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Serum concentrations and urinary excretion of pinacidil and its major metabolite, pinacidil pyridine-*N*-oxide following i.v. and oral administration in healthy volunteers

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Serum concentrations of pinacidil and its major metabolite pinacidil pyridine-*N*-oxide were determined following administration of both an intravenous solution and a sustained release oral preparation to healthy volunteers. Mean bioavailability of pinacidil was 57.1 ± 13.7%. Following intravenous administration, the mean $AUC_{0-8\ h}$ metabolite/$AUC_{0-8\ h}$ pinacidil ratio was 0.559 ± 0.272 and after oral administration, 0.825 ± 0.656. Only one subject had serum metabolite concentrations in excess of pinacidil during the intravenous study whereas three subjects achieved metabolite concentrations in excess of pinacidil during the oral study. The mean serum elimination half-life of metabolite was significantly longer than parent drug following intravenous administration ($P < 0.01$) but not after oral administration. No significant difference was found in the maximum measured metabolite concentration (C_{max}.m) between the studies. The time to C_{max}.m was significantly delayed ($P < 0.001$) following oral dosage. Twenty four hour urinary excretion of metabolite was significantly increased ($P < 0.001$) following oral administration whilst that of pinacidil was decreased ($P < 0.02$). These results suggest that pinacidil pyridine-*N*-oxide may be a 'first-pass' metabolite of pinacidil. In most patients pinacidil pyridine-*N*-oxide is unlikely to contribute significantly to the hypotensive effect of pinacidil.

Keywords pinacidil pinacidil pyridine-*N*-oxide metabolite

Introduction

Pinacidil ((±)-2-cyano-1-(4-pyridyl)-3-(1,2,2-trimethylpropyl)guanidine) is a novel hypotensive compound with a vasodilator mode of action (Petersen *et al.*, 1978; Arrigoni-Martelli *et al.*, 1980; Thoolen *et al.*, 1984). The pharmacokinetics and pharmacodynamics of the drug have been reported in both healthy volunteers and hypertensive subjects (Eilertsen *et al.*, 1982a; Carlsen *et al.*, 1981; Muiesan *et al.*, 1983; Ward *et al.*, 1984). The metabolism of pinacidil has been examined in the rat and dog and preliminary data have been reported following oral dosage in man (Eilertsen *et al.*, 1982b). The principal metabolite is pinacidil pyridine-*N*-oxide. ((±)-2-cyano-1-(4-pyridyl)-3-(1,2,2-trimethylpropyl)guanidine-*N*-oxide). This metabolite has been found to possess almost 25% of the pharmacological activity of the parent compound in rat and dog (Eilertsen *et al.*, 1982b). The present work was undertaken in order to determine serum and urine metabolite concentrations following intravenous and oral administration of pinacidil in healthy volunteers, and to assess the potential contribution of the metabolite to the hypotensive effect of pinacidil.

Methods

A total of 17 healthy volunteers aged 21–41 years participated in the study, which was approved by the Leicester Ethical Committee. All received 0.2 mg/kg body weight pinacidil as a single dose. Eight subjects received the drug both intravenously and orally as a sustained release capsule on two occasions separated by at least 1 week. Six further subjects received the drug intravenously and three received the drug orally. Blood samples were drawn at intervals up to 8 h and the serum stored at −20°C prior to analysis for pinacidil and pinacidil pyridine-*N*-oxide. Urine was collected for 24 h at timed intervals and measured aliquots stored at −20°C without preservative prior to analysis.

H.p.l.c. analyses of serum and urine concentrations of pinacidil and pinacidil pyridine-*N*-oxide were performed as previously described (Ward *et al.*, 1984).

The area under the serum concentration-time curve ($AUC_{0-8\ h}$) was determined using the trapezoidal rule and the serum elimination half-life ($t_{½,z}$) was determined by least squares linear regression analysis of the terminal portion of the decay curve.

Bioavailability was calculated using the expression; $AUC_{0-8\ h}$ oral × $100/AUC_{0-8\ h}$ i.v. Statistical analysis utilised the paired and two sample *t*-tests.

Results

Mean serum concentration-time profiles of pinacidil and pinacidil pyridine-*N*-oxide are shown for both routes of administration in Figure 1. Although the mean plots indicate that serum metabolite concentrations never exceed those of pinacidil, in the intravenous study one subject had an $AUC_{0-8\ h}$ metabolite/$AUC_{0-8\ h}$ pinacidil ratio greater than 1.0 and following oral administration, three subjects had a ratio greater than 1.0. Mean values for the metabolite/pinacidil ratio were 0.559 ± 0.272 and 0.825 ± 0.656 for the intravenous and oral studies respectively. Statistical analysis of the data by the paired *t*-test revealed a significant increase in the metabolite/pinacidil ratio following oral administration ($P < 0.05$). However, the two sample *t*-test, which utilised data from all 17 subjects, did not reveal a significant difference between the routes of administration.

The maximum measured metabolite concentration, (C_{max}m) and the metabolite serum elimination half-life, ($t_{½,z}$) did not differ significantly between the routes of administration. Mean values ± s.d. were as follows; C_{max}m i.v. = 52.4 ± 18.4 ng/ml; C_{max}m oral = 40.6 ± 14.2 ng/ml; $t_{½,z}$ i.v. = 3.33 ± 0.99 h; $t_{½,z}$ oral = 3.96 ± 1.79 h. The mean metabolite elimination half-life was significantly longer than pinacidil following intravenous administration ($P <$ 0.01) but not after oral administration ($P >$

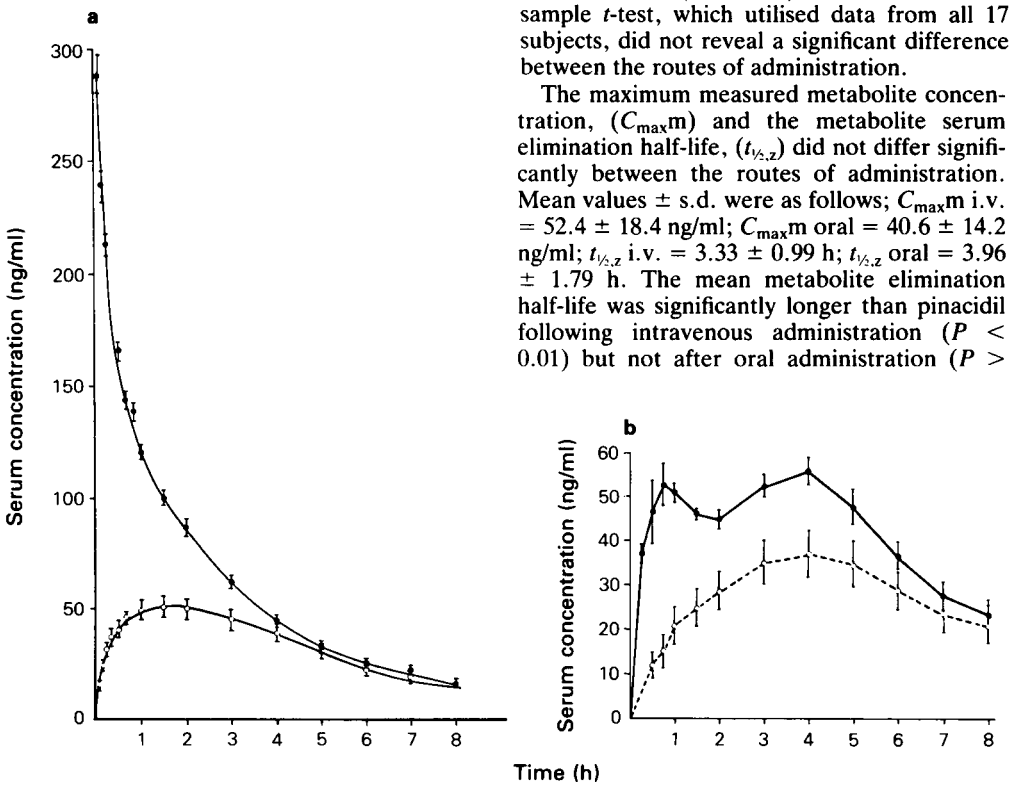

Figure 1 Serum concentration *vs* time profiles for pinacidil (•) and pinacidil pyridine-*N*-oxide (○) following (a) intravenous and (b) oral administration of pinacidil 0.2 mg/kg body weight. Values are the mean ± s.e. mean of duplicate estimations in (a) 14 subjects and (b) 11 subjects.

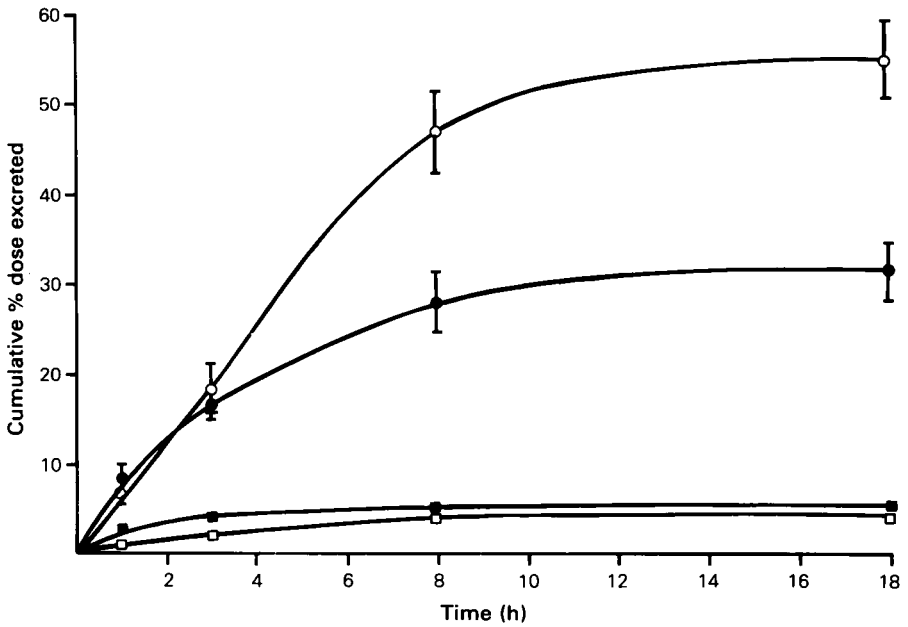

Figure 2 Cumulative urinary excretion of pinacidil (□) and pinacidil pyridine-*N*-oxide (○) following intravenous (closed symbols) and oral (open symbols) administration of pinacidil 0.2 mg/kg body weight in healthy volunteers.

0.05). The times to C_{max}m were 1.5 ± 0.6 h for the intravenous study and 4.0 ± 0.7 h for the oral study ($P < 0.001$).

The mean bioavailability of pinacidil, determined in eight subjects who received the drug by both routes of administration, was 57.1 ± 13.7%.

Cumulative urinary excretion of pinacidil and pinacidil pyridine-*N*-oxide, expressed as a percentage of the administered dose, is shown in Figure 2. Metabolite excretion was almost double during the 24 h following oral administration whereas pinacidil excretion decreased. Mean values were as follows: i.v. metabolite excretion = 31.6 ± 9.2%; Oral metabolite excretion = 54.8 ± 13.9% ($P < 0.001$); i.v. pinacidil excretion = 5.7 ± 1.3%; oral pinacidil excretion = 4.3 ± 1.0% ($P < 0.02$).

Discussion

Initial work on the metabolism of pinacidil in rat, dog and man following oral dosage has indicated that the major metabolite is pinacidil pyridine-*N*-oxide. Although three further metabolites were detected their concentrations in urine were insignificant and they were not identified (Eilertsen *et al.*, 1982b). Our findings in eleven healthy volunteers agree with these preliminary results regarding the percentage of an oral dose excreted as pinacidil pyridine-*N*-oxide but reveal that the urinary metabolite excretion is significantly lower following intravenous drug administration whilst pinacidil excretion is higher. The serum AUC metabolite/pinacidil ratios were equivocal in that data from eight subjects who received drug by both routes showed a significantly increased ratio after oral administration. However, the pooled results in all 17 subjects did not reach significance, perhaps as a consequence of interindividual variability in drug metabolism which is more evident following oral administration. Thus the range for the serum AUC metabolite/pinacidil ratio was 0.251–1.345 for intravenous administration but 0.274–2.541 for oral administration.

Our work suggests that orally administered pinacidil is susceptible to a 'first pass effect' and as the drug is thought to be completely absorbed (Eilertsen *et al.*, 1982a), it is possible that this is the reason for the low bioavailability reported for oral formulations (Farrow *et al.*, 1984).

Our results also indicate that, for most subjects, the rate limiting step in the elimination of metabolite is the rate of formation. This conclusion is supported by the finding that the amount of parent drug generally exceeds that of the metabolite but is apparently contradicted by the fact that the mean metabolite serum elimination half-life was significantly longer than pinacidil following intravenous administration

of drug. Theoretically, if the rate limiting step is the formation of metabolite then the serum elimination half-lives of metabolite and parent drug should not be significantly different. The observed difference in the intravenous study may result from inaccuracies in determining the metabolite elimination half-life over a limited time period. For the oral study, although there was no overall significant difference in elimination half-lives and the mean serum AUC metabolite/pinacidil ratio was less than 1.0, three subjects had ratios greater than 1.0 and their metabolite elimination half-lives were more than double pinacidil elimination half-lives. These findings suggest that in these three subjects, elimination of metabolite was the rate limiting step.

It has been demonstrated that the hypotensive effect of pinacidil is closely correlated to its serum concentration (Ward *et al.*, 1984) and if the metabolite is pharmacologically active in man to the same extent as in rat and dog (almost 25% of parent drug activity) then this work has shown that pinacidil pyridine-*N*-oxide is unlikely to contribute much to the hypotensive effect of pinacidil in the majority of subjects. However, as almost one third of the subjects had metabolite concentrations in excess of pinacidil following oral dosage, further work must be undertaken to identify the factors causing enhanced metabolism and reduced elimination of pinacidil and pinacidil pyridine-*N*-oxide.

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