acebutolol, namely 1-(4-acetamido-2-acetylphenoxy)-2-hydroxy-3-isopropylaminopropane (George & Collins, personal communication).

The mean (± s.d.) plasma levels of the two groups are given in Figure 1. As can be seen from the large standard deviations, absorption of the drug showed large intersubject variation especially in the patients, and the plasma level of acebutolol as measured disappeared more rapidly in the healthy volunteers. Using the data from 4 h and onwards the elimination half-life of acebutolol from the mean data of the healthy volunteers was calculated to be 3.1 h, whilst that of the patients was 12.0 hours. In the case of practolol reduced renal function has a much greater influence on the elimination of the drug (Kaye, Kumana, Franklin & Baker, 1975). The mean 24 h urinary recovery (expressed as a % of the dose) of acebutolol for the group of healthy subjects was 31.9%, whilst that for the patients was 1.8%.

These results suggest that the rate of elimination of acebutolol in patients with severe chronic renal failure is decreased from normal, and therefore such patients may require reduced dosage of the drug. The small amount of acebutolol recovered from the patients' urine suggests that compared to normals these subjects have a greater degree of non-renal elimination of acebutolol.

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PRAZOSIN IN NORMAL SUBJECTS: PLASMA LEVELS, BLOOD PRESSURE AND HEART RATE

Prazosin is a new antihypertensive agent with peripheral vasodilating properties. Pharmacological studies have indicated that in dogs, prazosin acts by a combination of interference with α-adrenoceptor function and a direct relaxant effect on vascular smooth muscle (Constantine, McShane, Scriabine & Hess, 1973); in rats the α-adrenoceptor blocking action has been demonstrated but not the direct vasodilatation (Wood, Phelan & Simpson, 1975). In rats and dogs prazosin is extensively metabolized in the liver and undergoes a significant 'first pass effect' (Pfizer, unpublished observations); metabolites are predominantly excreted in the bile and eliminated with the faeces, the plasma half-life of the parent drug being 1-2 h in both species (Pfizer, unpublished observations). Clinical experience has shown that prazosin is an effective antihypertensive agent, particularly in combination with other antihypertensive drugs, especially β-adrenoceptor blocking drugs (Cohen, 1970; Kincaid-Smith, Fang & Laver, 1973; Stokes &

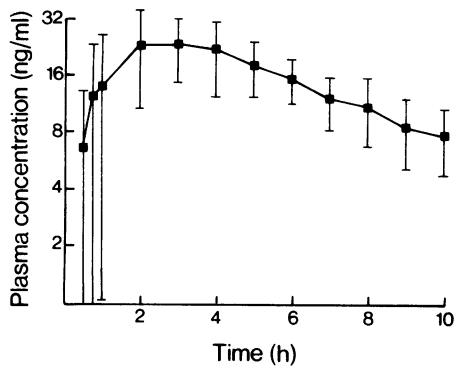

Figure 1 Mean plasma prazosin concentrations, (± s.d.) in ten normal subjects following a single tablet of prazosin (5 mg).

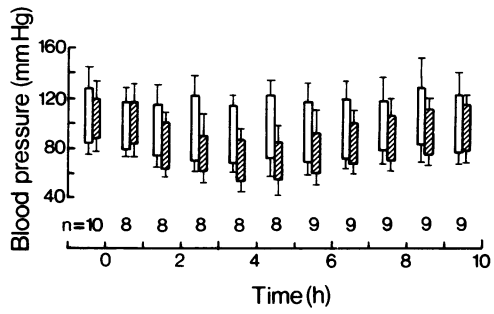

Figure 2 Blood pressures (□ lying; ■ standing) in normotensive subjects following prazosin (5 mg). The top of each bar represents the mean systolic blood pressure and the bottom represents the mean diastolic pressure; *n* is the number of subjects for each determination. s.d. is also shown.

Weber, 1974) and that there is a considerable individual variation in effective dosage (Bolli & Simpson, 1974). The effectiveness of the drug is relatively independent of the frequency of administration (Okun, 1974).

We have performed a study in which ten healthy volunteers, none of whom had taken any drugs within 4 weeks prior to the study, were given a single tablet of prazosin (5 mg) and had their plasma prazosin levels, blood pressures and heart rates monitored hourly for 10 hours. The subjects were six males and four females aged 19-24 years and weighing 61-89 kg (mean 75.6 kg ± s.d. 9.07). All subjects had fasted overnight prior to entering the study. They were given a standard light breakfast 2 h after taking prazosin and a light lunch 4.5 h after taking the drug.

Blood was sampled for plasma prazosin analysis through a 20G venous cannula (Medicut) in an arm vein. Plasma prazosin concentrations were assayed fluorometrically (Pfizer, unpublished observations). Prazosin was extracted into ethyl acetate after alkalinization of the plasma with NaOH and then extracted back from the ethyl acetate into 0.1N HCl. The concentration of prazosin in the acid phase was measured by means of an Aminco-Bowman spectrophotofluorometer (excitation 330 nm, emission 390 nm; uncorrected instrument settings). Blood pressure was measured in the lying and standing postures using an automatic blood pressure recorder incorporating controlled cuff inflation and deflation and a microphone attached to the cuff. With this instrument, the Korotkoff sounds and cuff pressures are recorded in digital form on magnetic tape and later analysed by a Digital PDP-8/F computer which calculates blood pressure and heart rate for each determination.

Mean plasma prazosin levels for the ten subjects are shown in Figure 1. Peak plasma concentrations (23 ng/ml ± s.d. 10.5) were attained 2-3 h after administration. Thereafter mean plasma concentration declined according to first order kinetics with a half-life of 3.9 hours.

There was some individual variation in absorption rate: two subjects attained peak plasma concentrations at 1 h, one at 4 h and one at 5 h; the others all attained peaks at 2-3 hours. This variability in absorption is reflected in the larger standard deviations of samples obtained during the absorption phase. Elimination rate showed less variation between individuals: the mean plasma half-life for the ten individuals during the elimination phase was 3.8 h ± s.d. 0.79.

In these normotensive subjects, prazosin had a marked effect on standing blood pressure without affecting lying blood pressure (Figure 2). Forty minutes after taking prazosin, two subjects felt too faint to stand for blood-pressure measurement: one recovered sufficiently after 5.5 h to allow standing blood pressure to be recorded but the other continued to feel faint for 10 hours. Subjects felt most faint during the first 3-4 h, i.e. as the standing blood pressure was falling. It should be noted that the dose given was much greater than that normally used when treatment is started in hypertensive subjects: because, as we also have noted, the effect of the first dose is often considerable (Gabriel, Meek & Ghosh, 1975), it is advisable to start with a dose of 0.25-0.5 mg.

Heart rate in both lying and standing postures was unaffected by prazosin. It is interesting that there was no increase in standing heart rate at the

time when the standing blood pressure was lowered.

In these ten normotensive volunteers who received a single oral dose of prazosin (5 mg), the effect of the drug on blood pressure was not closely related to the plasma concentration of the drug. Despite its relatively short plasma half-life, prazosin, in clinical use, can provide satisfactory control of blood pressure in hypertensive patients when given only twice daily (Okun, 1974; Bolli, unpublished observations). This suggests that tissue concentration at the site of action follows a different time course from plasma concentration. Tissue distribution studies of [^{14}C]-prazosin in dogs (Taylor & Schach von Wittenau, quoted by Hess, 1974) indicate that prazosin is widely distributed and is concentrated in vascular tissues. Unfortunately, no preparation of prazosin for intravenous use could be obtained; the degree of absorption, the effect of the 'first pass phenomenon' and the apparent volume of distribution of the drug could therefore not be assessed.

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ANTAGONISM OF FLUDROCORTISONE BY SPIRONOLACTONE AND CANRENONE

Spironolactone is a mineralocorticoid antagonist useful in hypermineralocorticoid states such as cardiac failure, cirrhosis, and some cases of hypertension. It is rapidly metabolized by dethioacetylation to its major metabolite canrenone, and to canrenoate-K and nonfluorigenic metabolites (Sadée, Dagcioglu & Schröder, 1973).

No significant difference was found between the antimineralocorticoid effects of spironaloctone and canrenoate-K following oral administration to rats (Kagawa, Bouska, Anderson & Krol, 1964). Equimolar doses of spironolactone and canrenoate-K led to similar plasma levels of canrenone following oral administration (Sadée *et al.*, 1973). It would appear likely from this information that canrenone is the active metabolite of spironolactone. One 50 mg tablet of canrenone (A-41910, Abbott Laboratories) has been shown to generate a higher plasma level of canrenone following oral administration than two 25 mg tablets of spironolactone (Aldactone A, Searle), (Castleden & Turner, 1972, personal communication). Canrenone therefore might be expected to be a more effective mineralocorticoid antagonist than spironolactone on an equal weight basis.

A human bioassay for mineralocorticoid