except UDP-glucuronic acid. Protein was determined by the Lowry[13] method using bovine serum albumin as the standard. Statistical comparison between means was made by Student's t-test.

*Results.* The majority of rats became neurologically impaired by the time they had received 9–11 injections (270–330 mg/kg) of acrylamide. Neurological deficits included ataxia and paralysis of the limbs, with outward splaying of limbs when placed on a flat surface. All rats were markedly neuropathic after receiving 14 injections (420 mg/kg).

Preliminary results established that the in vitro addition of acrylamide in concentrations up to 10 mM was without effect on UDP-GT activity towards either OAP or PNP. Chronic treatment of rats with acrylamide was also without effect on the activity of UDP-GT. No statistically significant differences in the glucuronidation of substrates was observed between control and treated groups (table 1). Further, acrylamide treatment did not significantly alter the liver/body weight ratio, total hepatic protein and microsomal protein content (table 2).

*Discussion.* These data point out the apparent tissue selectivity of the toxic effects of acrylamide. In neural tissue, acrylamide has been shown to disrupt the integrity of ER[2], alter protein synthesis[5,6] and interfere with normal neurophysiological function[14–17]. The data presented here suggest that acrylamide does not similarly affect hepatic tissue since UDP-GT activity was unchanged and no significant change in the protein content of the whole liver or microsomes was observed. This in itself is not surprising since the funcitons of ER in hepatic and neuronal tissue are quite different. The lack of effect of acrylamide on UDP-GT activity in vitro and in vivo, however, is striking when one considers that UDP-GT activity is known to be regulated by sulfhydryl groups[18–20] and that acrylamide has been shown to bind to these groups[21].

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## Effect of thiamine hydrochloride on the blood level of 2-formyl 1-methyl pyridinium oxime chloride (2-PAM.Cl) in rats

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*Summary.* The biological half-life of 2-PAM.Cl was found to increase in female rats pretreated with thiamine hydrochloride (10 mg/kg i.m.). No such effect was observed in the male rats.

One of the several reactivators of phosphorylated acetylcholinesterase (EC 3.1.1.7), such as 2-formyl 1-methyl pyridinium oxime chloride (2-PAM.Cl), was reported to be excreted rapidly from the body[3–5]. Nicotinamide was tried earlier to prolong its retention, but the results were inconclusive[6]. However, Swartz and Sidell[7] reported prolonged biological half-life of 2-PAM.Cl by thiamine hydrochloride in male human volunteers. We therefore reinvestigated the problem using both male and female rats to establish the influence of thiamine hydrochloride on the biological half-life of 2-PAM.Cl.

*Materials and methods.* Albino rats, weighing 150±5 g, maintained at this establishment were used in the present study. The rats were fed on Hind Lever Diet (approximately 10 g per day) and water ad libitum. Thiamine content in the diet was in the order of 0.6 mg per 100 g of food. The rats were divided into 2 groups, each group consisting of 5 male and 5 female rats. The first group received 2-PAM.Cl (30 mg/kg i.m.). The second group was pretreated with thiamine HCl (10 mg/kg i.m.) followed by 2-PAM.Cl (30 mg/kg i.m.) with a time interval of 15 min. Blood from both the groups was taken from orbital plexus at 3, 15, 30, 45, 120, 150 and 180 min in heparinized tubes. Blood oxime levels were determined by the spectrophotometric method of Creasey and Green[8]. The biological half-life of 2-PAM.Cl in the blood was calculated from the regression equation. Student's t-test was used for calculation of significance[9].

*Results and discussion.* The oxime was found in the blood within 3 min after i.m. injection. The blood level of the oxime reached its peak at 30 min in both sexes. On administration of thiamine HCl, the peak was at 45 min in the female and retention was also more than in the male. Without thiamine HCl, the male rat showed more retention than the female till 180 min. The biological half-life of 2-PAM.Cl was also more in the male than in the female and vice versa on pretreatment with thiamine HCl (table).

Studies in the intact animal and man indicated that 2-PAM.Cl and other pyridinium ions were rapidly excreted into the urine[3–4], thus it was felt that one possible way of prolonging the blood concentration of 2-PAM.Cl was to block its secretion by the tubule cells. It is well-established

Mean concentration of 2-PAM.Cl in blood (μg/ml) ± SE and its biological half-life with and without thiamine HCl

| Time after injection of oxime (min) | 2-PAM.Cl (30 mg/kg i.m.) | | Thiamine (10 mg/kg i.m.)+ 2-PAM.Cl (30 mg/kg i.m.) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Male* | Female | Male | Female | Pa | Pb | Pc | Pd |
| 3 | 4.23±0.96 | 4.27±0.25 | 5.15±0.98 | 3.28±0.70 | NS | NS | NS | NS |
| 15 | 4.56±0.44 | 4.60±0.75 | 4.49±0.69 | 4.76±0.32 | NS | NS | NS | NS |
| 30 | 5.09±0.49 | 5.48±0.42 | 5.98±0.38 | 4.46±0.31 | NS | <0.05 | NS | <0.05 |
| 45 | 4.64±0.46 | 4.67±0.47 | 5.45±0.60 | 5.50±0.50 | NS | NS | NS | NS |
| 120 | 2.48±0.41 | 1.67±0.38 | 2.68±0.58 | 3.77±0.65 | NS | NS | NS | <0.01 |
| 150 | 2.12±0.23 | 0.75±0.33 | 2.40±0.44 | 3.10±0.29 | <0.01 | <0.01 | NS | <0.001 |
| 180 | 1.58±0.18 | 0.28±0.19 | 1.60±0.10 | 3.08±0.48 | <0.001 | <0.05 | NS | <0.001 |
| Biological half-life 2-PAM.Cl (min) | 124 | 88 | 130 | 212 | | | | |

*5 rats were used in each case. Pa: Tests for significance on the sex difference in rats receiving only 2-PAM.Cl. Pb: Tests for significance on the sex difference in rats receiving only 2-PAM.Cl + thiamine HCl. Pc: Tests for significance for the effect of thiamine HCl in male rats. Pd: Tests for significance for the effect of thiamine HCl in female rats. NS: Not significant.

that thiamine HCl is secreted as an organic base in the renal tubules and that it competes with other weak base compounds for the secretory mechanism[10]. From this study it was seen that thiamine HCl had an overall effect on the female rats and retention of 2-PAM.Cl was highly significant at 150 and 180 min. The male rats did not respond to this effect. Little is known on influence of the sex of the animal on the retention of oximes. The results show a significant sex difference on the retention of 2-PAM.Cl, and it is well-established that the rat has an apparent distinction of showing more variation between the sexes in its response to chemicals than any other species[11].

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## Pharmacokinetics of pindolol in Africans

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*Summary.* The pharmacokinetics of pindolol were determined in 12 hypertensive African subjects after a single oral dose of the drug. The estimated pharmacokinetic parameters do not differ significantly in Africans from the values which have been obtained in other races.

Pindolol is one of the beta-adrenoceptor blockers now widely used all over the world. In Africa it finds its greatest use as an antihypertensive agent, and we have therefore determined certain of its pharmacokinetic parameters in this group of patients. The clinical pharmacokinetics of beta-adrenoceptor blockers have not been previously reported in Africans, although it is generally agreed that the pharmacokinetics of drugs need to be studied among each geographical or racial group in which the drugs are being used, since the pharmacokinetics may be affected by genetic or environmental factors and such effects may have important bearings on the clinical uses of the drugs.

*Materials and methods.* 12 patients, 4 males and 8 females, all Africans and aged between 30 and 64 years, were studied. They all had uncomplicated essential hypertension of mild to moderate severity. They were taken off all drugs for 2 weeks before the study to eliminate the possibility of any interaction between the beta-blocker and other drugs. Clinical examination and laboratory investigations did not reveal the presence of any significant impairment of renal or hepatic function in any of the patients.

On the experimental day, the patients reported at the clinical pharmacology laboratory at 10 a.m. after having had breakfast at 7 a.m. Pindolol was administered orally in a dose of 20 mg using the commercial preparation, Visken (Sandoz). One 10-ml sample of blood was withdrawn from an antecubital vein before the administration of the drug, and 6 further samples were drawn 0.5, 1, 2, 4, 6 and 8 h after the drug. Blood samples were collected into heparinized bottles and immediately centrifuged to separate the plasma which was then stored frozen until used.

Pindolol was determined in plasma using the fluorimetric method of Pacha[2]. The pharmacokinetic parameters were calculated from the experimental data for each individual, a one-compartment model being assumed. Means are given ± SE of mean.