Blood Pressure in Patients with Hypertension Following Intramuscular Chlorpromazine.* (21214)

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The effectiveness of chlorpromazine as an antiemetic agent(1,2,5) has resulted in extensive clinical trials of the drug to combat nausea and vomiting produced by drugs, irradiation and various disease states. Prior to its use in combination with antihypertensive agents, which not infrequently induce nausea and vomiting as undesirable side effects, it seemed worthwhile to evaluate the action of chlorpromazine alone on the blood pressure of hypertensive man.

Methods. Ten adults, 7 males and 3 females, with persistent benign essential hypertension were studied in the postprandial state. Fourteen separate injections of chlorpromazine in a range of dosage from 25 to 100 mg were given deep in the gluteal region. Blood pressures were measured in the arm with a mercury sphygmomanometer. The pulse rates and subjective manifestations were also recorded. Control observations on the pulse and blood pressure were made every 15 minutes for 1½ hours with the patient recumbent and during quiet standing. Similar observations were continued at 15 minute intervals for 3 hours after administration of the drug and subsequently at 30- to 60-minute intervals for an additional 3 to 7 hours.

Results. The effect of intramuscular chlorpromazine on the blood pressure, the average values for recumbent and standing blood pressures as well as the range of measurements during the control period are shown in the table. The standing blood pressure after intramuscular chlorpromazine in each instance is the lowest pressure observed during the experimental period and represents the maximal hypotensive effect. The recumbent pressure occurring concomitant with the maximal hypotensive effect is also recorded. The most striking action was the development of postural hypotension. The lowering of the standing blood pressure was apparent within 15 to 30 minutes after chlorpromazine was given, but the maximal effect did not occur until 3 to 4 hours had elapsed. The systolic pressure usually fell to normal or subnormal level and with 4 exceptions was accompanied by a similar lowering of the diastolic pressure. Recumbent pressures showed no significant change from those recorded during the control period. Even in this small series some variation in dose response is apparent.

All the patients experienced drowsiness, usually mild, and particularly with a dose of 50 mg or more. Patients 2, 3, 4, 7 and 8 complained of dizziness on standing at the time of the maximal hypotensive effect. In no instance did syncope occur and the dizziness was promptly relieved by resuming the recumbent position. In patients 3 and 4 the complaint of dizziness was relieved by mild exercise (slow walking), although this produced no remarkable change in the standing blood pressure or pulse rate. Compensatory tachycardia during standing was not a prominent feature and consisted of an increase in the pulse rate of 10 to 40 per minute. The blood pressure changes in patient 5 are presented in Fig. 1 to illustrate the typical response to chlorpromazine.

Discussion. To our knowledge, this is the first study demonstrating a consistent orthostatic fall in blood pressure following intramuscular administration of chlorpromazine to hypertensives. Previous investigations(3-5) have shown only a negligible effect of average doses on the blood pressure of the anesthetized dog and an occasional episode of transient postural hypotension in man following intramuscular administration of large doses. Two recent reports(6,7) describe the use of chlorpromazine in psychiatric disorders and men-

* Generously supplied by the Smith, Kline and French Laboratories. "Chlorpromazine is the generic name for SKF 2601-A, RP 4560, 'Largactil', 'Megaphen', 'Ampliactil', and the U. S. Trade Name 'Thorazine'."

TABLE I. Effect of Intramuscular Chlorpromazine on Blood Pressure of 10 Hypertensives.

	Blood pressure					
	Pre-injection				Minimal post-inj.	
	Recumbent		Standing			
Dose, mg	Avg	Range	Avg	Range	Recumbent*	Standing
100	172/113	165/110–190/120	152/110	145/110–162/110	170/120	125/105
75	187/120	185/120–190/120	185/122	175/120–180/125	170/120	125/110
50	169/108	158/102–180/120	165/116	158/114–178/120	170/118	100/ 68
50	210/106	194/100–222/108	196/110	188/104–200/115	160/100	80/ 50
50	213/111	200/100–220/118	188/118	162/118–218/120	210/110	100/ 60
25	239/125	232/120–246/128	210/128	204/128–212/130	210/120	130/ 80
50	232/124	225/120–240/140	214/136	210/120–230/140	202/108	112/ 80
50	231/143	220/140–246/150	212/152	210/150–228/155	220/130	100/ 80
25	232/116	222/110–242/130	217/127	210/126–236/130	228/128	176/120
50	224/118	214/118–234/118	203/125	190/120–230/130	190/116	142/108
25	233/130	230/128–240/130	197/123	192/120–200/128	164/ 98	118/ 80
25	190/103	180/ 92–200/120	167/112	148/ 98–180/120	160/ 94	128/ 90
50	190/110	182/110–202/110	172/117	158/108–192/130	144/ 98	90/ 70
50	196/106	195/100–200/120	174/100	162/ 94–180/116	188/ 98	96/ 76

* Immediately preceding lowest standing B. P.

tion postural hypotension as a prominent side effect following both oral and intramuscular administration of the drug, but no data on changes in blood pressure are presented.

The absence of a significant change in the recumbent blood pressure implies that the principal action of the drug is through the blockade of barostatic reflexes which normally sustain the blood pressure during standing. Pharmacological investigations of the cardiovascular actions of chlorpromazine have revealed that the drug has adrenolytic effects. Courvoisier *et al.*(3), who demonstrated an antagonistic action of chlorpromazine to the pressor effects of epinephrine and nor-epinephrine infusions, also found that the drug abolished the pressor response to carotid occlusion and central vagus stimulation. The adrenolytic action of chlorpromazine has been confirmed by Finkelstein *et al.*(8) and Melville (9). It should be emphasized, however, that the mechanism of action of the drug on blood pressure remains poorly defined.

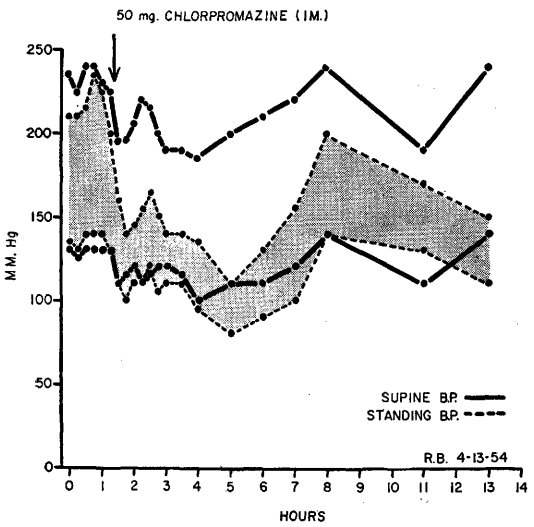

FIG. 1. Action of chlorpromazine on blood pressure of a 45-year-old colored male with hypertension. Note fall in systolic and diastolic pressures in standing position with inconsistent changes in recumbent pressures.

The postural effect of chlorpromazine in hypertensives may have clinical implications. Its effect on the blood pressure is similar to that of ganglionic blocking agents such as hexamethonium and it produces little or no change on the blood pressure during recumbency. The drug may be of value in combination with other antihypertensive agents whereby its hypotensive and antiemetic properties may be utilized to advantage.

Summary. Chlorpromazine, in an average dose of 50 mg, was administered by the intramuscular route to 10 human hypertensives. The drug was found to produce a significant decrease in blood pressure during standing, and in some instances, postural hypotension. Blood pressure in the recumbent position showed no significant change.

1. Friend, D. G., and Cummins, J. F., *J.A.M.A.*, 1953, v153, 480.

2. Brand, E. D., Harris, T. D., Borison, H. H.,

and Goodman, L. S., *J. Pharm. and Exp. Therap.*, 1954, v110, 86.

3. Courvoisier, S., Fournel, J., Ducrat, R., Kolsky, M., et Koetschet, P., *Arch. internat. de pharmacodyn. et de thérap.*, 1953, v92, 305.

4. Moyer, J., Kent, B., Knight, R., Morris, G., Huggins, R., and Handley, C. A., *Am. J. M. Sc.*, 1954, v227, 283.

5. Information published by Smith, Kline and French Laboratories.

6. Lehmann, H. E., and Hanrohan, G. E., *Arch. Neurol. and Psychiat.*, 1954, v71, 227.

7. Winkelman, N. W., *J.A.M.A.*, 1954, v155, 18.

8. Finkelstein, M., Spencer, W. A., Hamman, C. S., and Albert, S. N., *Fed. Proc.*, 1954, v13, 354.

9. Melville, K. I., *Fed. Proc.*, 1954, v13, 386.

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Conjugated Steroids V. Hydrolysis of Total Ketosteroids in Urine.* (21215)

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Numerous attempts have been made to effect a complete nondestructive hydrolysis of ketosteroids without affecting in any way the nature of the steroids. It has been possible to hydrolyze the ketosteroid glucuronides under mild conditions with enzymes prepared from bacteria(1) or spleen(2). Recently, Cohen and Oneson have described the hydrolysis of ketosteroid sulfates with dioxane-trichloroacetic acid(3). About 40% of the total ketosteroids of normal male urine are apparently conjugated as sulfates, of which slightly more than half is of the beta configuration. The sum of the ketosteroid sulfates and glucuronides exceeds the value obtained by routine hydrochloric acid hydrolysis by about 15%. This paper describes the hydrolysis of the total ketosteroids by the use of dioxane-HCl.

Methods. Urine residues are prepared in the same manner as for the hydrolysis of the ketosteroid sulfates(3). This involves extraction with butyl alcohol of acidified (pH 2-3) urine. The extract is washed with water and evaporated to dryness at temperatures not exceeding 60°. Portions of the butyl alcohol residues equivalent to 100 to 200 cc of urine are hydrolyzed by the addition of 10 cc of 1,4 dioxane containing 10% of concentrated hydrochloric acid. The alpha and beta fractions are assayed after their separation with digitonin according to the method of Frame (4).

Results. A concentration of acid which

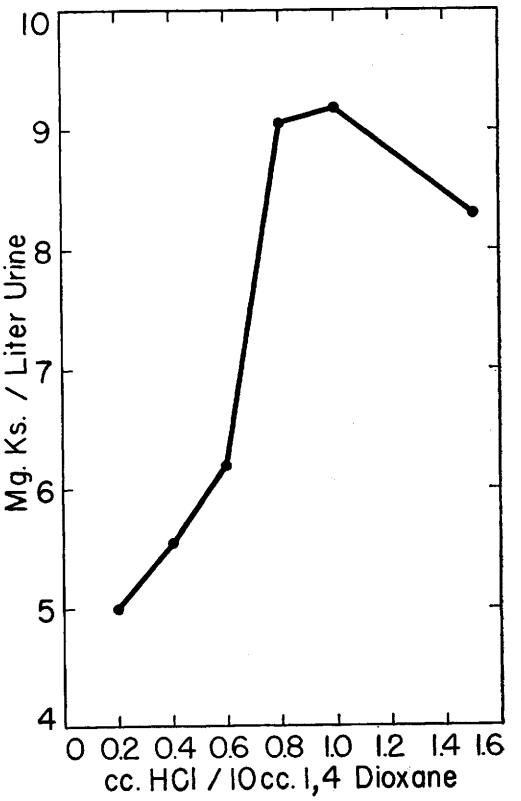

FIG. 1. Release of ketosteroids by dioxane HCl.

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