Table 2 Hb, antipyrine $T_{1/2}$, clearance and V_d in fifteen patients before and after correction of anaemia.

	Hb (g/100 ml)			$T_{1/2}$ (h)			Clearance (ml min kg ⁻¹)			V_d (l kg ⁻¹)		
	Before	After	P	Before	After	P	Before	After	P	Before	After	P
Fifteen patients												
Mean	4.06	9.72	<0.001	8.25	9.919		2.2857	1.86	<0.2	1.5537	1.488	NS
s.e. mean	0.336	0.216		0.6295	1.138	NS	0.27	0.1722		0.1674	0.141	
Nine patients												
Mean	3.2	9.46	<0.001	8.28	11.364	<0.05	2.315	1.7067	<0.21	1.5748	1.6264	NS
s.e. mean	0.14	0.24		0.897	1.66		0.3239	0.1871		0.1674	0.1674	
Six patients												
Mean	5.3	10.12	<0.01	8.2087	7.7506	NS	2.2496	2.0888	NS	1.5219	1.2808	NS
s.e. mean	0.47	0.35		0.8995	1.014		0.2136	0.3189		0.2622	0.1888	

population (Desai *et al.*, 1980). This could be due to reduced absorption of antipyrine in our patients. All the patients in this study had heavy hookworm infestation and worm infestation has been shown to affect absorption of fat and vitamins (Sheehy, *et al.*, 1962). Since the patients were very anaemic, iron was started immediately after the first antipyrine test and so the effect of hookworm infestation on absorption could not be studied in isolation. In six out of nine patients (Hb below 4 g/100 ml) V_d increased after correction of anaemia which could be due to improved absorption of antipyrine.

Although antipyrine clearance represents a more acceptable expression of drug elimination, for this study we have preferred to use $T_{1/2}$, since absorption of antipyrine may not have been complete, and the aV_d and clearance values could be fallacious. The correlation coefficient for % change in clearance was

$r = 0.7966$, $P < 0.001$, while the corresponding value for a V_d was 0.1915 (NS), indicating the relatively larger contribution of clearance to rate of elimination (Sultatos *et al.*, 1980).

Anaemia and hookworm infestation are common problems and further studies on pharmacokinetics of chemotherapeutic agents are necessary to predict whether dose adjustments are necessary.

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THE HYPOTENSIVE RESPONSE TO HYDRALAZINE, IN TRIPLE THERAPY, IS NOT RELATED TO ACETYLATOR PHENOTYPE

Hydralazine has been recommended for the treatment of hypertension when combined with a diuretic and a β -adrenoceptor blocker (Drug & Therapeutics Bulletin, 1979). It is metabolised by *N*-acetyl transferase in the liver. The activity of this enzyme has a polymorphic distribution, a population

being bimodally divided into fast and slow acetylators.

The clinical significance of this polymorphism in relation to the clinical hypotensive effect of the drug is uncertain. We therefore studied the dose/response relationship of hydralazine on the blood pressure of a

group of patients with essential hypertension whose blood pressure was not satisfactorily controlled with a diuretic and a β -adrenoceptor blocker, and related this effect to their acetylator status.

Twenty-seven patients with known essential hypertension participated in the study. Vasodilator therapy with hydralazine was commenced because their diastolic blood pressure was greater than 95 mmHg measured on two successive visits, during treatment with a combination of cyclopentiazide K 0.5 (Navidrex K) plus slow oxprenolol 320 mg per day (screening visits 1 and 2). The two groups were similar with respect to their sex, age and race distribution and in their severity of hypertension as indexed by their fundal changes, renal function and electrocardiogram. Patients were seen at 2 weekly intervals for 10 weeks and received increasing doses of hydralazine, in addition to their previous therapy, at each visit, unless intolerable adverse reactions necessitated withdrawal from the trial.

The dose steps prescribed were hydralazine 25 mg, 50 mg, 100 mg, 200 mg daily in two divided doses. After 8 weeks of active treatment, hydralazine was discontinued and the patients were seen 2 weeks later after treatment with a placebo tablet, twice daily, in addition to the thiazide and β -adrenoceptor blocker.

Blood pressure was measured using a London School of Hygiene sphygmomanometer at the same time of day at each visit, 6–8 h after the last dose of hydralazine. It was recorded ($\times 2$) after lying supine for 5 min and on standing for 3 min, Korotkoff Phase V was used for diastolic blood pressure. The average of the two recordings in each position was used for analysis. Heart rate was counted from the radial pulse for 20 s after the last blood pressure recording in each position. Weight was recorded. Adverse effects were elicited by questioning at each visit by asking the patient if they had noticed any change in themselves. At the completion of the trial the patients were divided into fast and slow acetylators by determining the ratio of monoacetyldapsone (MADDS)/dapsone (DDS) in the plasma 2 h after an oral dose of 50 mg dapsone. Plasma DDS and MADDS were estimated by quantitative thin layer chromatography (Ahmad & Rogers, 1980), and individuals were phenotyped according to the criteria of Gelber *et al.* (1971). The responses between the groups were compared using Student's *t*-test at each dose level. Within-group changes were determined using the ANOVA programme on the SSPS package and then significance examined with paired *t*-testing.

The results are summarized in Tables 1 and 2. There was a significant reduction of the lying and standing systolic and diastolic blood pressure in both groups. At the highest dose there was a reduction of 24/19 mmHg lying and 17/14 mmHg standing in the fast acetylators, and 22/16 lying and 20/19 standing in the slow. At none of the dose steps did the difference between the fast and slow acetylators approach

significance. There was no significant change in the mean weight of either group. There was a rise in both lying and standing heart rate in both groups of up to 6 beats/min but this increase did not reach significance.

Two of the patients in the slow acetylator group were withdrawn from the trial after the first dose step, one with headaches and the other with dizziness. They are therefore not included in the analysis. Two other slow acetylators complained of adverse reactions, one dizziness, the other breathlessness and tiredness, but they did complete all dose steps. Two of the fast acetylators did not complete the last dose step because of 'feeling dizzy' and two others complained of headaches and tiredness.

When hydralazine was added to anti-hypertensive therapy consisting of a β -adrenoceptor blocker and a diuretic, we were unable to demonstrate a difference in the hypotensive response between fast and slow acetylators of the drug. Similarly, Hunyor *et al.* (1975) added hydralazine or substituted the drug for previous hypotensive therapy in a group of 30 patients and found that the average dose of hydralazine to control blood pressure was not dissimilar in fast and slow acetylators. This does not agree with the findings of Zacest & Koch-Weser (1972), who have reported that the dose of hydralazine required to produce satisfactory lowering of blood pressure was 50% higher in fast as compared to slow acetylators when added to the therapy of patients on hydrochlorothiazide and propranolol.

The study design used in the project differed from that used by Zacest & Koch-Weser (1972) in that each patient received each dose (unless adverse effects developed) whereas they only treated their patients up to a dose giving 'satisfactory' control of blood pressure. It may be seen from Tables 1 and 2 that there is little advantage in using hydralazine in doses above 50 mg twice daily as little or no additional fall in blood pressure was seen at the higher doses used. In contrast to Kalowski *et al.* (1979), who treated a similar sized patient population, we were unable to demonstrate a difference between fast and slow acetylators in the susceptibility to adverse reactions. Therefore, we feel that it is not clinically important to determine the acetylator phenotype in patients being treated with hydralazine in triple hypotensive therapy, with a view to determining their short-term hypotensive response to the drug. However acetylator phenotyping may have some role in predicting those patients receiving hydralazine who may be susceptible to the drug induced lupus syndrome.

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Table 1 Systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) on lying and standing and weight during various phases of the trial

	<i>Hydralazine (mg/day)</i>					
	<i>Screen 2</i>		<i>25</i>		<i>50</i>	
	<i>F</i>	<i>S</i>	<i>F</i>	<i>S</i>	<i>F</i>	<i>S</i>
Lying SBP (mmHg)	178±5	170±6	164±3**	162±6	157±3**	156±4*
Lying DBP (mmHg)	113±4	112±3	105±1	102±2	104±2*	100±2*
Lying HR (beats min ⁻¹)	68±3	70±2	73±2	73±2	74±3	72±3
Standing SBP (mmHg)	167±4	164±6	159±4	151±6**	148±3**	150±4**
Standing DBP (mmHg)	115±3	114±4	110±3	104±4*	108±3	102±3**
Standing HR (beats min ⁻¹)	73±2	76±3	76±2	78±3	77±3*	74±3
Weight (kg)	71.5±3.0	75.7±3.8	71.9±3.1	78.7±3.5	72.8±3.2	75.7±3.7
<i>n</i>	(13)	(12)	(13)	(12)	(13)	(12)

	<i>Hydralazine (mg/day)</i>					
	<i>100</i>		<i>200</i>		<i>Washout</i>	
	<i>F</i>	<i>S</i>	<i>F</i>	<i>S</i>	<i>F</i>	<i>S</i>
Lying SBP (mmHg)	153±4**	150±6**	154±6**	148±6**	161±6*	163±8
Lying DBP (mmHg)	100±3**	95±4***	96±3**	96±3***	107±3*	104±4*
Lying HR (beats min ⁻¹)	74±2	73±2	71±2	75±2	72±2	71±2
Standing SBP (mmHg)	147±6**	139±5***	150±4**	144±8**	159±5*	149±6*
Standing DBP (mmHg)	102±3**	97±4***	103±3**	95±4**	110±3	105±5
Standing HR (beats min ⁻¹)	77±3	77±2	74±2	78±2	75±2	73±2
Weight (kg)	72.8±3.3	76.3±3.6	75.2±3.7	77.3±3.5	73.0±3.2	77.7±3.6
<i>n</i>	(13)	(12)	(11)	(12)	(13)	(12)

* $P < 0.05$,** $P < 0.01$ significant difference from Screen 2*** $P < 0.001$

F fast S slow acetylators

Table 2 Change in mean lying arterial pressure at various phases of the trial (mmHg)

	<i>Hydralazine (mg/day)</i>			
	<i>25</i>	<i>50</i>	<i>100</i>	<i>200</i>
Fast acetylators	-10±4	-13±4	-17±5	-18±4
Slow acetylators	-9±2	-13±3	-18±3	-18±3

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DEFECTIVE HYDROXYLATION OF BUFURALOL ASSOCIATED WITH SIDE-EFFECTS OF THE DRUG IN POOR METABOLISERS

Bufuralol is a non-selective β -adrenoceptor blocking drug with some degree of intrinsic sympathomimetic activity (Angium, Ro 3-4787). First studies in man have shown that bufuralol has a longer duration of action and a greater potency than propranolol (Kilborn & Turner, 1974; Tschopp *et al.*, 1978). This lipophilic compound is metabolised by the liver and three metabolites of bufuralol have been identified in human plasma: an alcoholic or carbinol derivative (1'-hydroxybufuralol), a phenol derivative (4-hydroxybufuralol) and a ketone derivative (Francis *et al.*, 1976; Balant *et al.*, 1980). The carbinol and the ketone derivatives have been synthesised and shown to possess β -adrenoceptor blocking activity similar to parent drug (Francis *et al.*, 1976). The main constituent next to the parent compound in human plasma is the active carbinol derivative (Balant *et al.*, 1978a; Balant *et al.*, 1980).

During the course of kinetic studies with bufuralol in healthy volunteers we observed a subject who developed side-effects. A 21 year old Caucasian male took, when fasting, a 30 mg bufuralol tablet. Two hours after the bufuralol intake he became ill: he was pale, presented with profuse sweating, suffered pronounced nausea and vomited, the pulse was 64 beats/min and blood pressure fell to 95/65 mmHg. These unpleasant side-effects of the drug disappeared within the next 4 h. In this subject, plasma bufuralol concentrations were unusually high and carbinol concentrations low. This observation and a similar case previously reported (Balant *et al.*, 1976) suggest a pharmacogenetic anomaly for aliphatic hydroxylation of bufuralol (Balant *et al.*, 1978b), as recently described for alicyclic hydroxylation of debrisoquine (Mahgoub *et al.*, 1977; Price Evans *et al.*, 1980), *N*-oxidation of sparteine (Eichelbaum *et al.*, 1979); Bertilsson *et al.*, 1980), hydroxylation of phenytoin (Sloan *et al.*, 1981), or other oxidated drugs (Sloan *et al.*, 1978).

The family of this 'outlier' subject was then tested with bufuralol and with debrisoquine. The protocol was approved by the Institution Ethical Committee and informed consent was obtained from each subject. Bufuralol and 1'-hydroxybufuralol plasma concentrations were measured using a high-performance liquid chromatographic method (Haefelfinger, 1980). Figure 1 shows plasma concentrations of bufuralol and 1'-hydroxybufuralol in the family of our subject (F.K.) and Table 1, the pharmacokinetic parameters. With the exception of the father (Ar.K.), bufuralol levels are high and 1'-hydroxybufuralol levels are extremely low, near the measurement limit of the assay (Table 1). The mother (E.K.) and the sister (A.K.), but not the father, presented the same pattern of vagal side-effects, including vomiting, as did our subject. These side-effects could be antagonised by an anticholinergic drug (hyoscine butylbromide, 20–40 mg i.m.) Members of this family have also been submitted to debrisoquine hydroxylation phenotyping (Price Evans *et al.*, 1980) and could be classified, excepting the father, as poor metabolisers for debrisoquine hydroxylation.

Polymorphic variation of drug hydroxylation is probably an enzymatic defect (Davies *et al.*, 1981) inherited as a single autosomal recessive trait (Price Evans *et al.*, 1980). Usually, subjects classified as poor metabolisers present merely an abnormal pharmacokinetics pattern of the drug and the direct clinical relevance of these blood concentration variations is often difficult to establish. With bufuralol a typical profile of side-effects emerges in poor metabolisers. We confirmed this finding in an additional study of 58 unselected caucasian volunteers. In this series 5 subjects (= 8.6%) were poor metabolisers for bufuralol. The same 5 subjects, and they alone, were found to be poor metabolisers for debrisoquine, a percentage comparable to the