man than phenobarbitone?

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During an investigation of calcium metabolism in epileptic patients (Richens & Rowe, 1970) it was noticed that serum calcium levels were lower than in normal controls, and that there was an inverse correlation between anticonvulsant drug dosage and the calcium level. The relationship between individual drugs and this abnormality was difficult to clarify because most patients were receiving multiple drug therapy. However, the order of correlation was pheneturide, primidone, phenytoin and phenobarbitone, the first drug being associated with the lowest serum calcium levels. The suggestion that induction of liver enzymes concerned with vitamin D metabolism was responsible for this abnormality has received firm support (Hahn, Birge, Scharp & Avioli, 1972; Stamp, Round, Rowe & Haddad, 1972). This hypothesis presupposes, however, that phenobarbitone is the least potent of the four drugs in inducing liver enzymes in man, and that pheneturide is the most potent. We present some evidence in support of this supposition.

The 24 h urinary excretion of glucaric acid is considered to be a measure of liver enzyme induction (Hunter, Maxwell, Carrella, Stewart & Williams, 1971). We have measured the excretion of this compound in 53 epileptic patients using a method based on that of Marsh (1963). The mean glucaric acid excretion of patients receiving the individual anticonvulsant drugs, regardless of other drug treatment, is shown in Table 1.

TABLE 1.

Drug	Number of patients	Mean glucaric acid ±SD (μM/24 h)
Pheneturide	14	360±143
Primidone	23	289±155
Phenytoin	40	247±200
Phenobarbitone	25	248±216

The mean (±SD) glucaric acid output of patients on pheneturide (360±143 μM/24 h) was significantly different ($P<0.001$) from that of patients not receiving the drug (212±177 μM/24 h).

As these results suggested that pheneturide was outstanding in its ability to induce glucaric acid production, a further study was performed in order to examine this property while controlling the influence of other drug therapy.

Eleven patients receiving pheneturide were matched in pairs with eleven patients having almost identical drug treatment with the exception of pheneturide. Age and sex were also matched as closely as possible. The mean glucaric acid excretion of those receiving pheneturide was 351±150 μM/24 h, which was significantly different ($P<0.01$) from that of the control group (172±90 μM/24 h).

These results indicated that pheneturide is a potent liver enzyme inducing drug in man, and that it may be considerably more powerful in this respect than phenobarbitone in doses which are prescribed for epileptic patients. Furthermore, they support the hypothesis that the disturbance of vitamin D metabolism in these patients is the result of liver enzyme induction.

This work was supported by grants from the Epilepsy Research Fund and Roche Products Limited.

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