ACQUIRED TOLERANCE TO DILATOR ACTION OF HYDRALLAZINE DURING ORAL ADMINISTRATION

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1 The effect on forearm blood flow of local intra-arterial infusion of hydralazine has been studied in twelve patients with essential hypertension and six normal subjects.

2 When the patients with hypertension were not taking hydralazine by mouth, they responded to intra-arterial infusions with a dose-dependent increase in forearm blood flow that was not significantly different from that in normal subjects.

3 When the patients were taking hydralazine by mouth, the increase in forearm flow in response to intra-arterial infusions was reduced and forearm vascular resistance did not fall as low as it did in the control study ($P < 0.01$).

4 In four patients, the response to intra-arterial hydralazine was attenuated to a major extent, and in three of these, there was little or no response to oral treatment. In eight patients, the response to intra-arterial hydralazine did not fall below one half of that in the control study and this minor reduction in sensitivity might be expected to impair, but not abolish, the response to oral treatment.

5 It is concluded that the resistance vessels commonly develop tolerance to the dilator action of hydralazine during long-term oral therapy. In some patients a high degree of tolerance develops and this is an important cause of failure to respond to oral treatment.

Introduction

The reduction in arterial pressure that results when hydralazine is given orally in the treatment of hypertension is less, and in some patients very much less, than would be expected from the results of intra-arterial (Åblad, Johnsson & Henning, 1961; Collier, Lorge & Robinson, 1978) or intravenous administration (Sannerstedt, Stenberg, Vedin, Claes & Werkö, 1972). The relatively small response to oral hydralazine can be accounted for only in part by factors such as metabolic inactivation during absorption and the operation of compensatory mechanisms that increase cardiac output. Failure to reduce peripheral resistance by as much as would be expected suggests that the arteriolar smooth muscle develops resistance to the dilator action of hydralazine during long-term oral treatment. We have investigated this possibility by examining the effect of oral treatment with hydralazine on the sensitivity of the forearm arterial bed to local infusions of the drug.

Methods

Studies were performed in six subjects who were both healthy and normotensive and fourteen patients with essential hypertension; clinical details are shown in Tables 1 and 2. All patients with hypertension were receiving a β -adrenoceptor blocking agent and a

diuretic; a few were also receiving α -methyldopa or an adrenergic neurone blocker. The investigation was approved by the Ethical Committee of St George's Hospital.

Forearm blood flow was measured by venous occlusion plethysmography using temperature compensated mercury-in-rubber strain gauges (Whitney, 1953), and drugs were infused into the brachial artery through a 26 SWG needle as described in detail previously (Collier *et al.*, 1978).

Hydralazine was infused into the brachial artery over a 2 min period and forearm blood flow was measured every 10 min for 30–40 min; the increase in flow 30 min after the dose was taken as the response. In most studies, a second, larger dose of hydralazine was given 40 min after the first, and in a few studies, a third dose was given after a further 40 min. In some patients the response to glyceryl trinitrate, sodium nitroprusside or adenosine triphosphate was assessed before giving the hydralazine; in each case, the drug was infused for 3 min periods at increasing dose levels to obtain a cumulative dose response curve.

Assessment of dose-response curves to intra-arterial hydralazine during oral administration

If the forearm arterial bed is already responding to an oral dose of hydralazine, the response to an

additional intra-arterial dose will appear reduced even if the sensitivity is unchanged. This effect has been allowed for by assuming that sensitivity is unchanged and that any decrease in forearm vascular resistance compared to the control study reflects the effect of the oral dose. The observed change has been used to establish the point on the control intra-arterial dose response curve that represents the new baseline. The percentage increase in flow that would be expected in response to incremental doses of 200 and 800 µg hydralazine has then been calculated.

Assessment of clinical response

The effectiveness of oral hydralazine in lowering arterial pressure was graded as:

- 0 = reduction in calculated mean arterial pressure of less than 10%
- + = reduction in calculated mean arterial pressure of 10% or more.

Drugs

The drugs used were hydralazine (Apresoline, Ciba), sodium nitroprusside (Nipride, Roche) and adenosine triphosphate (Adenotriphos, Rona). Glyceryl trinitrate was prepared in a form suitable for parenteral administration by the pharmacy of St George's Hospital.

Statistics

The Wilcoxon test (for paired or unpaired data as appropriate) was used to test the significance of differences between means.

Results

Normal subjects

The six normal subjects showed a dose-dependent increase in forearm flow 30 min after the intra-

arterial infusion of hydralazine (Table 1). In one subject, an attempt was made to induce tolerance acutely by giving an initial dose of 200 µg and then infusing the drug continuously at 5 µg/min for 150 min, following which a further dose of 200 µg was given; there was no reduction in sensitivity. Three of the subjects took hydralazine by mouth in a dose of 50 mg twice daily for 2 weeks and the intra-arterial study was then repeated. In two subjects the percentage increase in forearm flow exceeded that expected after allowing for the effect of the oral dose, but in the third it was reduced to about half; on average there was no change.

Hypertensive patients

Paired studies of the response to intra-arterial hydralazine were obtained in twelve patients; at the time of the control study, eight patients had never received hydralazine and in the other four it had been withdrawn for a minimum of 6 days. When they were not taking hydralazine by mouth, the patients showed an increase in forearm flow 30 min after intra-arterial hydralazine that was not significantly different from that in normal subjects (Table 2). When the patients were taking hydralazine, the increases in forearm flow were less in all patients except one, and the reduction in response was significant ($P < 0.01$). The observed responses were compared with the reduced responses predicted by allowing for the effect of the preceding oral dose. In two patients, the response was about the same as that predicted and in a further six it was half or more of the predicted value. In four patients, however, the response was attenuated to between 1/4.5 and 1/80 of that predicted, and the grossly impaired response in patient 14 (in whom no control study was obtained) suggests that she too had a greatly attenuated response.

In order to make sure that the reduced responses

Table 1 Response to intra-arterial hydralazine in normal subjects.

Subject	Age (years)	Sex	Acetylator phenotype	Oral hydralazine (mg/day)	% increase in forearm flow after i.a. hydralazine		Ratio of observed to predicted response
					200 µg	800 µg	
BR	48	M	Fast	—	245	727	1.3:1
				100	268	651	
JC	36	M	Fast	—	225	743	1:2
				100	102	—	
RD	34	M	Fast	—	132	412	1.5:1
				100	105	—	
PA	42	M	—	—	93	670	
TB	36	M	—	—	140	739	
RL	26	M	—	—	345	705	
Mean (no oral hydralazine)					197	666	

Table 2 Response to intra-arterial hydralazine in patients with hypertension

Patient	Age (years)	Sex	Acetylator phenotype	Oral hydralazine (mg/day)	% increase in forearm flow after i.a. hydralazine			Ratio of observed to predicted response	Clinical response to oral hydralazine
					200 µg	800 µg	3200 µg		
1	48	M	Slow	—	87	571	—	—	—
2	60	F	Fast	100	4	36	56	1:4.5	+
3	51	M	Fast	300	35	108	226	1:8	○
4	56	M	Slow	100	479	—	—	1:2	+
5	52	M	Slow	150	248	854	93	1:80	○
6	52	M	Fast	100	152	336	—	1:2	+
7	61	M	Slow	200	1	4	—	1:1	+
8	55	M	Fast	100	69	705	—	1:2	+
9	49	F	Slow	200	42	109	273	1:2	+
10	48	M	Slow	100	198	1792	—	1:1	uncertain
11	30	M	Slow	200	58	181	—	1:1	○
12	45	M	Slow	100	316	661	84	1:14	○
Mean (no oral hydralazine) (on oral hydralazine)					349	610	—	1:2	+
13	69	F	—	—	163	570	—	1:2	+
14	47	F	—	150	150	502	501	1:2	+
					447	1569	—	1:2	+
					24	111	—	1:2	+
					512	1968	—	1:2	+
					99	187	—	1:2	+
					90	334	295	1:2	+
					21	200	—	1:2	+
					212	759	—	1:2	+
					67	278	—	1:2	+
					250	927	—	—	Hydralazine not given
					92	222	—	—	uncertain
					167	402	—	—	Hydralazine not given
					—	—	<45	—	uncertain

Figure 1 Forearm vascular resistance 30 min after highest dose of hydralazine that was given intra-arterially in studies both on and off oral hydralazine. Forearm vascular resistance was calculated by dividing mean arterial pressure (mm Hg) by forearm blood flow ($\text{ml min}^{-1} 100 \text{ ml}^{-1}$ forearm).

did not result simply from the dilator effect of the oral dose, the results were also analysed by calculating the level to which forearm vascular resistance had fallen 30 min after the highest dose that was given in both studies (Figure 1). In all patients except one, forearm vascular resistance did not fall so low when the drug was being taken by

mouth as it had done in the control study; the absolute response was thus *smaller* despite the delivery of a *greater* total dose of hydralazine to the forearm, and this confirms the appearance of tolerance. The two methods of analysis agreed well since the four patients who showed a major attenuation of response by the first method were among the five who showed a major attenuation by the second. In patient 4, who had previously been shown to develop a high level of tolerance while taking the drug by mouth, an attempt was made to induce tolerance acutely. A dose of $800 \mu\text{g}$ was given intra-arterially and 110 min later when the response had waned, a further dose of $800 \mu\text{g}$ was given; the response to the second dose was not reduced.

Response to other dilator drugs

The response to intra-arterial sodium nitroprusside or glyceryl trinitrate was examined in seven patients who were taking hydralazine by mouth and in six patients who were not (Table 3); in all patients, the increases in forearm blood flow were within, or slightly above, the range previously found in normal subjects (Collier *et al.*, 1978; Robinson, Collier & Dobbs, 1979). The patients taking hydralazine included four in whom the response to that drug was greatly reduced.

In three normal subjects and two patients, the response to intra-arterial adenosine triphosphate was studied while on and off oral hydralazine; no consistent changes were found.

Discussion

The dilator effect of hydralazine is unusual in that its action is delayed and the response to a brief intra-arterial infusion takes 30–60 min to reach its peak (Collier *et al.*, 1978). The time course appeared similar in the patients with hypertension to that in normal subjects and it therefore seems justified to take the 30 min response as the basis for comparisons.

The results indicate that patients with hypertension have a normal sensitivity to hydralazine when they are not taking the drug by mouth. The exceptionally large percentage increases observed in three patients are unlikely to reflect a true increase in sensitivity: all three patients had unusually low forearm blood flow at rest (less than $1 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$) and the maximum flow achieved was less in absolute terms than that in most of the normal subjects. During long-term oral treatment with hydralazine the response to intra-arterial infusions is usually reduced and it appears that a variable degree of tolerance develops. In about two-thirds of the patients studied, the degree of tolerance was no more than slight, but

Table 3 Response to intra-arterial glyceryl trinitrate and sodium nitroprusside in patients on and off oral hydralazine

Patient	% increase in forearm flow			
	No hydralazine		Oral hydralazine	
	Glyceryl trinitrate (ng/min)			
	200	400	200	400
1	45	68		
2	110	162		
3	67	148		
4			54	96
	Sodium nitroprusside (ng/min)			
	200	400	200	400
1			56	79
2			53	112
10	89	172	107	163
11			11	42
12	55	85	35	56
13	35	42		
14			67	123

in one third it was considerable. The reduction in responsiveness appeared specific to hydralazine and it did not extend to any of the other dilator substances studied.

Tolerance to hydralazine has not previously been reported, but it is well recognized with glyceryl trinitrate and other organic nitrates (Schelling & Lasagna, 1967). The absence of tolerance to glyceryl trinitrate in a patient who had developed major resistance to hydralazine suggests that the mechanisms of tolerance are different. Similarly, the observation that oral hydralazine has no consistent effect on the response to adenosine triphosphate gives no support to the suggestion that hydralazine exerts its effect through a receptor for adenosine triphosphate (Worcel, 1978).

It was not possible to carry out a sufficient number of studies in individual patients to define the time course of the appearance and disappearance of tolerance. Since tolerance was never observed in the course of intra-arterial studies it can be concluded that it takes more than 2–3 h to appear and it seems likely that it develops over a period of a few days. Tolerance is reversible, and withdrawal of the drug for 6 days was sufficient for sensitivity to be restored to the normal range. The patients were all taking antihypertensive agents other than hydralazine, but in most cases these drugs were not changed in any way between studies and it seems unlikely that they contributed to the induction of tolerance. It seems probable that, as with other drugs, the development of tolerance is a function of both the concentration of hydralazine and the duration of the exposure. This may account for the failure to induce tolerance in the normal subjects since they received only 100 mg hydralazine per day and all three were fast acetylators; the effective dose would thus have been lower than that in any patient who achieved significant tolerance. A relation between dosage and the induction of tolerance would also account for the failure of hydralazine to reduce arterial pressure in some patients despite its use in doses of up to 800 mg/day (Gottlieb, Katz & Chidsey, 1972).

The importance of acetylator phenotype in determining the effectiveness of oral treatment with

hydralazine is widely recognized. The drug is well absorbed, but a substantial fraction is inactivated in the gut or liver, largely by acetylation, so that less than half of an oral dose gains entry to the systemic circulation (Reidenberg, Drayer, De Marco & Bello, 1973). The proportion inactivated varies with the acetylator phenotype of the individual and the plasma levels achieved after a standard oral dose are more than 50% higher in subjects who are slow acetylators than in those who are fast (Zacest & Koch-Weser, 1972). A poor response to a given dose of hydralazine may therefore be accounted for by fast acetylation and one patient in the present study who showed a very poor response was found to be a fast acetylator who had not developed a high degree of tolerance. It would be expected that the effects of fast acetylation could be overcome by increasing the oral dose by about 50% and it should therefore not prove a serious obstacle to effective treatment.

The present study indicates that the development of tolerance is also an important factor in determining the effectiveness of long-term treatment with hydralazine. In eight of the patients studied, tolerance was no more than minor in degree, and, at the lower end of the dose response curve, no more than a twofold increase in dose would be needed to restore the original response. In all except one of these patients (a fast acetylator), the clinical response was satisfactory. In four of the patients, however, tolerance was major in degree, and in three of these a sixteenfold increase in the intra-arterial dose failed to restore the original response. In none of these three patients was the clinical response satisfactory, and tolerance of this degree could only be overcome by increasing the dose of hydralazine to levels that carry an unacceptable risk of long-term immunological side effects. The development of a major degree of tolerance thus presents an insuperable barrier to the effective treatment of hypertension with hydralazine.

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