Cardiovascular Effects of Sedative Doses of Pentobarbital and Hydroxyzine

Thorkild W. Andersen, M.D. and J. S. Gravenstein, M.D.†*

Sedative doses of hydroxyzine or pentobarbital were tested in healthy volunteers in whom a challenging dose with mephentermine was employed to bring out subtle effects of these two drugs on the cardiovascular system. Both pentobarbital and hydroxyzine had significant cardiovascular effects. Pentobarbital increased systolic blood pressure and cardiac output while hydroxyzine decreased heart rate and cardiac output. Only hydroxyzine modified the effect of mephentermine on the circulation.

PREANESTHETIC medication with sedatives is widely practiced and it is generally believed that mild sedation produced with drugs such as pentobarbital (Nembutal) and hydroxyzine (Vistaril) has no important cardiovascular consequences. However, there is no information as to whether pentobarbital and hydroxyzine given in the usual low therapeutic doses have mild effects which, in turn, may modify the response of the body to other drugs subsequently given, and which may, in occasional patients, lead to unexpected reactions. The properties of hydroxyzine suggested that small cardiovascular changes might follow the administration of a therapeutic dose since, in the cat, hydroxyzine reduced the pressor response to epinephrine.[1] This effect was likened to the action of chlorpromazine. Hutcheon *et al.*[1] believed that hydroxyzine has weak vagolytic actions. It is conceivable, therefore, that preanesthetic medication with hydroxyzine could modify the response to a subsequently given sympathomimetic amine. Pentobarbital has been studied extensively in animals and it appears that small doses (5 mg./kg.) are capable of depressing cardiovascular responses, presumably at a central level.[2]

* Associate Professor, Department of Anesthesiology, College of Medicine, University of Florida, Gainesville, Florida.

† Professor and Chairman, Department of Anesthesiology, College of Medicine, University of Florida, Gainesville, Florida.

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Methods

Fourteen healthy, fasting male students volunteered for the experiment. Commercially available sodium pentobarbital (Nembutal), hydroxyzine (Vistaril), and mephentermine (Wyamine) were employed.

Subjects were studied twice. All drugs were given as single intravenous injections. In the first experiment, 3 of 6 of the subjects were given 0.4 mg. mephentermine base/kg. body weight, and 20 minutes later the first of 3 doses of pentobarbital. The doses were 0.15 mg./kg., 0.3 mg./kg. and 1.5 mg./kg., respectively, always given in the same sequence at 5-minute intervals. After the third dose observations were continued for 30 minutes. On another day, the same 3 subjects were given pentobarbital in the identical 3-dose schedule. Thirty minutes after the last dose, mephentermine 0.4 mg./kg. was injected and measurements were made for an additional 20 minutes. Three of the 6 subjects received the pentobarbital-mephentermine sequence in the first session and the reverse sequence later; three were tested by the mephentermine-pentobarbital sequence first and the reverse later. Another group of 8 subjects was tested in an identical manner, but hydroxyzine was substituted for pentobarbital. The doses of hydroxyzine were 0.15 mg./kg., 0.3 mg./kg. and 1.5 mg./kg., and the dose of mephentermine, 0.4 mg./kg. Again sequences were alternated. Arterial pressure were measured in the radial artery through an 18 gauge Cournand needle and a Statham transducer. Arterial pressure and the ECG were recorded continuously on a Grass polygraph. For the drug injections, a 17 gauge plastic catheter in the subclavian vein was kept patent throughout

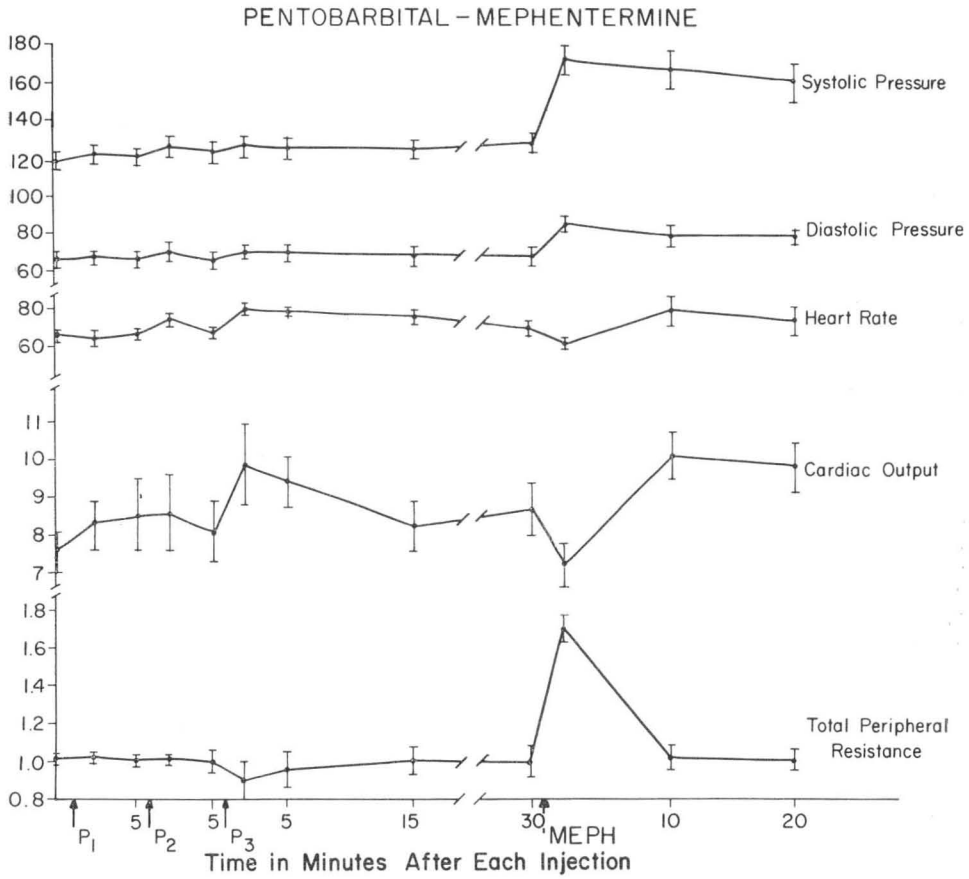

FIG. 1. Six subjects were given three graded doses of pentobarbital intravenously (P_1, P_2, P_3) and thirty minutes after the last dose of pentobarbital an injection of mephentermine. Mean values ± one standard error of the mean are shown. For dosages see text. The blood pressure is measured in mm. of mercury, heart rate in beats per minute, cardiac output in liters per minute and total peripheral resistance in arbitrary units. The abscissa shows the times when recordings were made.

the study by a slow intravenous infusion of 5 per cent dextrose in water. Cardiac output was determined by means of the dye dilution technique with indocyanine green (Cardio-Green *) and a Colson densitometer. Blood pressure, cardiac output and heart rate were measured immediately before and 96 seconds after each drug injection and every 5 to 15 minutes thereafter.

Total peripheral resistance was estimated by dividing mean arterial pressure by cardiac output and expressed in arbitrary units. The mean arterial pressure was assumed to be equal to the diastolic plus one-third of the pulse pressure. Stroke volume was assumed to equal cardiac output divided by heart rate. For the statistical analyses paired and unpaired two-tailed Student's *t*-tests were computed.[3]

Results

Figures 1 and 2 present the mean values from 6 experiments obtained with pentobarbital. Inspection of these curves shows the mephentermine effect clearly, but not an obvious effect from pentobarbital. Significant effects from pentobarbital, however, did exist. Thus, medication with the three doses of pentobarbital led to a statistically significant

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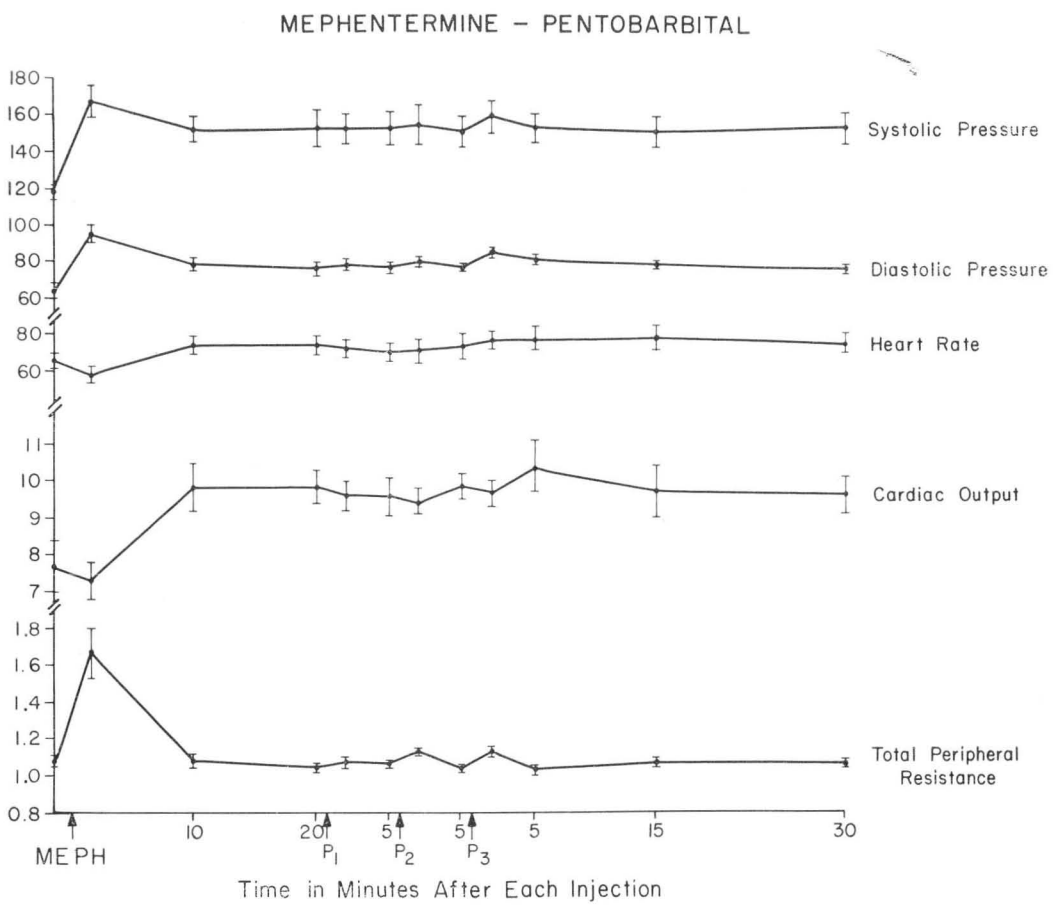

FIG. 2. Data from the same subjects shown in figure 1 except that here mephentermine was given first, followed by the same three doses of pentobarbital.

TABLE 1. Effect of Pentobarbital

	Mean Difference	t	P
SBP	+ 9.1	3.90	0.02
DBP	+ 0.8	0.72	0.50
MAP	+ 3.1	2.17	0.10
HR	+ 4.5	2.10	0.10
CO	+ 1.06	2.65	0.05
TPR	− 0.11	0.33	0.80
SV	+10.1	1.55	0.20

The mean differences obtained by subtracting the values before from the values recorded 30 minutes after the last pentobarbital injection are shown with t and P value.

The following abbreviations are used in all tables: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), and stroke volume (SV).

($P < 0.02$), if not very large, increase in systolic pressure and an increase in cardiac output ($P < 0.05$) (table 1). Pentobarbital did not significantly affect the response to mephentermine.

The mean effects of hydroxyzine alone and of mephentermine after hydroxyzine, as well as hydroxyzine after mephentermine, in 8 subjects, are shown in figures 3 and 4. Hydroxyzine had an effect in its own right as shown in figure 3. Heart rate and cardiac output decreased and total peripheral resistance rose. Statistical analysis (table 2) confirms the fact that the effects of hydroxyzine on heart rate and cardiac output are unlikely to have arisen by chance. Table 3 shows that premedication with hydroxyzine significantly increased and sustained the rise of the

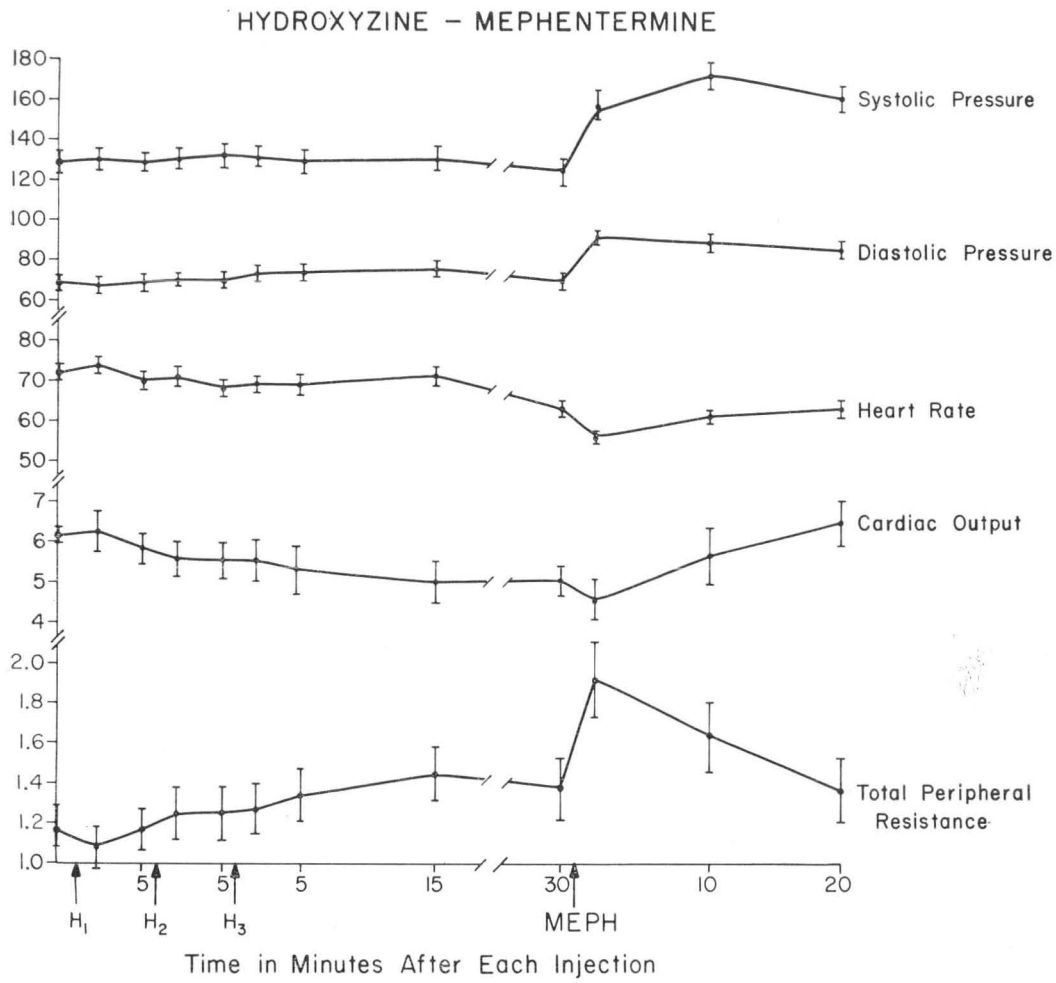

FIG. 3. Eight subjects were given three graded doses of hydroxyzine intravenously (H_1, H_2, H_3) and thirty minutes after the last dose of hydroxyzine, an injection of mephentermine. For dosage see text. Mean values ± one standard error of the mean are shown. The blood pressure is measured in mm. of mercury, heart rate in beats per minute, cardiac output in liters/minute, and total peripheral resistance in arbitrary units. The abscissa shows the time when the drugs were injected.

systolic blood pressure produced by the injection of mephentermine. An analysis of the differences between the 10 minute values and the values 96 seconds after injection of mephentermine, comparing subjects premedicated with hydroxyzine and those not so premedicated showed that premedication with hydroxyzine significantly enhanced not only the rise in systolic but also in diastolic blood pressure.

In a comparison of two groups, chance differences between the groups must be taken into account. For this reason, the analysis of table 4 was undertaken. This shows that the acute mean rise in blood pressure with mephentermine was larger in the group of 6 subjects (pentobarbital group) than in the group of 8 subjects (hydroxyzine group). By chance, the group which had the larger response to mephentermine was tested with pentobarbital and the group with the significantly smaller response to mephentermine was tested with hydroxyzine, yet the hydroxyzine group became significantly more respon-

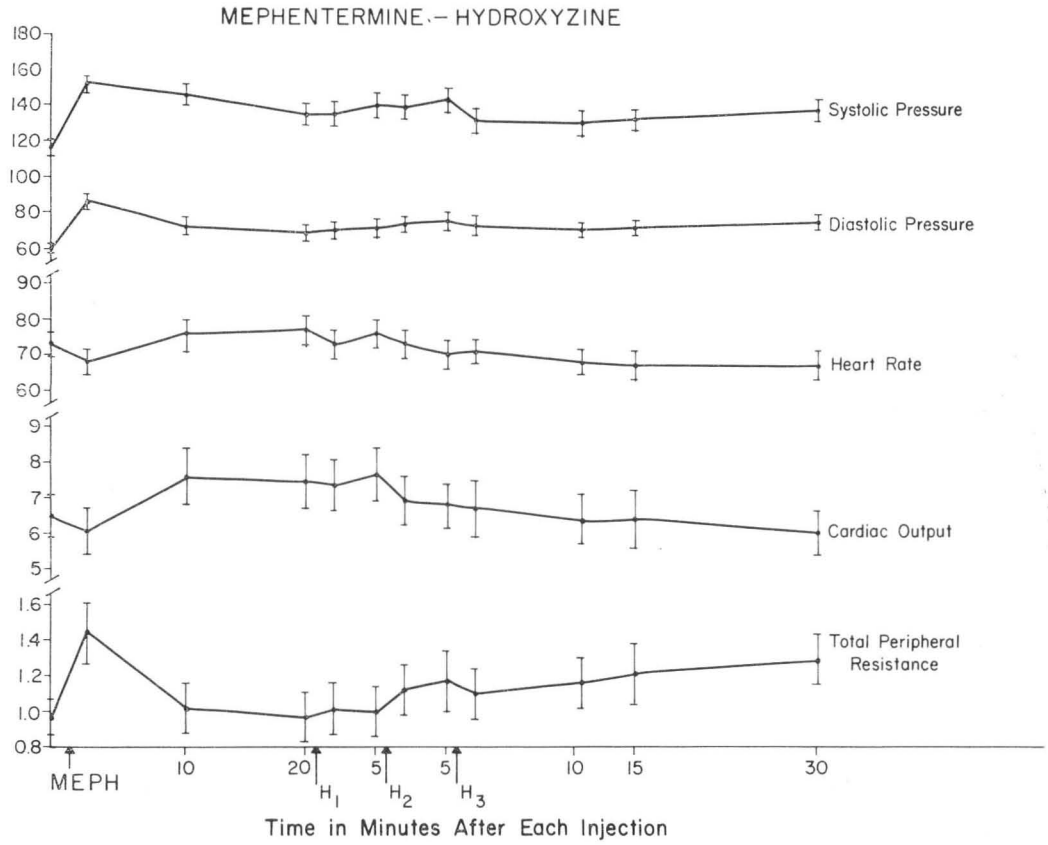

FIG. 4. Data from the same subjects shown in figure 3 except that here mephentermine was given first, followed by the same three doses of hydroxyzine.

sive to mephentermine after pretreatment with hydroxyzine than did the group receiving pentobarbital. The chance differences between the two groups, therefore, worked against the observed differences between hydroxyzine and pentobarbital.

TABLE 2. Effect of Hydroxyzine

	Mean Difference	t	P
SBP	−5.4	0.90	0.40
DBP	+0.5	0.17	0.90
MAP	−1.1	0.31	0.80
HR	−8.4	4.20	0.005
CO	−1.10	4.78	0.005
TPR	+0.19	1.90	0.10
SV	−6.45	2.04	0.10

Eight subjects were given three doses of hydroxyzine. The mean differences obtained by subtracting the "before drug control values" from the values recorded 30 minutes after the last hydroxyzine injection are shown together with t and P value. See text for hydroxyzine dosages.

In table 5 the action of the two sedatives is compared. Pentobarbital increased heart rate, cardiac output and stroke volume significantly more than did hydroxyzine, and hydroxyzine caused a significantly greater increase in total peripheral resistance than did pentobarbital.

Discussion

In the present study hydroxyzine produced cardiovascular effects different from those of pentobarbital. Pentobarbital caused a significant rise in systolic blood pressure and cardiac output and a slight increase in heart rate, whereas hydroxyzine caused significant decreases in heart rate and cardiac output and

TABLE 3. Effect of Hydroxyzine on Mephentermine Action

Time after Injection	96 Sec.			10 Min.			20 Min.		
	Mean Diff.	t	P	Mean Diff.	t	P	Mean Diff.	t	P
SBP	−0.7	0.25	0.90	+21.5	2.80	0.05	+17.3	2.50	0.05
DBP	−3.0	0.80	0.50	+ 8.1	1.52	0.20	+ 9.0	2.00	0.10
MAP	−2.8	0.98	0.40	+13.3	2.15	0.10	+12.1	2.33	0.10
HR	−2.00	0.76	0.50	− 4.80	1.35	0.30	− 4.60	1.12	0.30
CO	+0.01	0.013	0.99	− 0.49	1.44	0.20	+ 0.42	0.91	0.40
TPR	+0.06	1.60	0.20	+ 0.21	2.33	0.10	− 0.02	0.25	0.90

Eight subjects were given 0.4 mg./kg. mephentermine once alone and on a different day after premedication with hydroxyzine. Values recorded immediately before mephentermine injections were subtracted from the values recorded 96 seconds, 10 and 20 minutes after mephentermine injections. The mephentermine effects obtained in unpremedicated subjects were subtracted from the effects determined in subjects premedicated with hydroxyzine and the mean differences are shown together with Student t and P values.

an increase in total peripheral resistance. The difficulty in comparing these two drugs is that no reliable information exists on the relative effectiveness of pentobarbital as compared to hydroxyzine in terms of sedative or hypnotic power. The comparisons presented here can provide no more than an indication that clinical dosages of hydroxyzine are capable of influencing the cardiovascular system in one way, whereas pentobarbital in the dosage tested affected it in another manner.

The effects of hydroxyzine can be secondary to the bradycardia which caused a decrease in cardiac output and a compensatory reflex increase in total peripheral resistance with little change in blood pressure; or it may be assumed that the effects of hydroxyzine were produced by an increase in total peripheral resistance and reflex slowing of the heart with consequent decrease in cardiac output.

The effects of pentobarbital observed were not anticipated. Pentobarbital has traditionally been regarded as a circulatory depressant based on studies with anesthetic doses in animals or organ preparations. There is no information regarding the cardiovascular effects of pentobarbital in normal subjects. The increase in cardiac output observed in this experiment may be the result of centrally mediated or direct positive chronotropic action. In the absence of a significant decrease of total peripheral vascular resistance, an increase in blood pressure would result. Pentobarbital anesthesia in dogs causes similar changes.[4] It

TABLE 4. Differences in Response to Mephentermine Between Groups

Time after Injection	96 Sec.			10 Min.			20 Min.		
	Mean Diff.	t	P	Mean Diff.	t	P	Mean Diff.	t	P
SBP	+15.7	2.83	0.02	+8.0	1.20	0.30	+15.3	1.99	0.10
DBP	+ 7.0	2.24	0.05	+3.4	0.92	0.50	+ 5.6	1.58	0.20
MAP	+10.0	2.91	0.02	+5.0	1.10	0.30	+ 8.7	1.84	0.10
HR	+ 2.50	0.97	0.40	+2.00	0.48	0.70	+ 4.38	1.13	0.40
CO	− 0.04	0.07	0.95	+1.00	1.90	0.10	+ 1.14	2.39	0.05
TPR	+ 0.11	0.73	0.50	−0.04	0.42	0.70	− 0.04	0.04	0.98
SV	+ 6.00	0.66	0.60	+4.66	0.69	0.50	+ 7.91	1.02	0.40

The effects of mephentermine obtained in a group of 6 subjects are compared with those of another group of 8. The groups differed significantly in the response to a standard dose of mephentermine, in respect to blood pressure and cardiac output at different times. Positive values indicate the larger response in the group of 6 subjects.

TABLE 5. Effect of Pentobarbital Versus Effect of Hydroxyzine

	Mean Difference	t	P
SBP	+14.5	2.03	0.10
DBP	+ 0.3	0.09	0.95
MAP	+ 4.2	0.21	0.90
HR	+12.9	4.38	0.001
CO	+ 2.16	4.96	0.001
TPR	− 0.30	2.34	0.05
SV	+16.55	2.48	0.02

The differences between values recorded 30 minutes after the last hydroxyzine injection and the control values were subtracted from the corresponding values obtained in the subjects medicated with pentobarbital. The table indicates that pentobarbital caused a greater rise (or lesser fall) than hydroxyzine in all values with a positive sign.

is remarkable that in our subjects pentobarbital did not modify the response to mephentermine.

How much of the observed effects and interactions of pentobarbital and hydroxyzine were the result of central and how much of peripheral effects remains unknown. This remains to be studied in the experimental animal.

Summary

Small doses of hydroxyzine and pentobarbital were tested in healthy volunteers in whom a challenging dose with mephentermine was employed to bring out subtle effects of these two drugs on the cardiovascular system. Both pentobarbital and hydroxyzine had significant but differing cardiovascular effects. Only hydroxyzine modified the effect of mephentermine on the circulation. It enhanced and sustained the pressor effect of mephentermine.

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TRANSFUSION HEPATITIS Of 538 reported cases of transfusion-associated viral hepatitis, whole blood was received by 97 per cent and was the only material administered to 90 per cent. Single-unit transfusions accounted for 17 per cent of all cases. Since the risk of hepatitis generally increases with the number of units administered, proper emphasis should be upon reducing blood use at all levels rather than simply eliminating the single-unit transfusion. Risk of hepatitis following transfusion of pooled plasma and fibrinogen appears to be appreciably higher than that attributable to whole blood. Risk of hepatitis following administration of fibrinogen appears to be even greater than that following plasma. The only indications for the use of fibrinogen are specific deficiencies of this factor or of antihemophilic globulin. The all-age fatality rate was 11.2 per cent, and mortality was 5.5 per cent among persons under 40 years of age. (*Mosley, J. W.: Surveillance of Transfusion-Associated Viral Hepatitis, J.A.M.A. 193: 1007 (Sept. 20) 1965.*)