GRISEOFULVIN-TOLBUTAMIDE INTERACTION*

By

K. SAMU IYER, A. UMMER, P. NARAYANAN KUTTY MENON AND ZACHARIA VERGHESE

Departments of Pharmacology and Biochemistry, Calicut Medical College, Calicut.

Phenobarbitone stimulates the induction of enzymes which metabolise several drugs, thus antagonising their activity (18). It antagonises the oral anticoagulants, (3) griseofulvin (4) and phenytoin (16). Cullen and Catalano(8) have argued that since both griseofulvin and warfarin are antagonised by phenobarbitone, the administration of griseofulvin will have some effect on warfarin metabolism. They demonstrated an antagonism of warfarin activity by the concurrent administration of griseofulvin, suggesting some pattern and predictability in drug interaction. Coumarin anticoagulants potentiate tolbutamide (20). Phenylbutazone and phenyramidol potentiate oral anticoagulants (1,5). These two drugs also potentiate tolbutamide (20,9). Since griseofulvin antagonises warfarin, the present study was undertaken to examine whether concurrent administration of griseofulvin will have some effect on the activity of tolbutamide.

Several workers have screened drugs for their hypoglycaemic activity on rabbits starved for 18 hr (10,17). On the other hand, other workers have presented impressive evidence that starvation for 18 hr is not sufficient and rabbits must be starved for 48 hr in order to unmask the hypoglycaemic activity of compounds, particularly when such activity is mild, as in the case of certain indigenous plant products (19). Whereas the former will reveal any modification of tolbutamide activity by griseofulvin analogous to what is obtained in clinical situations, the latter may bring into relief any finer modification of the activity of tolbutamide by griseofulvin.

MATERIALS AND METHODS

Adult rabbits weighing approximately 1.5 kg were used for the experiments. Seventeen rabbits were fed griseofulvin 50 mg/kg orally daily for ten days. An equal number served as controls and were sham-fed. After being deprived of food for eighteen hr all were challenged with tolbutamide orally at a dose of 100 mg/kg. Blood was drawn from the ear veins just prior to the administration of tolbutamide and at 2 hr, 4 hr and 6 hr. Blood was collected in fluoride-citrate tubes and analysed for sugar by the Folin and Wu method.

The procedure was repeated in another group of rabbits subjected to starvation for 48 hr.

*Received 3-8-1970

TABLE I

Modification of the hypoglycaem effect of tolbutamide by griseofulvin

Period of starvation (hr)	*Mean hypoglycaemia mg% ±S.E.*					
	Control	*Test*	*Control*	*Test*	*Control*	*Test*
	2 hr		*4 hr*		*6 hr*	
18* (17)*	20.65±2.60	27.88±2.90	39.7±2.80	40.18±3.0	45.0±4.20	32.65±5.20
		P>0.05		P>0.75		P>0.05
48 (17)	22.6 ±1.24	26.10±1.09	37.700±.89	39.84±1.6	52.2±2.3	42.0 ±3.35
		P<0.05		P>0.05		P<0.05

1. Test animals received griseofulvin 50mg/Kg orally daily for 10 days followed by tolbutamide 100mg/kg on the 11th day.
2. Control animals received tolbutamide as test animals, but in place of griseofulvin were sham fed.

*Figures in parentheses indicate the number of animals.

RESULTS

The results are summarized in Table I. The difference in the mean values for the quantum of fall in blood sugar for the group of rabbits starved for 18 hr suggests a potentiation by griseofulvin of the tolbutamide - induced hypoglycaemia at 2 hr and antagonism at 6 hr. However this variation was not statistically significant. In the group of rabbits starved for 48 hr the pattern of variation was the same and the variations were statistically significant.

DISCUSSION

A number of drugs are known to potentiate the activity of sulfonylureas, sulfaphenazole (6), dicoumarol (20), phenylbutazone (9) and chloramphenicol (7). A number of drugs are also known to antagonise tolbutamide, neuroleptics (15) and propranolol (14). Hence investigation of effects of drugs on the activity of tolbutamide is important, since unforeseen hypoglycaemic episodes have been experienced in persons taking tolbutamide concurrently with other drugs. Particularly when there are grounds for suspecting that griseofulvin may in some way modify tolbutamide activity, it is imperative that such an interaction be investigated before unforeseen complications occur in patients. Griseofulvin has a structure similar to colchicine (21) and colchicine is known to potentiate several drugs like central depressants and sympathomimetics (22). Griseofulvin also potentiates alcohol (12).

We have already stated that Cullen and Catalano (8) anticipated the griseofulvin-warfarin antagonism. On the other hand phenytoin and dicoumarol were metabolised faster by the prior administration of phenobarbitone, also by a process of enzyme-induction. But the administration of dicoumarol in individuals treated with phenytoin resulted not in antagonism but in phenytoin intoxication (11).

The present study suggests that there may not be any real danger of either a severe hypoglycaemia or a serious nullification of the tolbutamide effect by the concurrent administration of griseofulvin. If these conclusions hold good for human beings also, a clinical mishap in either direction appears to be improbable. A study of the half life of tolbutamide with and without griseofulvin appears indicated. On the basis of some suspicion of probenecid having potentiated tolbutamide such a study was made with probenecid (2). The results were negative.

SUMMARY

Rabbits were given griseofulvin orally for ten days and challenged with oral tolbutamide. Their blood glucose responses were campared with those of control rabbits receiving the same dose of toulbtamide. Griseofulvin potentiated tolbutamide at 2 hr and blocked it at 6 hr.

REFERENCES

1. Aggelar, P.M., R.A.O. Reilley and L. Long. Potentiation of anticoagulant effect of warfarin by phenylbutazone. *New.Eng.J.Med.*, **276**:496, 1967.
2. Brook. R., J.J. Schrogie and H.M.Solomon. Failure of probenecid to inhibit the rate of metabolism of tolbutamide in man. *Clin. Pharmac. Ther.*, **9**: 314., 1968.
3. Burns, J.J., S.A. Cucinell, R. Koster and A.H. Conny. Application of drug metabolism to drug toxicity studies. *Ann.N.Y.Acad.Sci.*, **123**: 273, 1965.
4. Busfield, D., K.J. Child, R.M. Atkinson and E.J. Tonich. An effect of phenobarbitone on blood levels of griseofulvin in man. *Lancet.*, ii, 1042, 1963.
5. Carter, S.A. Potentiation of the effect of orally administered anticoagulants by phenyramidol hydrochloride. *New.Eng.J.Med.*, **273**: 423, 1965.
6. Christensen, L.K., J.M. Hansen and M. Kristensen. Sulphaphenazole induced hypoglycaemic attacks in tolbutamide treated diabetics. *Lancet*, ii, 1298, 1963.
7. Christensen, L.K. and L. Stosted. nhibition of drug metabolism by chloramphenicol. *Lancet.*, ii, 1397, 1969.
8. Cullen, S. and P.M. Catalano. Griseofulvin warfarin-antagonism. *J.Am.Med.Ass.*, **199**: 582, 1967.
9. Field, J.B, M. Ohta, C. Beyle and A. Remer. Potentiation of acetohexamide hypoglycaemia by phenylbutazone. *New.Eng.J.Med.*, **277**: 889, 1967.
10. Gupta, S.S., S.C.L. Verma, V.P. Garg and Mahesh Rai. Anti-diabetic effects of *Tinospora cardiflora*. *Ind.J.Med.Res.*, **55**: 733, 1967.
11. Hansen. J.M., M. Kristensen, L. Skovsted and L. Korsgaard Christensen. Dicoumarol induced diphenylhydantion intoxication. *Lancet.*, ii, 265, 1966.

12. Hilick-Smith, G. Drili's, Pharmacology in Medicine. *Mcgraw Hill Book Company, New York*, 3*rd Ed.* 1965, p. 1370.

13. Optiz, K. and A.Loeser. Reduction of the hypoglycaemic potency of antidiabetic substances by neuroleptic agents. *German Med. Monthly*, 7: 297, 1962.

14. Oreste De Divitiis., F. Gisrdano and A. Jocono. Tolbutamide and propranolol. *Lancet.*, i, 749, 1968.

15. Oser, B, Lin, Hawks. Physiological Chemistry. *McGraw Hill* 14*th Ed.* 1965, P. 1052.

16. Prescott, L.F. Pharmacokinetic drug interaction. *Lancet.*, ii, 1239, 1969.

17. Shah, D.S. A preliminary study of the hypoglycaemic action of heartwood of *Pterocarpus marasupium* root. *Ind. J. Med. Res.*, **55**: 166, 1967.

18. Sharpless, S.K. In the Pharmacological basis of Therapeutics. Edited by L.S. Goodman and A. Gilman, *Macmillan Co. New York* 3rd Ed. 1965.P. 115,

19. Shrotri, D.S. and R. Aiman. The relationship of the post absorptive state to the hypoglycaemic action studies on *Ficus bengalensis* and *Ficus glomerata*. *Ind.J.* Med. Res., **48**: 162, 1960.

20. Solomon, H.M. and J.J. Shrogie. Effect of phenyramidol and bishydroxycoumarin on the metabolism of tolbutamide in human subjects. *Metabolism*, **16**: 1029, 1967.

21. Weinstein, L. In the Pharmacological Basis of Therapeutics. Edited by L.S. Goodman and A. Gilman, *Macmillan Co., New York* 3rd Ed. 1297, 1965. 115.

22. Woodbury, D.M. In the Pharmacological Basis of Therapeutics. Edited by L.S. Goodman and A Gilman. *Macmillan Co., New York*, 3rd Ed. 1965. P. 340.