Racial differences in drug responses—a comparative study of trimazosin and α_1 -adrenoceptor responses in normotensive Caucasians and West Africans

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- 1 The possible racial differences in α_1 -adrenoceptor responsiveness and the blood pressure and heart rate responses following α_1 -adrenoceptor antagonism with trimazosin have been investigated in matched groups of six Caucasians and six Nigerians.
- 2 There were no significant differences between the racial groups in the blood pressure and heart rate responses to oral (200 mg) and intravenous (100 mg) trimazosin.
- 3 α_1 -adrenoceptor responsiveness was similar in both groups after placebo and following both active treatments.
- 4 There were only minor pharmacokinetic differences with the Caucasians having a larger volume of distribution, and a longer terminal elimination half-life for the metabolite, 1-hydroxy-trimazosin.
- 5 These results suggest a similarity in peripheral vascular α_1 -adrenoceptor mechanisms and show no major significant racial differences in the pharmacokinetics and pharmacodynamics of trimazosin.

Keywords α_1 -adrenoceptor response trimazosin pharmacokinetics pharmacodynamics Caucasians Africans

Introduction

For many years it has been recognised that racial factors may influence responsiveness to drugs, such as impaired mydriasis following standard doses of ephedrine and cocaine (Chen & Poth, 1929) and an insensitivity to atropine in Africans (Scott, 1945).

The ineffectiveness of β -adrenoceptor blockers in African hypertensives has been described in several studies (Humphreys & Delvin, 1968; Salako *et al.*, 1979; Seedat & Reddy, 1971), and it has also been shown that West African hypertensive patients did not respond to the combined α - and β -adrenoceptor antagonist, labetalol (Jennings & Parsons, 1976). Similarly, differences in the response to the selective α_1 -adrenoceptor antagonist, prazosin, have been described in Africans—a relative lack

of effect of low dose prazosin in hypertensive Nigerians (Falase *et al.*, 1976) and a delayed and reduced response among negroes compared with Caucasian patients in the United States (Mroczek & Finnerty, 1974).

These observations suggest either a difference in the pharmacokinetics of these drugs in different races or a difference in receptor responsiveness. A pharmacokinetic difference is likely to be particularly relevant if an active metabolite is involved in overall drug effect. Alternatively, there could be major differences in the factors controlling blood pressure or underlying hypertension in the two racial groups.

Trimazosin is a quinazoline derivative related to prazosin. It has a relatively selective but modest peripheral α_1 -adrenoceptor antagonism

in man (Reid *et al.*, 1983; Singleton, 1982) and has been shown to be effective in the management of both hypertension (Aronow *et al.*, 1977; De Guia *et al.*, 1973; Vlachakis *et al.*, 1975; Weber *et al.*, 1980) and heart failure (Aronow *et al.*, 1977; Awan *et al.*, 1979; Franciosa & Cohn, 1978; Weber *et al.*, 1980). Trimazosin, like prazosin, is metabolised by an oxidative pathway and its major metabolite in Caucasians is 1-hydroxy-trimazosin which has hypotensive effects in animals (Constantine, personal communication). Using a novel pharmacodynamic modelling technique, the hypotensive response to trimazosin in man has been correlated with the blood levels of both parent drug and 1-hydroxy-trimazosin (Meredith *et al.*, 1983).

This study compares the pharmacokinetics and pharmacodynamics of trimazosin in normotensive Caucasians and Nigerians and evaluates their respective α_1 -adrenoceptor responsiveness in the two groups.

Methods

Two groups of six subjects matched for age, sex and weight, gave their written informed consent to participate in the study. There were six healthy normotensive male Caucasian volunteers aged 21–35 years (mean 25.3 ± 4.8) and weighing 54–71 kg (mean 65.0 ± 6.6 kg) and six normotensive Nigerians (temporarily resident in Glasgow) aged 23–30 years (mean 27.5 ± 1.2) and weighing 56–71 kg (mean 66.4 ± 6.2 kg). Each subject received 100 mg intravenous trimazosin, 200 mg oral trimazosin and intravenous placebo (5 ml 0.9% sodium chloride solution), on separate study days at least 1 week apart, in a randomised latin-square design. The study was approved by the local Research and Ethics Committee.

Pharmacodynamics

Blood pressure and heart rate were measured after resting supine, for at least 10 min, and then on standing for up to 5 min at intervals throughout the day. Blood pressure was measured with a semi-automated sphygmomanometer (Sentron) and heart rate was measured on a continuous ECG recording from standard anterior chest leads displayed on a Grass polygraph model 7D. At 0, 1 and 4 h after drug administration blood was taken into heparinised tubes on ice, centrifuged at 4°C and the plasma separated and stored at -70°C for subsequent determination of renin and catecholamines.

Pressor responses to graded intravenous doses of the α_1 -adrenoceptor agonist, phenylephrine,

were performed at 1–3 h (early period) and 5–7 h (late period) after drug administration. Phenylephrine infusion was started at a dose rate of $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$. The rate was increased by up to four increments at 5 min intervals until a maximum rise of 45 mm Hg systolic or 30 mm Hg diastolic pressure was achieved. During the infusions blood pressure and heart rate were measured every minute.

Pressor dose-response curves were constructed by plotting the rise in mean arterial pressure against the log-dose of the pressor agent. The results were analysed by fitting all data points to a quadratic function from which the dose of agonist required to cause a rise of 20 mm Hg mean arterial pressure was derived for each individual subject (PD_{20}) (Sumner *et al.*, 1982).

Pharmacokinetics

At frequent intervals throughout the study period, blood samples were withdrawn from an indwelling intravenous cannula for subsequent measurement of whole blood concentrations of trimazosin and the metabolite 1-hydroxy-trimazosin. Twenty-four hour urine was collected following drug administration and aliquots assayed for drug and metabolite levels. Trimazosin was measured by h.p.l.c. with fluorescence detection (Hughes *et al.*, 1984). The limits of detection were 1 and 0.5 ng ml^{-1} and the coefficient of variation 5.1 and 6.2% for trimazosin and 1-hydroxy-trimazosin, respectively.

The pharmacokinetic data were analysed using computer-assisted least squares fitting. The intravenous data were most appropriately fitted to a two-compartment open model, which was extended to include a separate compartment to describe the profile of the metabolite as follows:

$$C = Ae^{-\alpha(t)} + Be^{-\beta(t)} \text{ for parent drug, and}$$

$$C(m) = \frac{V_c}{V_m} k_{1m} \left[\frac{A}{k_{mo} - \alpha} e^{-\alpha(t)} - e^{-k_{mo}(t)} + \frac{B}{k_{mo} - \beta} e^{-\beta(t)} - e^{-k_{mo}(t)} \right]$$

for the metabolite.

The oral data were most appropriately fitted to a one-compartment model which was extended to include a separate compartment to describe the profile of the metabolite as follows:

$$C = Ae^{-\beta(t-t_{1/2})} - e^{-ka(t-t_{1/2})} \text{ for drug and,}$$

$$C(m) = \frac{V_c}{V_m} k_{1m} \left[\frac{A}{k_{mo} - \beta} e^{-\beta(t-t_{1/2})} - e^{-k_{mo}(t-t_{1/2})} - \frac{A}{k_{mo} - ka} e^{-ka(t-t_{1/2})} - e^{-k_{mo}(t-t_{1/2})} \right]$$

for the metabolite.

The data were simultaneously fitted to these equations using non-linear least squares fitting with an inverse weighting for drug and metabolite concentrations. The parameters derived from this approach for intravenous trimazosin were the coefficients A and B , the hybrid first-order rate constants for drug disposition (α and β), the first-order rate constant describing metabolite elimination k_{mo} and the constant

$$\frac{V_c}{V_m} k_{1m},$$

where V_c and V_m are the volumes of the central and metabolite compartments, respectively.

Statistical analysis was by repeated measures analysis of variance for blood pressure and heart rate and by paired and unpaired t -tests and the Wilcoxon test for unpaired data elsewhere. Results throughout are expressed as means with standard deviation.

Results

Blood pressure and heart rate

Following treatment with intravenous trimazosin, there was no significant change in blood pressure or heart rate in the supine position, but there was a gradual fall in blood pressure in both groups in the erect position (Figure 1). In the Caucasians, the maximum hypotensive response occurred at about 4 h with blood pressure (5 min erect) falling to $100/63.5 \pm 15/12$ compared with $114/83 \pm 11/12$ with placebo. For the Nigerian subjects, the maximum hypotensive response occurred 4–6 h after treatment, blood pressure falling to $87/52 \pm 18/9$ at 6 h compared with $107/63 \pm 11/9$

after placebo (Figure 1). If the hypotensive effect is expressed in terms of AUC, the placebo corrected AUC in Caucasians was not significantly different from that of the Nigerians at -4965 ± 6676.1 and -5660 ± 7523 mm Hg h for the Caucasians and Nigerians, respectively. The falls in blood pressure were associated with increases in heart rate, although these did not achieve statistical significance.

After treatment with oral trimazosin there was a similar gradual fall in blood pressure, especially on standing (Figure 2). The maximum hypotensive response occurred 3–6 h among the Caucasians, blood pressure falling to a mean of $92/63 \pm 21/17$ at 4 h ($114/83 \pm 11/12$ with placebo) and associated with a modest increase in heart rate. For the Nigerian group, the hypotensive response tended to be more sustained, beginning at 2 h and continuing up to 8 h. Blood pressure fell to $85/51 \pm 18/11$ at 4 h and $95/59 \pm 15/9$ at 8 h, compared with placebo values of $103/72 \pm 9/10$ and $107/70 \pm 5/13$ respectively. The placebo-corrected AUC for the hypotensive effect were not significantly different (Wilcoxon test) at -6130 ± 4413.6 and -5717.5 ± 2767.8 mm Hg h for the Caucasians and Nigerians, respectively. Again, there was an associated increase in heart rate which was not statistically significant. Subjects in both groups experienced orthostatic symptoms at the times of the greatest fall in blood pressure. The heart rate responses were similar in both treatment groups and there was no difference in their response to placebo (Figure 3).

Pressor responsiveness to phenylephrine

Following placebo there was no significant difference between the racial groups, suggesting comparable α -adrenoceptor responsiveness,

Figure 1 Erect mean systolic (upper panel) and diastolic (lower panel) blood pressure following treatment with i.v. trimazosin (●—●) and control (◆—◆) in Nigerians ($n = 6$) and i.v. trimazosin (○—○) and control (◇—◇) in Caucasians ($n = 6$).

Figure 2 (a) Erect mean systolic and (b) diastolic blood pressure after treatment with oral trimazosin (●—●) and control (◆—◆) in Nigerians ($n = 6$) and oral trimazosin (○—○) and control (◇—◇) in Caucasians ($n = 6$).

Figure 3 Erect mean heart rate responses after treatment with intravenous trimazosin (○—○) and placebo (△—△) in Caucasians; and i.v. trimazosin (●—●) and placebo (▼—▼) in Nigerians, respectively.

but the inter-individual variability in response was considerable (Table 1).

After the administration of both intravenous and oral trimazosin the dose-response curves showed parallel shifts to the right compared with placebo, indicating α_1 -adrenoceptor antagonism in both groups (Figure 4). Following intravenous trimazosin the PD_{20} was significantly increased at the early time in both groups ($P < 0.02$) but not at the later time. Following oral trimazosin the PD_{20} was significantly increased at the early time in both groups ($P < 0.01$) and the Caucasians also showed a significant increase ($P < 0.05$) at the later time. Log-transformation of the PD_{20} prior to statistical analysis in each group did not alter the level of significance.

Plasma catecholamines and renin activity

There was no significant difference between the groups in the levels of supine plasma renin activity. In addition, there was no significant difference between the supine noradrenaline and adrenaline

levels in each group and their response to all treatments were similar.

Pharmacokinetics

Figure 5 shows representative concentration-time profile for both oral and intravenous trimazosin in a Nigerian subject. The similarity of the slopes for the elimination phase of the metabolite and the parent drug suggest that the rate of elimination of the metabolite was limited by its rate of formation. The derived pharmacokinetic parameters for the group are shown in Table 2. The mean calculated absolute bioavailability of trimazosin was not significantly different at 74% and 66% in Caucasians and Nigerians respectively and similarly there were no significant differences for the mean terminal elimination half-life and whole blood clearance of trimazosin. The volume of distribution was significantly greater ($P < 0.01$) in the Caucasians at 12.5 l compared to 9.2 l for the Nigerians. The time to achieve peak drug and metabolite concentrations in whole blood and the total urinary elimination of trimazosin and its major metabolite are shown in Tables 3 and 4, respectively.

Discussion

Following oral and intravenous administration there were no significant differences in the blood pressure responses to trimazosin in the two racial groups. However, there was a large inter-individual variability and the Nigerian group tended to show a greater fall in blood pressure following placebo. Thus, although the pattern of blood pressure fall following the active treatments tended to suggest a delayed maximum response

Table 1 Phenylephrine pressor dose-responses (mean $\pm$ s.d.) expressed as PD_{20} which is the dose of phenylephrine ($\mu\text{g kg}^{-1} \text{min}^{-1}$) required to raise mean arterial pressure by 20 mm Hg

	Early		Late	
	Caucasians	Nigerians	Caucasians	Nigerians
Placebo	2.2 $\pm$ 0.7	1.6 $\pm$ 0.8	2.7 $\pm$ 0.3	2.4 $\pm$ 1.2
Oral trimazosin	*6.4 $\pm$ 1.9	*5.6 $\pm$ 1.0	*4.7 $\pm$ 1.7	3.3 $\pm$ 1.8
Mean dose ratio	3.2 $\pm$ 1.3	4.5 $\pm$ 2.7	1.9 $\pm$ 0.9	1.7 $\pm$ 0.9
Intravenous trimazosin	*4.5 $\pm$ 1.3	*5.2 $\pm$ 2.3	3.2 $\pm$ 0.8	3.3 $\pm$ 2.1
Mean dose ratio	2.2 $\pm$ 1.0	4.5 $\pm$ 3.4	1.2 $\pm$ 0.3	1.3 $\pm$ 0.6

* $P < 0.05$ compared with placebo.

Figure 4 Representative pressor responses to intravenous infusions of phenylephrine. Responses after placebo (●—●), i.v. trimazosin (○—○) and oral trimazosin (◆—◆) at 1–3 h and 5–7 h. in (a) Caucasians and (b) Nigerians.

among the Nigerians these differences were not significant after placebo correction.

The response to the pressor effects of intravenous phenylephrine was similar in both groups, both on active treatment and following placebo. Although no statistically significant difference occurred between the Nigerians and Caucasians, the size of the groups and large inter-individual variation results in low power to detect modest differences. However, our result suggests that the α_1 -adrenoceptor mediated vasoconstrictor mechanisms are similar in the groups studied. The resting plasma renin activity and catecholamine levels in the supine position in both groups were not significantly different.

Following oral and intravenous administration there were no significant differences between the racial groups in the terminal elimination half-life, the AUC and the clearance of trimazosin. For the metabolite, 1-hydroxy-trimazosin, there were minor pharmacokinetic differences: the metabolite elimination half-life was significantly longer after oral trimazosin in Caucasians and tended also to be longer after i.v. trimazosin. However, as the AUC for the metabolite was not significantly different in the two racial groups,

Figure 5 A representative concentration-time profile for trimazosin (○—○) and 1-hydroxytrimazosin (●—●) after (a) i.v. administration and (b) oral treatment in a Nigerian subject.

Table 2 Derived trimazosin pharmacokinetic parameters

	Intravenous administration		Oral administration	
	Caucasians	Nigerians	Caucasians	Nigerians
AUC drug ($\mu\text{g ml}^{-1} \text{ min}$)	1988 $\pm$ 281	2359 $\pm$ 540	2910 $\pm$ 715	2996 $\pm$ 862
AUC metabolite ($\mu\text{g ml}^{-1} \text{ min}$)	2908 $\pm$ 1062	1911 $\pm$ 1211	2714 $\pm$ 978	2841 $\pm$ 1611
$t_{1/2\beta}$ (min)	191 $\pm$ 46	172 $\pm$ 27	179 $\pm$ 71	165 $\pm$ 25
$k_{\text{mo}} t_{1/2}$ (min)	99 $\pm$ 11	76 $\pm$ 24	96 $\pm$ 22*	62 $\pm$ 14*
Clearance (ml min^{-1})	52 $\pm$ 8.4	44 $\pm$ 10.5	—	—
V_{ss} (l)	12.5 $\pm$ 2.2**	9.2 $\pm$ 1.0**	—	—
F (%)	—	—	73.6 $\pm$ 16.5	66.2 $\pm$ 22.9

* $P < 0.01$ ** $P < 0.001$ Caucasians compared with Nigerians**Table 3** Time to achieve peak drug and metabolite concentrations after oral trimazosin

	Peak drug concentration ($\mu\text{g ml}^{-1}$)	Peak metabolite concentration ($\mu\text{g ml}^{-1}$)	$t_{(\text{max})}$ (h)
Caucasians	11 $\pm$ 3.4	— 4.0 $\pm$ 0.7	1–2 2–5
Nigerians	13.9 $\pm$ 6.7	— 9.4 $\pm$ 0.7	1–2 1–4

Table 4 Total urinary elimination of trimazosin and 1-hydroxy-trimazosin

	Trimazosin	1-hydroxytrimazosin
<i>i.v.</i>		
Caucasians	2.0 $\pm$ 0.7%	18.0 $\pm$ 7.4%
Nigerians	2.1 $\pm$ 0.7%	23.8 $\pm$ 12.9%
<i>Oral</i>		
Caucasians	1.0 $\pm$ 0.4%	*7.2 $\pm$ 3.7%
Nigerians	1.7 $\pm$ 0.6%	*14.4 $\pm$ 5.2%

* $P < 0.05$ (Caucasians compared with Nigerians)

Although there was no significant difference in trimazosin clearance between both racial groups, the mean ratio of the AUC metabolite: AUC trimazosin after intravenous trimazosin tended to be greater in Caucasians (1.5) compared to Nigerians (0.8). The clearance of the metabolite can be inferred from the relation-

$$\frac{\text{AUC (m)}}{\text{AUC (d)}} = \frac{\text{fm} \cdot \text{FH(m)} \cdot \text{CL}}{\text{CL(m)}}$$

(Houston, 1982) where fm is the fraction of drug converted to metabolite, FH(m) is the systemic availability of metabolite. A value in excess of 1.0 suggests that the clearance of metabolite is slower than that of parent drug as neither fraction can exceed 1 (Rowland & Tozer, 1980) and in this study it may indicate that metabolite clearance tended to be faster in Nigerians. There was a significant difference ($P < 0.01$) between the volume of distribution in Caucasians and the Nigerians, for which there is no clear explanation.

Racial factors which influence the responsiveness to drug therapy in man are not all clearly identified. Both genetic and environmental factors contribute. These factors may include variations in pharmacodynamics resulting from structural differences in receptor proteins with altered binding to the parent drug, or its metabolite, leading to a reduced response (Vessel, 1980). Alternatively, there may be pharmacokinetic variations such as reduced first-pass metabolism, as a result of genetic differences in activity of hepatic enzyme systems, resulting in exaggerated pharmacological responses, or a failure to generate active metabolites, or the involvement of alternate pathways of metabolism, resulting in the production of different, even toxic metabolites (Kalow, 1982). Racial differences in the oxidative metabolism of several drugs have been previously described (Andoh *et al.*, 1980); Mbanefo *et al.*, 1980; Spector *et al.*, 1980; Woolhouse *et al.*, 1979). However, although trimazosin is metabolised by an oxidative pathway, both racial groups produced similar amounts of the major metabolite 1-hydroxy-tri-

mazosin and did not show any differences in their pharmacodynamic responses to both active treatments. Differences due to environmental factors have also been described (Fraser *et al.*, 1977) such as hepatic enzyme induction by protein-rich diets (Alvares *et al.*, 1976; Anderson *et al.*, 1979; Hietanen, 1980; Kappas *et al.*, 1976, 1978). In this study subjects were matched for age, sex and weight and were living in the same environment and eating a similar diet. Thus, the explanation for the minor pharmacokinetic differences is not clear. No subject abused alcohol or other drugs.

In conclusion, the overall pharmacodynamic profile of trimazosin was similar in the two racial groups. As the responsiveness to the pressor effects of intravenous phenylephrine suggested a similarity in α_1 -adrenoceptor dependent peri-

pheral pressor mechanisms, the pharmacokinetic difference in the volume of distribution may reflect differences in tissue or plasma protein binding but are unlikely to account fully for the apparent racial differences in response to α -adrenoceptor blockers described elsewhere. Although racial differences in responsiveness have been described with β -adrenoceptor blockers it has not been possible in this study to show similar differences in α -adrenoceptor antagonism.

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References

- Alvares, A. P., Anderson, K. E., Conney, A. H. & Kappas, A. (1976). Interactions between nutritional factors and drug biotransformation in man. *Proc. Nat. Acad. Sci., U.S.A.* **73**, 2501–2504.
- Anderson, K. E., Conney, A. H., Kappas, A. (1979). Nutrition and oxidative drug metabolism in man. Relative influence of dietary lipids, carbohydrate and protein. *Clin. Pharmac. Ther.*, **26**, 493–501.
- Andoh, B., Idle, J. R., Sloan, T. P., Smith, R. L. & Woolhouse, N. (1980). Inter-ethnic and inter-phenotype differences among Ghanians and caucasians in the metabolic hydroxylation of phenytoin. *Br. J. clin. Pharmac.*, **9**, 292P–293P.
- Aronow, W. S., Tobias, J. Hughes, D., Siegal, J. & Easthope, J. (1977). Comparison of trimazosin and methyldopa in hypertension. *Clin. Pharmac. Ther.*, **22**, 425–429.
- Aronow, W. S., Greenfield, R. S., Alinadadian, H., Danaby, D. T. (1977). Effect of the vasodilator trimazosin versus placebo on exercise performance in chronic left ventricular failure. *Am. J. Cardiol.*, **40**, 789–793.
- Awan, N. A., Hermanovich, J., Whitcomb, C., Skinner, P. & Mason, D. T. (1979). Cardiac circulatory effects of afterload reduction with oral trimazosin in severe congestive heart failure. *Am. J. Cardiol.*, **44**, 126–131.
- Chen, K. K. & Poth, E. J. (1929). Racial differences as illustrated by the mydriatic actions of cocaine, ephthalamine and ephedrine. *J. Pharmac. exp. Ther.*, **36**, 429.
- De Guia, D., Mendlowitz, M., Russo, C., Vlachakis, N. D. & Antram, S. (1973). The effect of trimazosin in essential hypertension. *Curr. Ther. Res.*, **15**, 339–348.
- Falase, A. O., Salako, L. A. & Aminu, J. M. (1976). Lack of effect of low doses of prazosin in hypertensive Nigerians. *Curr. Ther. Res.*, **19**, 603–611.
- Franciosa, J. A. & Cohn, J. N. (1978). Haemodynamic effects of trimazosin in patients with left ventricular failure. *Clin. Pharmac. Ther.*, **23**, 11–18.
- Fraser, H. S., Mucklow, J. C., Bulpitt, C. J., Khan, C., Mould, G. & Dollery, C. T. (1977). Environmental effects on antipyrine half-life in man. *Clin. Pharmac. Ther.*, **22**, 799–808.
- Hietanen, E. (1980). Modifications of hepatic drug metabolising enzyme activities and their induction by dietary proteins. *General Pharmacology*, **11**, 443–450.
- Houston, J. B. (1982). Drug metabolite kinetics. *Pharmac. Ther.*, **15**, 521–552.
- Hughes, M. A., Meredith, P. A. & Elliott, H. L. (1984). The determination of trimazosin and its metabolite CP23445 in whole blood by high pressure liquid chromatography using fluorescence detection. *J. pharmac. Methods*, **12**, 29–35.
- Humphreys, G. S. & Delvin, D. G. (1968). Ineffectiveness of propranolol in hypertensive Jamaicans. *Br. med. J.*, **2**, 601–603.
- Jennings, K. & Parsons, V. (1976). A study of labetalol in patients of European, West Indian and West African origin. *Br. J. clin. Pharmac.*, **3**, 773S–775S.
- Kalow, W. (1982). Ethnic differences in drug metabolism. *Clin. Pharmacokin.*, **7**, 373–400.
- Kappas, A., Alvares, A. P., Anderson, K. E., Pantuck, E. J., Pantuck, C. B., Chang, R. & Conney, A. H. (1978). Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. *Clin. Pharmac. Ther.*, **23**, 445–450.
- Kappas, A., Anderson, K. E., Conney, A. H. & Alvares, A. P. (1976). Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin. Pharmac. Ther.*, **20**, 643–653.
- Mbanefo, C., Bababunmi, E. A., Mahgoub, A., Sloan, T. P., Idle, J. R. & Smith, R. L. (1980). A study of the debrisoquine hydroxylation polymorphism in a Nigerian population. *Xenobiotica*, **10**, 811–818.

- Meredith, P. A., Kelman, A. W., Elliott, H. L. & Reid, J. L. (1983). Pharmacokinetic and pharmacodynamic modelling of trimazosin and its major metabolite. *J. Pharmacokin. Biopharm.*, **4**, 323-335.
- Mroczek, W. J. & Finnerty, F. A. Jr. (1974). Prazosin—a double-blind evaluation. In *Prazosin—evaluation of a new antihypertensive agent*. Ed. Cotton, F. Amsterdam: Excerpta Medica.
- Reid, J. L., Meredith, P. A. & Elliott, H. L. (1983). Pharmacokinetics and pharmacodynamics of trimazosin in man. *Am. Heart J.*, **106**, 1222-1228.
- Rowland, M. & Tozer, T. N. (1980). *Clinical pharmacokinetics: Concepts and application*. Philadelphia: Lea & Febiger.
- Salako, L. A., Falase, A. O. & Aderounmu, A. F. (1979). Placebo controlled, double-blind clinical trial of alprenolol in African hypertensive patients. *Curr. med. Res. Opin.*, **6**, 358-363.
- Scott, T. G. (1945). The eye of the West African negro. *Br. J. Ophthalmol.*, **29**, 12.
- Seedat, Y. K. & Reddy, J. (1971). Propranolol in the South Africans non-white hypertensive patient. *S. Afr. med. J.*, **45**, 284-285.
- Singleton, W., Saxton, C. A. P. D., Hernandez, J. & Pritchard, B. N. C. (1982). Post-junctional selectivity of α -blockade with prazosin, trimazosin and UK-33274 in man. *J. cardiovasc. Pharmac.*, **4**, S145-S151.
- Spector, R., Choudhury, A. K., Chiang, C. K., Goldberg, M. J. & Ghoneim, M. M. (1980). Diphenhydramine in orientals and caucasians. *Clin. Pharmac. Ther.*, **28**, 229-234.
- Sumner, D. J., Elliott, H. L. & Reid, J. L. (1982). The analysis of pressor dose response. *Clin. Pharmac. Ther.*, **32**, 450-458.
- Vessel, E. S. (1980). Gene-environment interactions in drug metabolism. In *Proceedings of the First World Conference of Clinical Pharmacology*. Ed. Turner, P. & Padgham, C., pp. 63-79. London: Macmillan.
- Vlachakis, N. D., Mendlowitz, M. & De Guzman, D. (1975). Treatment of essential hypertension with trimazosin, a new vasodilator agent. *Curr. Ther. Res.*, **17**, 564-569.
- Weber, M. A., Brewer, D. D., Jan, B. S., Drayer, I. M., Aronow, W. S., Lipson, J. L. & Ricci, B. A. (1982). A vasodilator that avoids renin stimulation and fluid retention: Antihypertensive treatment with trimazosin. *Clin. Pharmac. Ther.*, **32**, 572-578.
- Weber, K. T., Kinasowitz, G. T., West, J. S., Janicki, J. S., Reichek, N. & Fishman, A. P. (1980). Long-term vasodilator therapy with trimazosin in chronic cardiac failure. *New Engl. J. Med.*, **303**, 242-250.
- Woolhouse, N. M., Andoh, B., Mahgoub, A., Sloan, T. P., Idle, J. R. & Smith, R. L. (1979). Debrisoquine hydroxylation polymorphism among Ghanians and Caucasians. *Clin. Pharmac. Ther.*, **26**, 584-591.

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