& Prichard, 1967; Hunter, Boakes, Laurence & Stern, 1970). There is evidence that the pressor effect of noradrenaline is not potentiated in these subjects (Horwitz, Goldberg & Sjoerdsma, 1960; Elis, Laurence, Mattie & Prichard, 1967). Svedmyr showed that protriptyline (a tricyclic antidepressive agent) potentiated the pressor effect of noradrenaline and, to a lesser extent, that of adrenaline (Svedmyr, 1968).

In the present study four healthy volunteers (age range: 30–48 years) received infusions of adrenaline, noradrenaline, phenylephrine and isoprenaline before and after a tricyclic antidepressive agent (imipramine). Two of them also received infusions before and after an hydrazine monoamine oxidase inhibitor (phenelzine). Infusions were given for periods of 5 min at each concentration (steady state usually occurring after 3 min), the concentrations being increased in a logarithmic fashion.

Infusions in subjects taking the tricyclic antidepressive agent (imipramine) revealed potentiation of the pressor effects of noradrenaline (4–8 times), adrenaline (up to 2 times) and phenylephrine (up to 3 times). Further investigations in which the subjects were fully atropinized (Chamberlain, Turner & Sneddon, 1967), indicate that these pressor effects are not solely due to the atropine-like action of imipramine.

Infusions in subjects taking the monoamine oxidase inhibitor (phenelzine), revealed potentiation of the pressor action of phenylephrine (2 times), but no potentiation of the pressor effect of noradrenaline or adrenaline. There was no potentiation of the tachycardia produced by isoprenaline.

Similar studies are in progress in two subjects taking the non-hydrazine monoamine oxidase inhibitor, tranylcypromine.

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REFERENCES

CHAMBERLAIN, D. A., TURNER, P. & SNEDDON, J. M. (1967). Effects of atropine on heart-rate in healthy man. *Lancet*, **2**, 12–15.

ELIS, J., LAURENCE, D. R., MATTIE, H. & PRICHARD, B. N. C. (1967). Modification by monoamine oxidase inhibitors of the effect of some sympathomimetics on the blood pressure. *Br. med. J.*, **2**, 75–78.

HORWITZ, D., GOLDBERG, L. I. & SJOERDSMA, A. (1960). Increased blood pressure responses to dopamine and norepinephrine produced by monoamine oxidase inhibitors in man. *J. Lab. clin. Med.*, **56**, 747–753.

HUNTER, K. R., BOAKES, A. J., LAURENCE, D. R. & STERN, G. M. (1970). Monoamine oxidase inhibitors and L-dopa. *Br. med. J.*, **3**, 388.

SVEDMYR, N. (1968). The influence of a tricyclic antidepressive agent (protriptyline) on some of the circulatory effects of noradrenaline and adrenaline in man. *Life Sci.*, **7**, 77–84.

Absorption, distribution and elimination of ^{14}C-amiloride in normal human subjects

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The potassium-retaining, pyrazine-carboxamide diuretic, amiloride, labelled with ^{14}C in the guanidine side chain (specific activity 0·5 μCi/mg) has been given in doses of 20 mg orally on two occasions to each of six, normal fasting subjects. Amiloride is not protein bound or metabolized in man and ^{14}C counts reflect drug concentration in body fluids.

Despite the use of two different tablet formulations, plasma and urinary concentrations of amiloride were comparable for each individual. Peak mean plasma concentrations (47·5 ng/ml$\pm$13·8 S.D.) were achieved at 4 h and detectable plasma activity per-

sisted at 48 h in only two experiments. Urinary amiloride increased rapidly in the first 4 h and achieved a cumulative mean of 49·8 %(±10·6 S.D.) of the oral dose in 72 hours. Mean overall recovery of drug in 72 h amounted to 87·9 %(±14·1 S.D.) of the administered dose. In six of the twelve experiments over 95% was recovered.

^{14}C-amiloride was cleared at a rate exceeding creatining clearance when mean plasma concentrations exceeded 30 ng/ml. The remainder of the ^{14}C label was found in the faeces. This corresponds to the duration of significant diuretic activity. The calculated volume of distribution of amiloride is approximately 250% of body volume (*c.f.* a similar distribution in the nephrectomized dog: Baer, Jones, Spitzer & Russo, 1967). The natriuretic response to amiloride is related to both plasma and urinary drug concentrations and the reduction in urinary potassium excretion is sufficient to account for the elevation in plasma potassium concentrations seen after amiloride. Mean increases in plasma potassium correlate with plasma drug concentrations (r=0·64).

Calculations based on these observations indicate that amiloride probably achieves a concentration (approximately 2×10^{-5} M) at its presumed site of action in the distal renal tubule comparable to that which reduces sodium transport in isolated tissues (Salako & Smith, 1970).

The drug concentrations found in our normal subjects are similar to those of the only other comparable study (Weiss, Hersey, Dujovne & Bianchine, 1969) and provide a basis for comparison with the pharmacokinetics of amiloride used therapeutically.

REFERENCES

BAER, J. E., JONES, C. B., SPITZER, S. A. & RUSSO, H. F. (1967). The potassium sparing and natriuretic activity of N-amidino-3,5-diamino-6-chlorpyrazinecarboxamide hydrochloride dihydrate (amiloride hydrochloride). *J. Pharmac. exp. Ther.*, **157**, 472–485.

SALAKO, L. A. & SMITH, A. J. (1970). Effects of amiloride on active sodium transport by the isolated frog skin; evidence concerning site of action. *Br. J. Pharmac.*, **38**, 702–718.

WEISS, P., HERSEY, R. M., DUJOVNE, C. A. & BIANCHINE, J. R. (1969). The metabolism of amiloride hydrochloride in man. *Clin. Pharmac. Ther.*, **10**, 401–406.