PRELIMINARY COMMUNICATIONS

Enhancement of Methyldopa Metabolism with Barbiturate

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Summary

The spurious increase in serum catecholamine levels associated with methyldopa treatment can be reduced by the simultaneous administration of phenobarbitone. This accelerating effect of phenobarbitone on methyldopa metabolism has been demonstrated in relation to both adrenaline and noradrenaline, and investigations suggest that it is due to the effect of barbiturate on the activity of metabolizing enzymes.

Introduction

It is known that the duration and degree of activity of drugs may closely depend on the activity of metabolizing enzymes situated in the reticular endoplasm of the liver cells, and that some drugs can influence the metabolism of others. In addition to its theoretical importance the significance of enzyme induction cannot be disregarded in clinical practice, examples being the acceleration of dicoumarin metabolism, and thus a reduction in its anticoagulant activity, by barbiturates (Cucinell *et al.*, 1965) and the enhancement of aminopyrine metabolism by phenylbutazone (Conney, 1967). Though opinions differ on the mode of action of methyldopa (Sourkes, 1954; Dollery and Harington, 1962) it has proved highly effective in hypertension of varying aetiology and is widely used. The question arose whether the metabolism of methyldopa could be influenced by other drugs and in particular by barbiturates.

Catecholamine excretion is decreased rather than increased by methyldopa (Sjoerdsma, 1960). Gifford and Tweed (1962) found that treatment with methyldopa was consistently accompanied by spuriously high values for urinary catecholamines, as determined by the fluorescent method of Hingerty (1957),

which were apt to lead to erroneous diagnoses of phaeochromocytoma. When methyldopa was added to normal urine and determined by a modified Hingerty's method the samples showed fluorescence in the same wave band as urinary catecholamines, and this interference was shown to be the cause of the spurious results (Gifford and Tweed, 1962). This false positive reaction suggested to us the possibility of studying the metabolism of methyldopa and its metabolites by determining serum catecholamine levels.

Method

The first step was to find out whether in patients on long-term treatment with methyldopa the administration of a barbiturate changed the serum catecholamine levels. These levels fluctuated so much in patients not taking a barbiturate that comparisons were difficult. Therefore changes of catecholamine concentration were determined after a large dose of methyldopa with and without barbiturate respectively.

We selected 12 patients free from any such conditions as congestive heart failure, phaeochromocytoma, or liver disease which might have affected the absorption or excretion of the drug. No other medication was given and the patients were allotted alternatively to the barbiturate group and to the control (non-barbiturate) group. After determining the initial levels of serum catecholamine the six patients in the control group were given 1,000 mg of methyldopa (Dopegyt, EGYT Pharmacochemical Works, Budapest) at 8 a.m. and another 1,000 mg at 8 p.m. on the same day. Serum catecholamine levels were determined at 24, 48, and 72 hours respectively after the first dose of methyldopa. The six patients in the barbiturate group were given 0.165 g of phenobarbitone (Sevenal, Chinoin) intramuscularly one evening, and the next day phenobarbitone 0.165 g was given at 8 a.m. and 8 p.m. together with 1,000 mg of methyldopa. Phenobarbitone 0.165 g twice daily was continued for another two days. Moderate somnolence was noticeable in the patients on barbiturate, but those in the control group were also slightly drowsy. There were no other side effects.

Results

The average total catecholamine, adrenaline, and noradrenaline concentrations and the average standard mean error for the two groups are presented in the Table. The initial levels in each case are recorded in the column for day 1. The findings show that in patients in the control group given only methyldopa catecholamine levels rose much higher than in patients in the phenobarbitone group. The difference is unequivocal both in the maximum levels recorded the day after the administration of methyldopa and in the decrease observed on subsequent days.

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Changes of Catecholamine Concentrations after Methyldopa and Barbiturate

No. of days:		Methyldopa (6 Patients)				Methyldopa and Barbiturate (6 Patients)			
		1*	2	3	4	1*	2	3	4
Catecholamine (µg/l.)	Mean	2.88	275.5	18.7	10.48	1.61	37.35	8.02	3.70
	S.E.	0.26	99.2	4.73	3.18	0.45	15.63	4.16	1.16
Adrenaline (µg/l.)	Mean	1.34	107.6	7.66	4.44	0.61	14.78	3.96	1.38
	S.E.	0.20	35.51	2.16	1.56	0.18	9.38	2.5	0.45
Noradrenaline (µg/l.)	Mean	1.52	167.0	10.85	6.08	1.0	22.55	4.06	2.28
	S.E.	0.12	68.17	2.04	1.62	0.22	9.10	1.52	0.72

* Initial levels.

Discussion

This study shows that a false increase in serum catecholamine induced by the administration of methyl dopa level can be reduced by the simultaneous administration of barbiturate. Presumably methyl dopa metabolism is accelerated by barbiturate. Buhs *et al.* (1964) showed that in man about half of ingested methyl dopa is absorbed and that 50-90% of the amount absorbed is excreted within 48 hours. Of the metabolites methyl dopa-mono-O-sulphate is found in largest quantities, and most probably the site of this phase of breakdown is the liver. Smaller amounts of 3-O-methyl-alphamethyl dopa are demonstrable in the urine, and also alphamethyl dopamine in the so-called neutral fraction, which is actually the first stage of methyl dopa metabolism in man.

Since at least part of methyl dopa metabolism takes place

in the liver and the effect of barbiturates on the microsomal enzymes of the liver has been proved, we suggest that methyl dopa metabolism may be accelerated by barbiturates through enzyme induction. This phenomenon may have practical implications in the treatment of hypertensive patients.

References

- Buhs, R. P., *et al.* (1964). *Journal of Pharmacology and Experimental Therapeutics*, **143**, 205.
 Conney, A. H. (1967). *Pharmacological Reviews*, **19**, 317.
 Cucinell, S. A., Conney, A. H., Sansur, M., and Burns, J. J. (1965). *Clinical Pharmacology and Therapeutics*, **6**, 420.
 Dollery, C. T., and Harington, M. (1962). *Lancet*, **1**, 760.
 Gifford, R. W., and Tweed, D. C. (1962). *Journal of the American Medical Association*, **182**, 493.
 Hingerty, D. (1957). *Lancet*, **1**, 766.
 Sjoerdsma, A. (1960). *Annals of the New York Academy of Sciences*, **88**, 933.
 Sourkes, T. L. (1954). *Archives of Biochemistry and Biophysics*, **51**, 444.

MEDICAL MEMORANDA

Strychnine Poisoning Treated Successfully with Diazepam

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We report the use of diazepam in the emergency management of strychnine poisoning.

Case History

A West Indian child aged 13 months was found playing with white tablets and had one in his mouth. Fifteen minutes later he screamed loudly and became rigid. He remained rigid with intermittent crying until in the ambulance on the way to hospital, when he had a convulsion and a respiratory arrest. He was given mouth-to-mouth resuscitation and external cardiac massage. In the casualty department he continued to have fits repetitively and had five brief respiratory arrests within a short space of time. His airway was maintained and oxygen was given. During these convulsions he remained conscious and had facial grimacing with opisthotonos. At this time the nature of the tablets was unknown.

Diazepam 2.5 mg given subcutaneously did not produce relaxation, but 2.5 mg intravenously, given in the course of an episode of severe muscle spasm complicated by respiratory arrest, produced immediate relaxation. His reflexes were still exaggerated and occasional extensor thrusts were evoked by minimal stimuli. By this time the tablets were morphologically identified as Easton's syrup (later confirmed by chromatography). Endotracheal intubation was carried out after the intravenous administration of suxamethonium and he was maintained with 100% oxygen and intermittent positive-pressure respiration. Gastric lavage was performed with sodium bicarbonate solution 45 minutes after ingestion of Easton's syrup tablets. An intramuscular injection of desferrioxamine mesylate was given because of the iron content of the tablets.

The child continued to be hyperreflexic but was breathing spontaneously, and intermittent positive-pressure respiration was discontinued. No more convulsions occurred, and six hours later the endotracheal tube was removed. He had a residual croup which was treated with ampicillin and he was discharged after seven days. Follow-up two months later showed no obvious neurological sequelae.

Comment

Easton's syrup tablets have long been regarded as "tonics." They are available in two strengths (*Martindale's Extra Pharmacopoeia*, 1967). Formula A contains iron phosphate 200 mg, quinine sulphate 50 mg, and strychnine hydrochloride 1 mg, while formula B is half this strength. Formula A is the widely used tablet and is dispensed in a sugar-coated form which is particularly attractive to children (Southby, 1965).

Strychnine produces excitation of all portions of the central nervous system by increasing the level of neuronal excitability as a direct result of selectively blocking inhibition (Goodman and Gilman, 1970). Nerve impulses are therefore enhanced. The convulsions occurring as a result of this decreased inhibition are characterized by tonic extension of the body and all limbs in a symmetrical fashion. These intermittent thrusts are initiated by any sensory stimulus, usually when the strychnine concentration is lower than that required for a sustained tonic convulsion. Further toxic effects involve contractions of the diaphragmatic, thoracic, and abdominal muscles, leading to respiratory arrest. The ensuing hypoxaemia finally results in the terminal medullary paralysis (Thienes and Haley, 1964).

Tolerance to strychnine is variable. As little as 2 mg has proved to be unpleasant and 15 mg has caused death. Nevertheless, recovery has been reported with an intake of 1 g and over (Thienes and Haley, 1964). Based on the mother's memory, we believe the intake in this case to be between 10 and 20 tablets, equivalent to between 10 and 20 mg of strychnine.

The standard management has long rested on the prevention of convulsions and support of respiration by relying on depressants of the central nervous system which sufficiently antagonize strychnine to allow respiration to continue (Thienes and Haley, 1964; Goodman and Gilman, 1970). The use of intravenous barbiturates and endotracheal intubation with intermittent positive-pressure respiration has been found to be effective (Statham, 1956; Hawkins, 1962).

The role of diazepam as an anticonvulsant has been reviewed by Brett (1970). We could find only one previous record of its use in strychnine poisoning (Heidrich and Ibe, 1969). Diazepam has an inhibitory effect on polysynaptic reflexes in the spinal

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