Biochemical Pharmacology, Vol. 34, No. 3, pp. 447–448, 1985.
Printed in Great Britain.

0006-2952/85 $3.00 + 0.00

DEBRISOQUINE PHENOTYPING IN EPILEPTIC PATIENTS TREATED WITH PHENYTOIN AND CARBAMAZEPINE

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Pharmacogenetic factors play an important role in the interindividual variation of phenytoin metabolism activity (1). Sloan et al. (2) observed after application of a single dose of phenytoin to healthy volunteers that formation of 4-OH-phenytoin was reduced in those persons who were phenotyped as poor metabolizers of debrisoquine. From these results a common, inherited regulation of phenytoin and debrisoquine metabolism was assumed. If this could be confirmed in epileptic patients taking phenytoin chronically, a selection of those patients might be possible who develop unexpectedly high phenytoin levels upon relatively low doses. Therefore, the determination of the hydroxylator phenotype was performed by application of a single test dose of debrisoquine to epileptic patients receiving phenytoin monotherapy or a combination with further antiepileptics.

Methods

126 patients (18-65, median 39 years) on long-term phenytoin therapy were included in the study. 47 patients received additionally carbamazepine, primidone, valproic acid, ethosuximide, or clonazepam. After an oral dose of 5 to 10 mg debrisoquine (< 55 kg body weight 5 mg; ≤ 80 kg: 7.5 mg; > 80 kg: 10 mg), urine was collected for 5 hours. The median debrisoquine dose was 0.11 mg/kg. The reported g.l.c. procedure (3) for debrisoquine and 4-hydroxydebrisoquine was modified by applying a fused silica OV-101 capillary column and using bupivacaine as internal standard. Phenytoin serum levels were determined by routine fluorescence immuno assay (TDX, Abbott) during steady state and were corrected for dose and body weight.

Results and Discussion

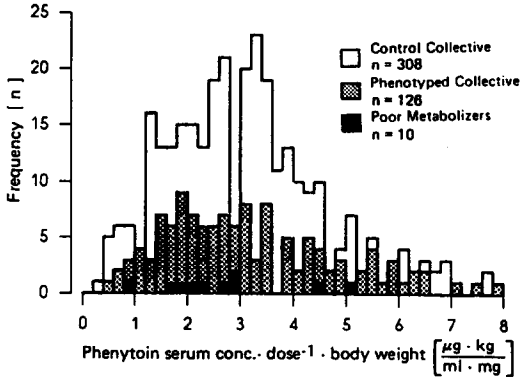

Fig.: Poor metabolizers of debrisoquine among epileptic patients taking phenytoin. The frequency distribution for corrected phenytoin steady state serum levels is also given for a larger separate collective to confirm the median of the phenotyped group (2.9 ug • kg/ml • mg).

10 patients were found with a metabolic ratio (MR) for urinary recovery of debrisoquine and 4-hydroxydebrisoquine greater 10. These persons are considered to represent the homozygous poor metabolizer phenotype (4). The figure shows that this poor metabolizer state is clearly not associated with the occurrance of relatively high phenytoin levels. Thus, a common regulation of phenytoin and debrisoquine hydroxylation could not be confirmed.

	extensive metabolizers MR < 1	extensive metabolizers MR > 1	poor metabolizers MR > 10
Phenytoin monotherapy (n = 79)	62	10	7
Phenytoin + carbamazepine (n = 26)	12	12*	2
Phenytoin + PB⊕, V, Prim., Eth., or Clon. (n = 21)	15	5	1

⊕PB = phenobarbital, V = valproic acid, Prim. = primidone, Eth. = ethosuximide, Clon. = clonazepam

*Significantly more extensive metabolizers of debrisoquine with MR >1 in the group receiving phenytoin + carbamazepine than in the group with phenytoin alone ($P < 0.001$; $X^2 = 11.3$).

Table: Frequency of certain metabolic ratio values of debrisoquine/ 4-hydroxydebrisoquine in patients receiving different antiepileptic drug therapy.

Among the extensive metabolizers of debrisoquine, MR values were mostly < 1 (table), thus being lower than reported for healthy controls (4). This shift might indicate an inducing effect due to long-term antiepileptic drug treatment.

Interestingly, MR values > 1 were frequently found in patients receiving carbamazepine together with phenytoin. This highly significant difference points to an interaction of carbamazepine and debrisoquine metabolism. Further studies will clarify whether carbamazepine and debrisoquine partly share a common enzyme in their metabolism.

References

1. Kutt, H., et al., (1966), Neurology 16, 594
2. Sloan, T.P., et al., (1981), Clin. Pharmacol. Ther. 29, 493
3. Lennard. M.S., et al., (1977) J.Chromatogr. 133, 161
4. Woolhouse, N.M., et al., (1981), Clin. Pharmacol. Ther. 26, 584