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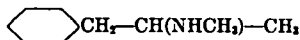
## THE USE OF METHEDRINE AS A VASOCONSTRICTOR WITH SPINAL ANESTHESIA \*

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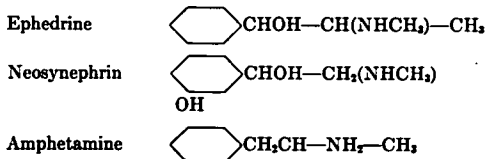
THIS is a preliminary report of some of the results of a study of one of the newer vasoconstrictors—"methedrine hydrochloride"—used to support blood pressure during spinal anesthesia. As a control, a similar study was made of a group of patients to whom ephedrine was given. I am also including a group who received neosynephrin, for further comparison.

Methedrine † is the trade name of Burroughs Wellcome and Co. for d-desoxyephedrine. It has the chemical formula



It is also described as N-Methylamphetamine or methylbenzedrine (d-phenylisopropylmethylamine) (1). The levo form is comparatively inactive while the racemic form is intermediate.

Ephedrine, neosynephrin and amphetamine are structurally very similar:



\* From the Department of Anesthesia, The Samuel Merritt Hospital, Oakland, Calif.

† The Methedrine used in this study was supplied through the courtesy of Burroughs Wellcome & Co.

Methedrine or d-desoxyephedrine was first prepared by Ogata in 1919 but it received little attention until 1938 when the Germans advocated it as superior to amphetamine for its central euphoric and waking effects. The emphasis has been on this effect, but in December, 1943, Dodd and Prescott (2), of London, reported on their use of methedrine as a peripheral vasoconstrictor, to support blood pressure during surgical operations.

They used methedrine to restore blood pressure in 54 of 130 patients undergoing surgery; "anesthetics included all those in common use." They used doses from 15 to 30 mg. intramuscularly or 10 to 20 mg. intravenously. In most instances the intramuscular route was used. In 97 per cent of their cases the systolic pressure was raised, in from two to eighteen minutes, from an average of 67 mm. to an average of 135 mm. from where it settled to an average of 124 mm., or 91 per cent of the average preoperative level (137 mm.) One injection sufficed in 81 per cent of cases. In 2 per cent there was no response. They considered methedrine to be, clinically, superior to adrenalin, ephedrine and pholderin as a pressor agent. They state that its effect lasts from one to six hours in most instances and report one case in which it lasted for forty-eight hours.

#### PHARMACOLOGY

Since most investigators have been interested in the general stimulant effect of d-desoxyephedrine, the majority of reports are concerned with its primary action of elevation of the mood, increase in the urge to work and combating sleepiness and fatigue. The Germans have remarked favorably of its action in elevating the mood of patients after operation or of persons suffering from chronic disease. For these purposes it is used in doses of 3 to 9 mg.

It counteracts alcoholic intoxication without affecting the concentration of alcohol in the blood and doses of 15 mg. or more parenterally are reported (2) capable of abolishing the sedative effect of 1/6 grain of morphine and 1/150 grain of scopolamine without affecting the analgesic properties of the morphine.

There are some undesirable side effects in the normal individual—uneasiness and tension, poor appetite, hot and cold sensations, heaviness of the head, headaches, dizziness and disturbance of the sleep the night after the drug is taken (1). With larger doses there is a rise of blood pressure (e.g., from 120 to 180 mm. systolic), palpitation, tachycardia and dryness of the throat (2). However, Dodd and Prescott (2) stated that surgical patients with a low blood pressure have tolerated amounts as high as 60 to 70 mg. parenterally without any untoward effects.

The effect on the circulation is peripheral, as demonstrated by Larsen and confirmed by others. He also reported that there is a decreased minute volume output in the perfused frog's heart. In man,

moderate doses act as a pressor agent by vasoconstriction of the peripheral vessels; larger doses act directly on the heart (2). Doses of 15 mg. or more cause an increase in the rate and depth of respiration, although there is no effect on respiration, respiratory quotient, basal metabolic rate or body temperature from the ordinary doses used for euphoric and stimulating effects. Ivy and Goetzel made the comment that d-desoxyephedrine is more toxic per milligram than amphetamine. The acute toxicity as tested on the rat is one-eighth to one-tenth that of ephedrine (2). Its analeptic action as tested on mice is one and a half times that of amphetamine. However, this varies with the anesthetic agent.

Some of these are, of course, undesirable qualities from the anesthesiologist's viewpoint, but in the patients comprising the present study there was no readily apparent effect on respiratory rate nor was there any definite or consistent counteraction of preoperative sedation.

## PRESENT STUDY

The present study was undertaken to observe the effect of methedrine when used in the same manner as ephedrine in connection with spinal anesthesia.

TABLE I  
SEX AND AGE DISTRIBUTION

	Drug		
	Methedrine	Ephedrine	Neosynephrin
Total Cases.....	152	151	146
Males.....	83	76	74
Females.....	69	75	72
Age Range: Oldest.....	83	83	79
Youngest.....	18	15	17
10-19 years.....	2	10	3
20-29 years.....	14	24	23
30-39 years.....	39	30	41
40-49 years.....	38	35	38
50-59 years.....	36	21	15
60-69 years.....	18	20	22
70-79 years.....	4	9	4
80-89 years.....	1	2	0
Total.....	152	151	146

It has been my practice to inject 50 mg. of ephedrine hydrochloride or sulfate subcutaneously and into the intraspinal ligament along with 1 per cent procaine after making the skin wheal with 1 per cent procaine alone and before the spinal needle is inserted. The patient is in the right lateral recumbent position. All anesthetic agents used were in

solution. An average of two minutes elapses between the administration of the ephedrine and the anesthetic agent.

Methedrine was given in the same manner at first in doses of 15 mg. This was, however, insufficient and, on trial, doses of 30 mg. caused an abrupt and undue rise in blood pressure level, i.e., from 120 mm. to 160 mm. systolic and from 80 to 100 mm. diastolic in five minutes. Twenty-five milligrams also proved too much; therefore, 20 mg. was selected as the optimum dosage.

TABLE 2  
DISTRIBUTION OF OPERATIONS

Region Involved	Methedrine	Ephedrine	Neosynephrin
Lower extremities.....	10	12	22
External pelvic.....	69	56	53
Lower abdominal.....	44	65	62
Upper abdominal*.....	29	18	9
Total.....	152	151	146

\* Includes nephrectomy.

TABLE 3  
DISTRIBUTION OF CASES ACCORDING TO LENGTH OF OPERATION AND PRESSOR AGENT WITH REQUIREMENT FOR ADDITIONAL PRESSOR AGENT (EPHEDRINE 15 TO 25 MG. OR NEOSYNEPHRIN 2 TO 3 MG.)

Length of Operation	Drug	Total	No Additional Vasoconstrictor	Add. V.C. Once	Add. V.C. Twice	Add. V.C. Three Times
Under 30 minutes	Methedrine	25	23	2		
	Ephedrine	28	26	2		
	Neosynephrin*	23	19	4		
31 minutes to 60 minutes	Methedrine	73	54	17	2	
	Ephedrine	60	48	11	1	
	Neosynephrin	62	35	22	5	
61 minutes to 90 minutes	Methedrine	31	21	9	1	
	Ephedrine	33	26	3	4	
	Neosynephrin	39	17	14	7	1
91 minutes to 120 minutes	Methedrine	15	10	3	2	
	Ephedrine	16	12	4	0	
	Neosynephrin	15	4	8	1	2
Over 2 hours	Methedrine	8	2	6	0	
	Ephedrine	14	8	5	1	
	Neosynephrin	7	3	3	1	
Total	Methedrine	152	110-72.3%	37-24.3%	5-3.2%	
	Ephedrine	151	120-79.4%	25-16.5%	6-3.9%	
	Neosynephrin	146	78-53.4%	51-34.9%	14-9.5%	3-2.05%

\* Neosynephrin—21 cases had initial dose under 5 mg.  
26 had initial dose of 7 mg.; 5 mg.; 6 mg.

TABLE 4  
ANESTHETIC AGENTS USED TO PRODUCE SPINAL ANESTHESIA

Initial Vasoconstrictor	Anesthetic Agent	Total	Alone	Combined with General Anesthesia
Methedrine 20 mg.	Metycaine	41	37	4
	Procaine	23	19	4
	Pontocaine with Procaine	88	50	38
	Total	152	106	46
Ephedrine 50 mg.	Metycaine	56	40	16
	Procaine	34	29	5
	Pontocaine with Procaine	61	29	32
	Total	151	98	53
Neosynephrin 5 or 6 mg.	Metycaine	66	53	13
	Procaine	22	14	8
	Pontocaine with Procaine	58	30	28
	Total	146	97	49
	Grand Total	449	301	148

\* 21 patients received less than 5 mg.; 26 received 7 mg.

This dosage was given to 152 unselected, consecutive adult patients receiving spinal anesthesia, regardless of size, sex or age or type and dosage of anesthetic agent.

This control group consisted of 151 patients appearing consecutively and similarly unselected who received 50 mg. of ephedrine.

Following the completion of the methedrine series another group received neosynephrin. Here, however, there was some variation in the dosage. The majority were given 5 or 6 mg.; 29 patients had less than 5 mg. (as little as 2½ mg.); 70 patients received 5 mg.; 21 had 6 mg.; and 26 patients had 7 mg. The neosynephrin was given subcutaneously in the deltoid region by an assistant at the time that I was infiltrating the site of puncture. There were 146 patients in this series.

Table 1 shows the distribution of cases in the three groups. It is apparent that they are quite similar as to sex and age distribution. Table 2 shows the regional distribution of the operations. Here again the series are roughly equivalent, with a few less upper abdominal cases in the neosynephrin series. The three series also had an equivalent distribution among operations of various lengths (table 3), and the anesthetic agents used were in the same proportion (table 4).

The method of giving a routine dose of vasoconstrictor drug was elected so that a few criteria could be selected from the results for the whole group as a means of judging their relative value.

When the cases are reviewed and classified according to the number of times vasoconstrictors were given it is apparent that in the shorter operations it was seldom necessary to give ephedrine (25 mg.) or neosynephrin (2 or 3 mg.) subsequent to the initial injection. Sometimes fluids were given in addition (table 7), but many times the additional vasoconstrictor only was given either because it was felt that intravenous fluids were not necessary or that they could be given more conveniently in the patient's room when the operation was nearly completed.

Methedrine and ephedrine were almost equally effective, with ephedrine having somewhat the edge (table 3). Of the 152 patients who received methedrine 110, or 72.3 per cent, required no additional vasoconstrictor, while of those receiving ephedrine 120, or 79.4 per cent, required no additional vasoconstrictor. An additional pressor agent was given once to 24.3 per cent of patients in the methedrine series and 16.5 per cent of those in the ephedrine series. A second additional injection was required in 3.2 per cent of those in the methedrine group and 3.9 per cent of those in the ephedrine group.

TABLE 5  
TIME AFTER INITIAL CLOSE WHEN FIRST ADDITIONAL VASOCONSTRICTOR\* GIVEN

	Minutes									Unknown
	Total Cases	Less than 20	20 to 29	30 to 39	40 to 49	50 to 59	60 to 75	75 to 120	Over 2 Hours	
Methedrine.....	42	2	4	10	5	8	8	3	1	1
Ephedrine.....	31	3	3	5	6	4	5	4		1
Neosynephrin.....	68	12	8	12	11	10	8	6		1

\* Ephedrine or Neosynephrin.

In the neosynephrin series the first injection was sufficient in only 53.4 per cent, or 78 cases. One additional injection was required in 34.9 per cent, two in 9.5 per cent and three in 2.0 per cent, or 3 cases.

In those cases in which an additional vasoconstrictor was necessary (table 6) there were only six instances in which this was necessary under thirty minutes when methedrine or ephedrine was given initially. With neosynephrin there were 12 cases requiring further support in less than twenty minutes and 20 in less than thirty minutes. Most of these were those 29 patients who received less than 5 mg.

After the first thirty minutes it was more often necessary to give an additional dose with methedrine than with ephedrine, although the difference is not great. Neosynephrin as I employed it was, however,

TABLE 6

DISTRIBUTION OF CASES ACCORDING TO LENGTH OF OPERATION AND ANESTHETIC AGENT WITH REQUIREMENTS FOR ADDITIONAL PRESSOR AGENTS (EPHEDRINE OR NEOGYNEPHRIN)

	Metycaine*					Procaine*					Pontocaine with Procaine				
	Total Cases	Total	No VC	1X	2X	Total	No VC	1X	2X	3X	Total	No VC	1X	2X	3X
Under 30 min.	76	47	42	5	0	26	24	2	0	0	3	2	1	0	0
31 to 60 min.	195	93	66	23	4	33	26	3	2	0	69	46	21	2	0
61 to 90 min.	103	16	14	1	1	11	8	2	0	1	76	42	22	12	0
91 to 120 min.	46	6	4	1	1	3	2	1	0	0	37	20	14	1	2
Over 2 hours	29	1	0	1	0	6	2	2	2	0	22	11	11	0	0
<b>Total</b>	<b>449</b>	<b>163</b>	<b>128</b>	<b>31</b>	<b>6</b>	<b>79</b>	<b>64</b>	<b>10</b>	<b>4</b>	<b>1</b>	<b>207</b>	<b>121</b>	<b>69</b>	<b>15</b>	<b>2</b>
	100%	100%	77.29%	19.08%	3.68%	100%	81.01%	12.6%	5.06%	1.26%	100%	58.2%	33.3%	7.4%	0.96%
	100%	36.3%				17.59%					46.1%				

\* Includes continuous spinal.

definitely less effective and yet, when used in larger doses, it caused an inordinate rise in the blood pressure level and a marked bradycardia.

There was a moderate initial rise in the blood pressure level with methedrine, averaging 15 mm. of mercury systolic and 8 mm. of mercury diastolic. This was not usually noticeable with ephedrine. There was little change in pulse rate with either drug and no observable increase in respiratory rate.

TABLE 7

OCCURRENCE OF NAUSEA AND VOMITING AND ADMINISTRATION OF OXYGEN AND FLUIDS

	Total	Nausea	Vomiting	Oxygen	Fluids I.V
Methedrine . . . . .	152	24	1	40	12
Ephedrine . . . . .	151	26	8	46	17
Neosynephrin . . . . .	146	29	7	41	7

It is, of course, obvious that there are many factors causing variation in blood pressure readings under anesthesia; emotion, height of spinal anesthesia, type of operation, position of patient on the table, the skill of the surgeon, to name a few. However, one factor which seemed worthy of investigation in this study was the difference in anesthetic agents. Pontocaine with procaine was used more often than either metycaine or procaine alone. Of course, the reason it was used was that either the operation or the surgeon required more time than could be allowed with either metycaine or procaine. Yet (table 4) it is true that additional vasoconstrictors were required more often when pontocaine and procaine were used than with either of the other two drugs, i.e., 41.8 per cent compared to 18.99 per cent for procaine and 22.17 per cent for metycaine. I bring in this factor because (table 4) in the methedrine series there are relatively more patients who received pontocaine with procaine than in the other two groups. Thus, it would

seem that methedrine is slightly more effective than ephedrine in maintaining blood pressure levels with spinal anesthesia.

Two other factors which may be mentioned are: (1) the incidence of nausea and vomiting and (2) blood pressure value at the conclusion of the operation. Nausea occurred an equal number of times in each group, but there was less vomiting when methedrine was used. For the group to whom methedrine was given the average blood pressure reading preoperatively (before administration of anesthesia) was 126 mm. systolic and 85 mm. diastolic and at the conclusion of the operations the average pressure was 127 mm. systolic and 82 mm. diastolic. For ephedrine the average preoperative pressure was 123 mm. systolic and 79 mm. diastolic, and the immediate postoperative pressure was 126 mm. systolic and 79 mm. diastolic. For neosynephrin the average was 121 mm. systolic and 80 mm. diastolic preoperatively and 115 mm. systolic and 77 mm. diastolic postoperatively.

It was expected that there would be some counteraction by the methedrine to the preoperative sedatives administered to these patients. This was not obvious, although it did seem that they felt better during and particularly after their operation than the others. Present conditions made it impossible to carry out a careful postoperative follow-up. Further observations must be made to determine whether this impression is true or merely one stemming from expectations. These observations will also include the use of methedrine whenever an additional dose of pressor drug is necessary.

There are insufficient cases in which a general anesthetic was administered supplementary to the spinal agent to make an evaluation accurate, but it can be said that there was no obvious need for increase in the usual concentrations or dosage of these agents.

#### DISCUSSION

That the administration of a vasoconstricting drug in conjunction with spinal anesthesia is desirable is generally accepted by anesthetists. There are differences of opinion regarding the agents and technics used. Some prefer the administration of ephedrine, neosynephrin or adrenalin and pituitrin a short time (ten to fifteen minutes) before the anesthetic agent, believing that they have thus afforded opportunity for the vasoconstrictor to be effective before the more rapidly acting anesthetic agent causes a fall in blood pressure.

Others advocate the administration of smaller doses (e.g., ephedrine 25 mg.) subcutaneously just before making the spinal puncture and then giving additional doses (10 to 25 mg.) intravenously if hypotension does develop. They argue that less time is consumed and that if there is a last minute delay in the operation or difficulty performing the puncture there is less chance of producing a dangerous rise in blood pressure, while at the same time affording most patients protection against an undue fall in pressure. If hypotension does develop it can



be quickly and easily corrected with additional ephedrine administered intravenously.

The technic presented here has the advantage of simplicity in that the vasoconstrictor is given at the same time and with the same syringe and needle that are used in infiltrating the sight of puncture. It is quite apparent from this series of unselected cases that there is no danger of hypertension with methedrine in 20 mg. doses or ephedrine in 50 mg. doses. The same cannot be said for neosynephrin as employed here.

It is further apparent that these drugs in the doses used are effective in maintaining blood pressure levels in most instances. It is my belief that it is better to prevent hypotension by adequate dosage than to correct it once it has developed.

#### CONCLUSION

Methedrine has proved moderately more effective than ephedrine as a vasoconstrictor for use with spinal anesthesia and definitely more so than neosynephrin. In addition, methedrine offers the probable added advantage of leaving the patient less depressed and in a more elevated mood postoperatively.

#### SUMMARY

Using a standard method on three series of 150 unselected consecutive adult patients each, methedrine, ephedrine and neosynephrin were compared to determine their value as supportive vasoconstrictors in conjunction with spinal anesthesia. Methedrine (d-desoxyephedrine) is the most effective and offers the additional advantage of giving the patient a postoperative elevation of mood.

#### REFERENCES

1. Ivy, A. C., and Goetzel, F. R.: d-Desoxyephedrine: A Review, *Bull. War. Med.* 3: 60-77 (Jan.) 1943.
2. Dodd, Harold, and Prescott, Frederick: The Use of Methedrine in Surgical Operations, *S. G. & O.* 77: 645-656 (Dec.) 1943.

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