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STUDIES ON THE ABSORPTION AND EXCRETION OF [^{14}C]-BETHANIDINE IN MAN

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Bethanidine is a hypotensive drug with a chemical structure and pharmacological properties allied to guanethidine. It produces postganglionic sympathetic adrenergic blockade by preventing the release of noradrenaline (Boura & Green, 1963). Boura, Duncombe, Robson & McCoubrey (1962) studied the metabolism of the drug in the cat. They found that it was well absorbed and was excreted unchanged in the urine. When the concentrations of the drug in different tissues were measured, adrenergic nerves and ganglia showed the highest level and it was suggested that the antiadrenergic activity was related to a selective affinity for these tissues.

Two clinical trials using bethanidine have been reported (Montuschi & Pickens, 1962; Smirk, 1963). These workers showed the drug to have a powerful hypotensive action. It was more rapid in action than guanethidine and its effect usually lasted less than 12 hr. Diarrhoea was very unusual. Some tolerance occurred frequently, but was easily managed.

This paper reports the results of studies of the absorption and excretion of bethanidine in man. We were particularly interested in the importance of abnormal renal function since many hypertensive patients have some degree of renal functional impairment. Our results also clarified the mechanism of certain clinical properties of the drug.

METHODS

The subjects studied were in hospital and some had normal renal function while others had various renal disorders with impairment of renal function which varied clinically from mild to severe. None was receiving hypotensive drugs, although most had mild hypertension. In all, the endogenous creatinine clearance was estimated, using the method of King & Wootton (1956) for determination of serum and urinary creatinine levels.

The urinary excretion of bethanidine was studied by the use of bethanidine labelled with ^{14}C at the benzyl carbon atom. The dose given was 500 μg, either orally or by intravenous injection. Urine was collected at fixed intervals after the drug had been given. The amount of drug excreted in the urine was determined by counting the radioactivity of 0.5 ml. of urine in a Packard Tri-Carb liquid scintillation counter, using PPO and dimethyl POPOP in spectral quality dioxane (Merck). A correction was made for quenching by adding 0.1 μg of [^{14}C]-bethanidine to another 0.5-ml. aliquot of each urine sample and measuring the increment of count rate. By this method the accuracy of measurement is probably about $\pm 10\%$.

RESULTS

The total amount of bethanidine excreted in the 24 hr after an oral dose was measured in thirty-three subjects. The relationship between the amount excreted by each subject

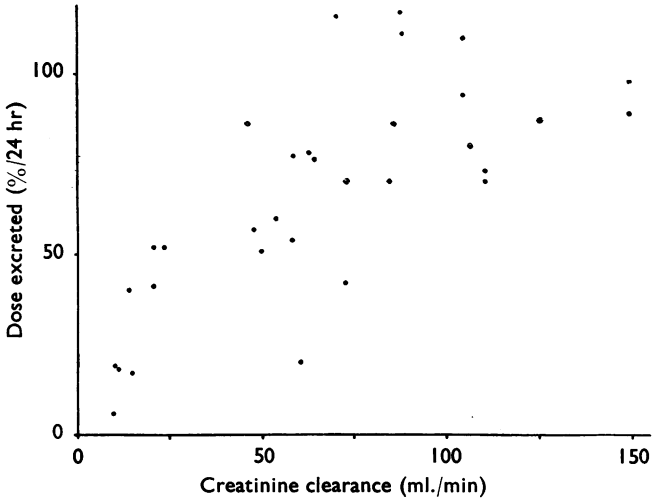

Fig. 1. The relationship between the creatinine clearance and the percentage of an oral dose of [^{14}C]-bethanidine excreted in 24 hr in thirty-three subjects.

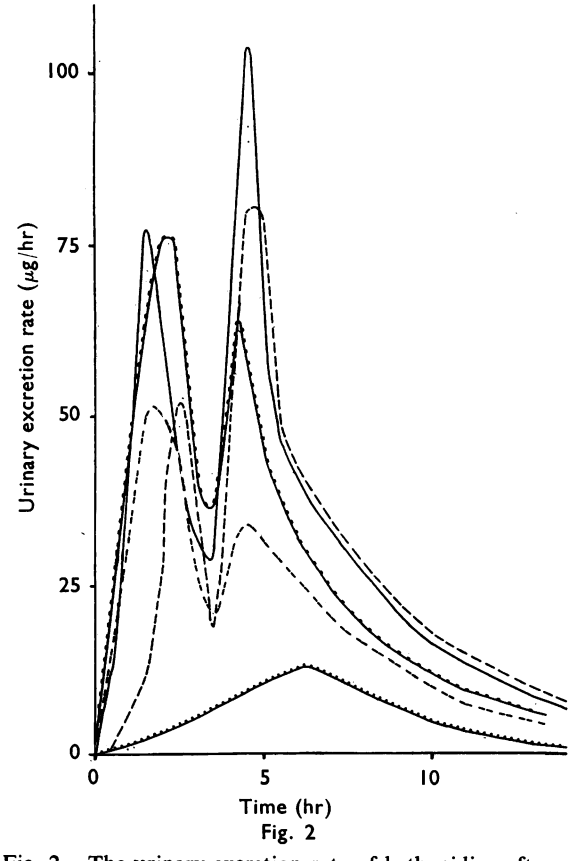

Fig. 2

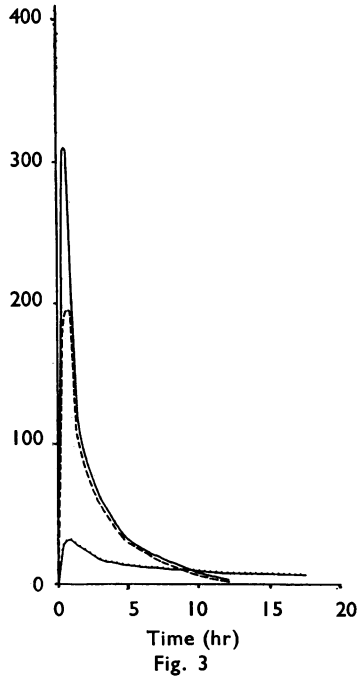

Fig. 3

Fig. 2. The urinary excretion rate of bethanidine after an oral dose in four " normal " patients (upper four lines) and one patient with renal failure (lowest line).

Fig. 3. The urinary excretion rate of bethanidine after an intravenous dose in two " normal " patients (upper two lines) and one patient with renal failure (lowest line).

and the creatinine clearance is shown in Fig. 1. There is a highly significant correlation between the proportion of the dose excreted and the creatinine clearance ($r=0.7$, $P<0.0001$). In patients with a normal creatinine clearance, virtually all of the administered dose was excreted within 24 hr, but as the creatinine clearance declined the amount of the drug appearing in the urine decreased proportionately.

The time course of excretion of bethanidine after an oral dose was studied in five subjects by measuring the amount appearing in the urine every 30 min (Fig. 2). Four of the subjects had endogenous creatinine clearances greater than 100 ml./min; their excretory rates rose rapidly to reach a peak at 1.5 to 2.5 hr after administration, fell temporarily, and then again rose to reach another peak at 4 to 5 hr. Following the second peak the excretory rates declined rapidly and exponentially, reaching a low level by the end of 12 hr. The fifth subject had severe renal disease with a creatinine clearance of 20 ml./min; his excretory rate remained low throughout and never reached a very high level.

The time course of excretion following an intravenous dose of [^{14}C]-bethanidine was studied in three subjects (Fig. 3). Two had good renal function; their excretory rates rose rapidly to a maximum which was much higher than that after oral administration. The rates then fell rapidly and exponentially and in both cases the " half-life " was between 2 and 2.5 hr. By the end of 12 hr the rate of excretion had become very low and by the end of 24 hr all of the administered dose had been excreted. The third subject had severely impaired renal function. The excretory rate reached a much smaller maximum and then fell exponentially. The fall was slower than in the subjects with normal renal function, and had a " half-life " of 8 to 10 hr. By the end of 24 hr only 54% of the administered dose had appeared in the urine. The low excretory rate in this subject was not due to a raised renal threshold for, when two oral priming doses of 10 mg of unlabelled bethanidine were given and were followed by a further intravenous dose of labelled drug, the excretory rate and the total amount excreted in 24 hr remained unchanged.

DISCUSSION

Our results in patients with normal renal function show that nearly all of an oral dose of bethanidine is excreted in the urine. Absorption must be almost complete for this to occur. The rate of absorption must also be rapid, for the early peak of urinary excretion occurs 1.5 to 2.5 hr after administration.

In these subjects two peaks were constantly seen during excretion after an oral dose, but only one peak occurred after intravenous administration. Following the second peak of an oral dose or the single peak of an intravenous dose, the excretory rate declined rapidly and exponentially. In the two subjects who received an intravenous dose, all of the drug appeared in the urine. Evidently renal excretion was virtually the only mechanism by which the drug was cleared from the plasma and the exponential decline in the excretory rate was no doubt therefore due to a similar exponential decline in the plasma bethanidine level (the half-time being 2 to 2.5 hr). In the patients given an oral dose of bethanidine we were thus able to infer the fluctuations in the plasma level from the time course of the excretory rate.

Our results show that there is an approximately linear relationship between the creatinine clearance and the amount of bethanidine excreted in the urine within 24 hr. The excretory

rate in the subject with renal failure given an intravenous dose of bethanidine was much lower than normal and declined more slowly with a " half-life " of 8 to 10 hr. The rate of decline of the excretory rate, although slow, was still too rapid to be accounted for by the amount of bethanidine that appeared in the urine. We concluded that an extra-renal as well as a renal mechanism might have become important in clearing bethanidine from the plasma. In normal subjects, urinary excretion is presumably too rapid for this mechanism to be quantitatively important.

The results that we have obtained clarify certain properties of the drug observed clinically. Munro-Faure (quoted by Montuschi & Pickens, 1962, and Smirk, 1963) observed that the hypotensive effect began 1 to 2 hr after oral administration, was maximal 4 to 5 hr after, and persisted for about 12 hr. These observations agree well with our measurements of the excretory rate (and hence plasma level) of bethanidine, and suggest that the hypotensive effect is directly proportional to the plasma level. It seems likely that, following intravenous administration of bethanidine, the hypotensive effect would come on rapidly, be maximal 0.5 to 1.5 hr after administration, and would last 6 to 8 hr.

Montuschi & Pickens (1962) observed a prolonged effect of bethanidine when the blood urea was high. We consider that this is likely to be due to impaired renal excretion which may well result in higher and more sustained plasma bethanidine levels.

SUMMARY

1. The urinary excretion of [^{14}C]-bethanidine has been studied in man.

2. In subjects with normal renal function almost all of the administered dose appears in the urine whether the drug is given orally or intravenously.

3. In patients with diminished renal function, the excretion of the drug is much slower and appears to be incomplete.

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