J. Pharm. Pharmacol., 1965, **17**, *Suppl.*, 115S–117S Received May 6, 1965

SHORT COMMUNICATION

The urinary excretion of aminoglutethimide in man

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AMINOGLUTETHIMIDE (Elipten, α-ethyl-α-*p*-aminophenylglutarimide) is used clinically as an anticonvulsant drug and it is therefore of interest to determine its metabolic fate in man. It is chemically related to the hypnotic drug glutethimide (α-ethyl-α-phenylglutarimide) which is extensively metabolised *in vivo* (Kebrle, Schmid, Hoffmann, Vuilleumier & Bernhard, 1959).

EXPERIMENTAL

Aminoglutethimide forms a coloured Schiff's base with *p*-dimethylaminobenzaldehyde (Ehrlich's reagent) and this reaction has been utilised in estimating the glutarimide in solution. Various amounts of aminoglutethimide in absolute ethanol (9 ml) were treated with Ehrlich's reagent, 1 ml (Werner, 1939), and the intensity of the yellow colour formed was measured at 440 mμ, this wavelength being the absorption maximum of the Schiff's base formed between aminoglutethimide and the reagent. A linear relationship between colour intensity and concentration of drug was obtained for the range 0–15 μg aminoglutethimide per ml of the final solution.

To devise a method for extracting aminoglutethimide from urine, the partition of the drug between aqueous and organic phases was investigated. This was done by shaking equal volumes of various organic solvents with an equal volume of distilled water containing aminoglutethimide (50 μg/ml) for 30 min at room temperature. The two phases were each saturated with the opposite phase before their use in partition experiments. Aliquots of the organic layers were evaporated to dryness and the residues of aminoglutethimide were determined by the procedure described above. Dichloromethane extracted the aminoglutethimide almost completely. The partition was pH dependent and when the aqueous solution had pH 6 was entirely in favour of the dichloromethane.

pH of aqueous phase	2·2	3·05	3·95	5·1	6·1	7·4	8·9	13·1
% of aminoglutethimide remaining in dichloromethane (mean of 4 values)	4·2	37·1	72·1	98	99·8	99·2	98·8	8·7

For the estimation of aminoglutethimide in human urine, samples were adjusted to pH 7 and shaken (30 min) with 50 ml and then with 25 ml dichloromethane. The combined organic layers were dried (30 min) over

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anhydrous sodium sulphate (20 g). The desiccant was filtered off and washed twice with dichloromethane (50 ml). Combined washings and extract were evaporated to dryness and the residue dissolved in absolute ethanol (5 ml). Suitable aliquots of this solution were diluted to 9 ml with ethanol and assayed for aminoglutethimide as previously described. As a control, a 50 ml sample of urine containing no aminoglutethimide was treated in an identical manner. At the dilutions employed in the assay itself, this produced no measurable colour with Ehrlich's reagent. The recovery of aminoglutethimide added to urine at the levels of 2 and 4 mg/50 ml was 86% (s.d. 1·6%).

TABLE 1. CHROMATOGRAPHY OF EXTRACTS OF URINE FROM MEN DOSED WITH AMINOGLUTETHIMIDE (250 mg ORALLY)

Solvent system	Rf value		
	Extract of test Urine	Aminoglutethimide	Urea
n-Butanol : acetic acid : water 12 : 3 : 5 v/v	0·44 0·72	0·73	0·44
Chloroform : methanol .. .. 1 : 1 v/v	0·29 0·93	0·93	0·29
Carbon tetrachloride : acetic acid : water (lower layer) .. .. 1 : 2 : 1 v/v	0·06 0·34	0·34	0·06
Aqueous sodium chloride 10% w/v	0·60 0·74	0·74	0·59

Chromatograms run on Whatman No. 1 paper by the ascending technique. Compounds detected with *p-NN*-dimethylaminocinnamaldehyde.

Finely powdered aminoglutethimide (250 mg and 500 mg) was administered orally to two healthy men on three separate occasions. All urine passed 24 hr before and 24 and 48 hr after administration of the drug was collected. Aliquots (50 ml) of the urine were adjusted to pH 7, extracted

TABLE 2. REACTION OF CHROMATOGRAMS OF EXTRACTS OF URINE FROM MEN DOSED WITH AMINOGLUTETHIMIDE (250 mg ORALLY) TO VARIOUS PROCEDURES

Procedure	Reaction		
	Extract of test urine	Aminoglutethimide	Urea
Ultraviolet light (350 mμ) ..	Rf 0·72 absorbs	absorbs	not detected
Ehrlich's reagent	Rf 0·44 yellow colour Rf 0·72 yellow colour	yellow colour	yellow colour
Nitrous acid-(naphthyl)ethylene-diamine (Bridges & Williams, 1963)	Rf 0·72 purple colour	purple colour	not detected
p-NN-dimethylaminocinnamal-dehyde HCl (Bridges & Williams, 1963)	Rf 0·72 permanent red colour Rf 0·44 red colour turning to yellow	Permanent red colour	red colour fading to yellow
Sodium hypochlorite-potassium iodide-starch (Jackson & Moss, 1960)	Rf 0·44 Blue black colour Rf 0·72 blue black colour	blue black colour	blue black colour

All reagents were applied to the paper chromatograms as sprays. Solvent system was n-butanol : acetic acid : water 12 : 3 : 5 v/v.

and assayed for aminoglutethimide as described previously. Chromatography of the urine extracts on Whatman No. 1 paper showed the presence of two Ehrlich-positive spots, one of which was urea. The other spot had the same mobility as aminoglutethimide in several solvent systems (Table 1) and gave similar colour reactions with various reagents (Table 2). This spot could not be demonstrated in extracts of control urine. All Ehrlich-positive material in the extracts was therefore estimated in terms of aminoglutethimide.

TABLE 3. URINARY EXCRETION OF AMINOGLUTETHIMIDE* AFTER ORAL ADMINISTRATION TO TWO MEN

Dose administered (mg)	Day	mg Aminoglutethimide excreted in urine in 24 hr	
		Subject A†	Subject B†
250	1	87·7	85·4
	2	33·7	12·4
250	1	74·8	84·7
	2	15·1	—
500	1	221·9	222·5
	2	32·7	59·9

* As Ehrlich-positive material estimated in dichloromethane extracts of urine.
Results corrected for 100% extraction. †Means of 3 determinations on each sample.

The results (Table 3) show that most of the aminoglutethimide excretion occurred in the first 24 hr. The average total excretion after 48 hr represents 39% of the 250 mg dose and 54% of the 500 mg dose.

This evidence suggests that after an oral dose of 250 or 500 mg of aminoglutethimide, the drug is absorbed and excreted unchanged to a considerable extent in the urine. The metabolic fate of α-ethyl-α-*p*-aminophenylglutarimide thus appears to differ significantly from that of α-ethyl-α-phenylglutarimide.

Acknowledgement. Grateful acknowledgement is made for a generous gift of aminoglutethimide from Ciba Laboratories, Horsham, Sussex.

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