NEUROLOGICAL EFFECTS FOLLOWING INTRATHECAL ADMINISTRATION OF VASOCONSTRICTOR DRUGS IN RHESUS MONKEYS *†‡

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INTRODUCTION

THE intrathecal injection of vasoconstrictor drugs in conjunction with spinal anesthesia was practiced prior to 1911 (1, 2). Barker, in 1912 (3), postulated that vasoconstrictor agents given by this route produced tissue damage from ischemia of the nerve roots. In 1928 Labat (4) discouraged their use with the idea that "the blood vessels of the brain and spinal cord are not supported by muscles and aponeuroses. Lack of blood in these vessels as a result of vasoconstrictor action might result in complete collapse and possibly result in the death of the patient."

Due to objections such as these, even though unsupported by clinical or experimental data, vasoconstrictor drugs were not commonly used intrathecally prior to 1940. In 1940 Pitkin (5) advocated the prolongation of spinal anesthesia by using a mixture of "nonoxidizing epinephrine" which consisted of epinephrine, ephedrine, gliadian acetate, procaine, alcohol and water. He reported that with the use of this mixture, spinal anesthesia was greatly prolonged and the toxicity of the anesthetic agent was reduced more than six times.

Romberger in 1943 (6), Romberger and Ratcliff in 1947 (7), Prickett, Gross, and Cullen in 1945 (8), Potter and Whitacre in 1946 (9), Whitacre and Potter in 1948 (10), Rooney and Karp in 1949 (11), Taylor in 1950 (12), Bonica, Backup, and Pratt (13), and many others

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reported several thousand cases in which epinephrine, ephedrine or some other vasoconstrictor drug was injected intrathecally in conjunction with spinal anesthetics. All of these authors reported the prolongation of spinal anesthesia following the use of these drugs. Pitkin *et al.* in 1940 (5) and Bray *et al.* in 1949 (14) reported that the addition of ephedrine alone to solutions of local anesthetic agents did not prolong the duration of spinal anesthesia to any great extent. Brockmeyer and McGowan in 1949 (15) and Crawford and Ausherman in 1950 (16) used intrathecal neosynephrine to potentiate spinal anesthesia. Bray and his associates claimed that only epinephrine appreciably prolonged the spinal anesthesia produced by nupercaine. Ruben and his co-workers in 1947 (17), 1948 (18) and 1949 (19) found that ephedrine and several other vasoconstrictor agents possessed spinal anesthetic properties. Priddle and Andros in 1950 (20) reported the primary anesthetic property of epinephrine in man.

Since none of these authors reported any serious neurological complications or any significant changes in blood pressure and pulse rate, it appears that intrathecal injection of vasoconstrictor agents in conjunction with spinal anesthetics is a safe practice. On the other hand, from their clinical observations, no definite recommendations have been made as to the optimal concentration and dosage of each of these vasoconstrictor drugs. Furthermore, no information is given in these studies as to toxic dosages and concentrations or the effects of these agents on the spinal cord. As pointed out above, Pitkin has claimed that the toxicity is reduced more than six times with the use of his recommended mixture which contained vasoconstrictor agents. We have been unable to find any reports of experimental evidence in substantiation of this claim. The purpose of the present study is to obtain information as to the relative toxicity of certain vasoconstrictor drugs in the central nervous system when administered intrathecally. In a preliminary study the effects of intrathecal injections of various dosages of ephedrine sulfate were demonstrated by Brizzee and Wu (21). The present paper is a continuation of those studies with emphasis on neurological signs, symptomatic effects and the general condition of the animals.

METHOD

Rhesus monkeys weighing 2.1 to 4.0 kg. were used in this study. Intravenous thiopental sodium, 5 to 15 mg. per kilogram, was administered prior to each lumbar puncture. Before making the intrathecal injection of the drug each animal was allowed to recover partially from the intravenous anesthesia, thereby permitting a more detailed observation of neurological signs. The physical properties of the solutions of epinephrine, ephedrine and neosynephrine are given in table 1.

TABLE 1

PHYSICAL PROPERTIES OF EPINEPHRINE, EPHEDRINE AND NEOSYNEPHRINE

Drug	Concentration (mg./cc.)	Specific Gravity	pH
Epinephrine Hydrochloride	0.5	1.006	3.80
	1.0	1.007	3.75
Ephedrine Sulfate	10.0	1.006	6.62
	16.6	1.008	6.57
	25.0	1.010	6.44
	50.0	1.012	6.23
Neosynephrine Hydrochloride	10.0	1.008	4.93
	25.0	1.010	4.24*
	50.0	1.012	4.16*
Saline (Sodium Chloride) A	9.0	1.006	6.84
B	9.0	1.006	3.75

* Freshly prepared aqueous solution.

The dosages of epinephrine, ephedrine, and neosynephrine used in this experiment varied from ten to one hundred times the clinical dose. The lethal dose of each drug administered intrathecally was not statistically determined. Generally speaking, it appeared that the lethal dose of epinephrine hydrochloride was 2.0 plus mg. per kilogram, whereas 1.0 plus mg. per kilogram was the maximal tolerated dose.

The lethal doses of ephedrine sulfate and neosynephrine were 76 mg. per kilogram and 30 mg. per kilogram, respectively, while the maximal tolerated doses were 30 mg. per kilogram and 15 mg. per kilogram, respectively.

Experiments were conducted in two series, acute and chronic. In the acute series each animal received a single injection of the vasoconstrictor drug. In the chronic series the animals received five to ten small doses of the drug over a period of seven to twelve days.

Experiments in acute and chronic series with intrathecal saline controls at pH 3.75 and 6.84 were also conducted and the neurohistological results have been previously published (21).

OBSERVATIONS

Epinephrine Hydrochloride: Neurological Signs and Symptoms

The symptoms following the intrathecal injection of epinephrine in relation to its dosage are summarized in table 2. Most of the monkeys which received doses of epinephrine less than 0.15 mg. per kilogram showed no neurological signs except a slight rise of blood

TABLE 2

INTRATHECAL INJECTION OF EPINEPHRINE HYDROCHLORIDE—SYMPTOMS AND SIGNS

Epinephrine Hydrochloride				No. of Animals		Observations								
						Neurological Findings							Systemic Effects	
							Time in Min.							
Dosage mg./kg.	Concentration mg./cc.	Volume of Solution Injected Intrathecally cc./cm. Length Vertebral Column	Injection Time in Min.				0*	5	10	20	45	Time in Min.	Blood Pressure mm. Hg.	Heart Rate per Min
0.08–0.15	0.5–1.0	0.007–0.025	1–5	5	60%	Negative						0	105±15	100±20
												5	140±20	140±10
					40%	Hind Limbs						10	120±20	90±30
						Hyperextension	–	2+	+	–	–	15	110±20	90±30
						Rigidity	–	+	+	–	–	20	100±20	90±30
						Tremors	–	2+	+	–	–			
						Knee jerk	+	2+	2+	–	–			
0.3	1.0	0.025–0.03	5–8	3		Hind Limbs						0	105±15	100±20
						Hyperextension	+	2+	+	–	–	5	150±10	140±10
						Rigidity	–	+	+	–	–	10	170±30	120±30
						Tremors	–	3+	+	+	–	15	110±10	120±20
						Knee jerk	+	2+	2+	+	+	20	90±15	110±20
						Sensory	4+	4+	4+	4+	4+	25	100±15	100±20
0.6	1.0	0.05–0.06	7–15	3		Hind Limbs						0	105±15	100±20
						Hyperextension	–	3+	3+	2+	–	5	210±20	160±20
						Rigidity	–	3+	2+	2+	–	10	230±30	140±40
						Tremors	–	4+	4+	2+	–	15	190±20	140±20
						Knee jerk	+	4+	4+	3+	+	20	150±40	130±20
						Sensory	4+	3+	2+	+	3+	30	120±30	120±20
0.9–1.1	1.0	0.09–0.11	15–30	3		Hind Limbs						0	105±15	100±20
						Hyperextension	–	4+	–	–	–	5	240±10	170±10
						Rigidity	–	4+	–	–	–	10	300±20	240±50
						Tremors	–	3+	+	+	2+	15	300±30	180±50
						Knee jerk	+	3+	+	–	3+	20	280±40	170±50
						Sensory	4+	3+	–	–	–	30	240±60	135±30
						Lower Abdomen						40	120±30	100±30
						Sensory	4+	3+	+	–	–	60	100±20	100±20

* Animal under light pentothal® sodium anesthesia.

pressure and an increase in heart rate within the first five to ten minutes.

In animals given epinephrine in doses of 0.3 mg. per kilogram, hyperextension, rigidty and fine tremors of the muscles of the hind limbs developed two to three minutes following the injection. Changes of blood pressure and heart rate in these animals were definite but of short duration. There were no detectable disturbances of skin sensation.

More severe and prolonged hyperextension, rigidity and tremor occurred following intrathecal administration of epinephrine in doses of 0.6 mg. per kilogram. The knee jerk was markedly hyperreactive for ten to fifteen minutes. During this period the quadriceps muscles in some cases responded vigorously to weak stimuli with intensification of the tremor. Cutaneous sensation over the hind limbs and abdomen was decreased. Flexor reflexes were elicited only by strong stimuli. Some paresis of the lower part of the body, lasting approximately thirty to forty-five minutes, was apparent. Recovery was gradual.

A dose of 0.9 to 1.1 mg. per kilogram of epinephrine produced marked hypertonicity. Rigidity and tremor usually developed suddenly and diminished gradually within three to five minutes. During the next forty-five minutes the monkey lay quietly on the table with all muscles flaccid but not completely paralyzed. A flexor reflex of the hind limbs and lower abdomen could be elicited with a strong stimulus. Occasionally spontaneous tremors of the gastrocnemius muscle were noted. During the first thirty minutes the blood pressure varied from 280 to 300 mm. of mercury and the heart rate rose to a peak of 290 per minute. The heart rate gradually returned to normal with return of muscular tonus. The knee jerk during this recovery period became hyperreactive and at the same time the tremor again became more pronounced. In some instances the erector pili muscles over the entire body became activated. At the end of an hour the muscles of the hind limbs had not regained sufficient strength to support the animal's weight. A certain degree of muscular weakness of the hind limbs persisted following the last five injections of the animals in the chronic series which received doses of this magnitude. Two animals which received three injections of 1.0 mg. per kilogram exhibited no residual symptoms. It was repeatedly confirmed that the neurological signs following a single intrathecal injection of epinephrine were transitory. With the dose of epinephrine below 0.15 mg. per kilogram the duration of effect was ten to fifteen minutes; 0.3 to 0.6 mg. per kilogram, thirty to forty-five minutes; and 0.9 to 1.1 mg. per kilogram, forty-five to sixty minutes. Recovery from such a single injection was complete without evidence of disturbance of reflex activities and motor strength.

Seven monkeys received a continuous intrathecal injection of epinephrine, with the duration of injection varying from two to four hours. The systemic effects were the criteria for regulating the rate of the injection in each case. The rate of injection was so regulated that the blood pressure of the animal varied between 200 to 240 mm. of mercury and the heart rate between 180 to 260 per minute. Three monkeys received 1.6, 1.9, and 2.0 mg. per kilogram of epinephrine in a two hour period and one monkey 2.0 mg. per kilogram in a four hour period. Hyperextension, rigidity, tremor and hyperactive knee jerks were noted only within the first ten minutes following the injection. Three monkeys were given epinephrine in doses of 0.88, 1.4 and 2.6 mg. per kilogram, respectively, in the four hour period. The clinical picture in these animals differed in that hyperextension, rigidity and tremors were present almost constantly during the entire period of injection. All efforts to keep these seven monkeys alive proved futile. During the period of continuous injection, the animals seemed to be in fairly good condition, but 150 minutes after the injection, Cheyne-Stokes respiration and finally a gasping type of respiration developed

in all. One hour or less after the onset of respiratory difficulty the monkeys were *in extremis*. The respiratory failure could not be well explained by muscular paralysis since the level of motor disturbance was below the midthorax (sixth thoracic). Additional factors, such as hypertension and tachycardia, prolonged disturbance of blood supply to the spinal cord and the possibility of the effect of epinephrine upon the higher centers of the nervous system, should be considered.

Ephedrine Sulfate: Symptoms and Signs

Signs comparable to procaine spinal anesthesia were observed in a number of the animals receiving intrathecal ephedrine. In table 3 the neurological signs and systemic effects following single injections of various doses and concentrations of ephedrine are summarized. The blood pressure showed no unusual changes during the intrathecal injection of ephedrine. With the dose below 15 mg. per kilogram the blood pressure was increased from 100–120 mm. to 140–160 mm. of mercury, while with larger doses it fell to 110, 100 and even 90 mm. of mercury. The heart rate increased slightly from ninety to 120 per minute to 132 to 140 per minute without reference to the dosage. With a lethal dose the heart rate slowed from 180 to 200 per minute to sixty to eighty per minute with a decline of blood pressure to below 60 mm. of mercury within thirty minutes.

Following doses of 75.9 to 105.8 mg. per kilogram of a 5 per cent solution, the general condition of the animals deteriorated rapidly and they were killed at one and four hours, respectively. Analgesia was noted over the entire body with paralysis of all the spinal segments. It was repeatedly noted that during the intrathecal administration of ephedrine a latent period of fifteen to twenty minutes occurred between the administration of the drug and the onset of analgesia and of twenty to twenty-five minutes for paralysis. High concentrations and a large dose of ephedrine did not seem to reduce this period of latency.

Injections of 1 to 5 per cent solutions of ephedrine in doses of 6 to 8 mg. per kilogram produced analgesia of the feet and perineum with a decrease in general sensory perception of the legs and thighs. The motor impairment was limited to the feet. Hopping and pacing reflexes disappeared but the animal was able to stand with flexed digits (claw foot). The duration of effect was one to two hours and recovery was complete.

Following a dose of 12 to 18 mg. per kilogram of 1.66 or 2.5 per cent solution analgesia developed, with complete paralysis of the hind limbs. The duration of effect was two to three hours. The same dose with a 5 per cent concentration gave essentially the same neurological picture; the duration, however, was three to four hours. One animal exhibited respiratory difficulty associated with paralysis of the higher spinal segments following five successive injections.

TABLE 3

INTRATHECAL INJECTION OF EPHEDRINE SULFATE—SYMPTOMS AND SIGNS

Ephedrine Sulfate				No. of Animals	Observations								
					Neurological Findings						Systemic Effects		
						Time in Min.							
Dosage mg./Kg.	Concentration mg./cc.	Volume of Solution Injected Intrathecally cc./cm. Length Vertebral Column	Injection Time in Min.			0*	5	15	30	60	Time in Min.	Blood pressure mm. Hg.	Heart rate per Min.
6–8	10	0.06–0.07	10	3	Sensory *L6–L4*	4+	3+	+	−	+	0	100–120	98–120
					Sensory *L1*	4+	4+	2+	−	+	5	110–120	95–120
					Knee Jerk	+	3+	2+	+	+	15	120–140	132
	50	0.015–0.02	3	2	Reflexes—Pacing	+	−	−	−	−	30	120–140	132
					Hopping	+	−	−	−	−	60	120–140	120–132
					Righting	+	+	+	+	+			
12–18	16.6	0.066	10	2	Sensory *L1*–T12, 75%	4+	3+	2+	−	−	0	100–120	90–120
					Paresis, Hind Limb	−	−	−	+	+	5	110–120	95–120
					Knee Jerk	+	3+	2+	−	−	15	140–160	144
	25	0.060	10	2	Reflexes—Pacing	+	−	−	−	−	30	140–160	144
					Hopping	+	−	−	−	−	60	120–140	144
	50	0.030	5	3	Righting	+	+	+	+	+			
30	25	0.12	20	1	Sensory T10–T8	4+	4+	2+	−	−	0	100–120	90–120
					Paralysis T–12	−	−	−	+	+	5	110–120	100–140 95–120
					Knee Jerk	−	2−	2−	−	−	15	110–130	100–140 120–98
	50	0.06	15	8	Reflexes—Pacing	+	−	−	−	−	30	100–120	132–144 100–98
					Hopping	+	−	−	−	−	60	100–90	132–144 110–100
					Righting	+	+	+	+	+	120	100–90	132–144 110–100
75.9–105.8	50	0.15–0.18	30–60	2	Sensory C1	4+	4+	−	−	−	0	100–120	90–120
					Paralysis C4	−	−	−	+	+	5	120–110	180–200
					Knee Jerk	+	2+	2+	−	−	15	100–90	160–94
					Reflexes—Pacing	+	−	−	−	−	30	60–	160–80
					Hopping	+	−	−	−	−	60	60–	60–80
					Righting	+	+	+	−	−		Sacrificed	

* Animal under light pentothal sodium anesthesia.

TABLE 4

INTENSIFICATION OF NEUROLOGICAL SIGNS FOLLOWING INCREASE IN CONCENTRATION OF EPHEDRINE SULFATE

Dosage mg./Kg.	Concentration mg./cc.	Volume Injected in cc.	Neurological Signs								
			Knee Jerk, Duration in Min.					Analgesia		Paresis	
			Normal	5'	10'	15'	20'	Level	Duration in Min.	Claw Feet	Duration in Min.
7	10	2.5	+	+	2+	+	+	L-6	90	−	45
7	25	1.0	+	2+	2+	+	−	L3-L4	120	+	90
7	50	0.5	+	2+	3+	−	−	L-1	190	+	120

Three animals tolerated 10 successive injections of the 5 per cent solution in doses of 30 mg. per kilogram. Two of these monkeys were killed at the completion of injection and the third was kept for thirty days. Muscular weakness of the hind limbs was still apparent at the end of this period; however, marked improvement was noted between the fourteenth and thirtieth days.

The influence of various concentrations of ephedrine in small doses was determined in monkeys of the same age and weight. Each received three injections, in doses of 7 mg. per kilogram, of 1.0, 2.5 and 5 per cent solutions, respectively, in an interval of ten days. The results are shown in table 4.

With the low concentration the effect was mild and duration was short, while with the higher concentration the effect became more distinct and the duration was increased.

The pressure of cerebrospinal fluid was increased slightly following the intrathecal injection of 2.5 and 5 per cent ephedrine. Apparently the animals were not affected by the increased pressure as no signs of meningismus were noted. Injection of saline solution in control animals did not produce any notable increase on cerebrospinal fluid pressure.

Neosynephrine: Symptoms and Signs

In table 5 the effects of intrathecal injection of neosynephrine are summarized in relation to its concentration, volume and dosage. Administration of 3.0 mg. per kilogram of neosynephrine in 1 per cent solution did not change muscular tone or the reflex activity. The blood pressure increased from 120 mm. to about 150 mm. of mercury within fifteen minutes. The heart rate increased from eighty to ninety per minute to 120 or 140 per minute in ten minutes. Muscular weakness was frequently noted during the first fourteen to twenty minutes. During this period the pacing, hopping and righting reflexes were all positive and apparently normal, but the animal ex-

TABLE 5

INTRATHECAL INJECTION OF NEOSYNEPHRINE HYDROCHLORIDE—SYMPTOMS AND SIGNS

Neosynephrine Hydrochloride				No. of Animals	Observations										
					Neurological Findings								Systemic Effects		
						Time in Min.									
Dosage mg./kg.	Concentration mg./cc.	Volume of Solution Injected Intrathecally cc./cm. Length Vertebral Column	Injection Time in Min.			0*	5	10	20	45	90	180	Time in Min.	Blood pressure mm. Hg.	Heart Rate per Min.
3.0	10	0.025–0.03	5	2	General Depression	−	−	−	−	−	−	−	0	100–120	90–120
					Hind Limbs								5	125–140	80–90
					Knee Jerk	+	+	+	+	+	+	+	15	140–160	120–140
					Sensory	4+	4+	4+	4+	4+	4+	4+	30	130–150	130–140
					Motor—Strength	4+	3+	3+	2+	3+	4+	4+	45	120–130	120–140
					Reflexes—Pacing	+	+	+	+	+	+	+	60	100–130	120–140
					Hopping	+	+	+	+	+	+	+			
6.0	10	0.05–0.06	10	2	General Depression	−	−	−	−	−	−	−	0	100–120	90–120
					Hind Limbs								5	160–180	60–80
					Knee Jerk	+	+	2+	2+	+	+	+	15	160–180	80–200
					Sensory	4+	4+	3+	3+	3+	4+	4+	30	120–170	120–170
					Motor—Strength	4+	3+	3+	2+	2+	4+	4+	45	120–160	130–150
					Fine Tremors—Toes	−	2+	2+	+	−	−	−	60	120–150	120–150
					Reflexes—Pacing	+	+	+	+	+	+	+	90	120–140	120–145
					Hopping	+	+	+	+	+	+	+			
					Righting	+	+	+	+	+	+	+			
9.0	10	1.10	15	3	General Depression	−	−	+	2+	2+	+	−	0	100–120	90–120
					Hind Limbs								5	260–280	50–120
					Knee Jerk	+	2+	2+	2+	2+	+	+	15	280–300	80–240
					Sensory	4+	3+	2+	2+	2+	3+	4+	30	220–260	200–240
					Motor—Strength	4+	3+	2+	2+	2+	3+	4+	45	150–200	180–240
					Fine Tremors—Toes	−	2+	2+	+	−	−	−	60	140–160	160–180
					Reflexes—Pacing	+	+	+	+	+	+	+	90	140–160	140–180
					Hopping	+	+	+	+	+	+	+	90	140–160	140–180
					Righting	+	+	+	+	+	+	+	180	120–140	120–160

hibited some difficulty in walking. When given sodium pentothal® intravenously without the intrathecal administration of neosynephrine, the same animal exhibited none of these symptoms ten minutes following the injection. The weakness of the hind limbs, therefore, probably is not due to the effect of the thiobarbiturate.

A dose of 6.0 mg. per kilogram of 1 per cent neosynephrine resulted in a slightly hyperreactive knee jerk and fine tremors of the toes which persisted for about twenty minutes. There was no disturbance of skin sensation or hyperextension of the hind limbs. Pacing, hopping and righting reflexes were present throughout, although sluggish. The blood pressure was usually increased to 170 to 180 mm. of mercury within fifteen minutes, and the heart rate was first decreased to sixty to eighty per minute and then increased to 200 or more per minute. The animal was usually very weak and quiescent for approximately an hour and gave normal responses to ordinary stimuli.

Following injection of a 1 per cent solution in a dose of 9.0 mg. per kilogram, the same symptoms developed as when the dosage was 6.0 mg. per kilogram. All symptoms and signs were exaggerated, however, and the duration of the effect of the drug was prolonged to ninety or more minutes. The blood pressure increased to as much as 280 to 300 mm. of mercury, while the heart rate was reduced to sixty or less per minute and then increased to 240. Occasionally, there was a short period of transition, with slow and rapid beats occurring alternately, before tachycardia took place. The animal exhibited marked weakness and did not respond to painful stimuli for ninety to 150 minutes.

Following a dose of 12 to 14 mg. per kilogram in a 4 to 5 cc. volume administered over a thirty to forty-five minute period, the animal exhibited marked generalized depression which lasted approximately 180 minutes. The knee jerk was hyperreactive throughout this period. Skin sensation over the trunk and limbs was decreased. Painful stimuli elicited a feeble flexor reflex whereas mild stimuli, such as touching and scratching, did not produce any response. Righting reflexes were absent. Tremor of the toes was a constant feature but the large muscles of the legs and thighs were rarely involved. When the animal gradually recovered from such a general depression, partial paresis of the hind limbs, with occasional spontaneous flexion and extension, was noted. Analgesia was present all over the body, but was not as marked over the head and neck. Skin sensation over the lower abdomen and hind limbs was markedly diminished with a return to normal after approximately four hours. The blood pressure was over 300 mm. of mercury, and the heart rate over 260 per minute during the first sixty to ninety minutes after the injection. This animal

survived ten such daily injections and appeared to be in fairly good condition at the end of this series.

Doses of neosynephrine of 15 mg. per kilogram in 2.5 per cent and 5 per cent solutions gave a picture similar to that produced by 14 mg. per kilogram in 1 per cent solution, already described. A period of general depression was invariably present following the injection although the duration was slightly reduced with 2.5 and 5.0 per cent concentrations. The knee jerk was hyperreactive for a short period before its disappearance. Paresis was more profound with 5 per cent than with 2.5 per cent solutions but the motor paralysis was not complete. Occasional spontaneous extensions and flexions of hind limbs were still present. The duration of paresis with the 2.5 per cent solution was six hours, while with the 5 per cent solution it was eight or more hours. Systemic effects were about the same, regardless of the concentration of the drug.

Successive injections of 15 mg. per kilogram in 2.5 per cent solution gave a different picture from that produced by the initial injection of the same dose. Following the second injection, complete paralysis of the flaccid type over the hind limbs became distinct. This persisted for more than two hours. After the fifth injection, paralysis of the feet persisted. In general, it was observed that with each successive injection the level of analgesia and paralysis was increased. The animals became incontinent with regard to voiding of urine after the sixth injection. General depression noticed immediately after the injection was intensified and prolonged by successive injections and the amount of sodium pentothal required to quiet the animal was less with each injection of neosynephrine. On many occasions, such a general depression made the determination of the level of analgesia extremely difficult but the knee jerk was always hyperreactive before its disappearance. The systemic changes of blood pressure and heart rate in successive injections were essentially the same as after the first injection.

Fifteen minutes after injection of a dose of 30 mg. per kilogram in 5 per cent solution, the paralysis was noticed as high as the mid-thoracic area while analgesia occurred as high as the lower cervical level. The animal was depressed and lay quietly without moving for three or more hours. Respiration was labored with occasional gasping. The heart rate during the first twenty minutes was 40 to 60 per minute with many irregularities. After this period it increased to 200 to 240 and sixty minutes later fell to 120 to 160. The blood pressure during the first thirty minutes was 240 to 300 mm. of mercury, but fell steadily to 120 mm. during the next four hours. The knee jerk disappeared within eighteen minutes, but was noted to be hyperreactive for ten to fifteen minutes preceding its loss. Paralysis of the lower extremities and abdomen was persistent for ten or more

hours. At the end of the second day, paresis of the hind limbs persisted. One monkey received three such injections within a period of six days. Total spinal anesthesia was noted following the second and third injections. The blood pressure fell to 100 to 90 mm. of mercury within sixty minutes and artificial respiration was required. Paralysis in this monkey disappeared on the third day after the first injection, but full recovery of muscular strength did not occur after the second and third injection.

DISCUSSION

The animal of choice in this experimental investigation was the Rhesus monkey. Lumbar punctures can be done repeatedly in this species and a free flow of spinal fluid can be obtained with little or no difficulty.

Co Tui and his associates in 1942 (22) studied the acute toxicity of spinal anesthetic agents in the rabbit and cat and emphasized the use of spinal cord length as a consistent basis for the calculation of the dosage. The volume of solution used by these authors was 0.02 cc. per centimeter of spinal cord length, but the rate of injection was not mentioned. In our study early experiences convinced us that the rate of injection was very important. When a sublethal dose is given to the animal, the rate of injection must be slow because rapid injection of the same dose in the same volume and concentration often resulted in immediate death of the animal. The rate of injection used in this experiment (0.06 cc. per centimeter of spinal cord every ten to thirty minutes) proved very satisfactory.

Bieter *et al.* in 1936 (23) and Co Tui and his associates in 1944 (24) studied the tissue changes following administration of spinal anesthetic agents in experimental animals and emphasized the concentration of the drug rather than the total dose in terms of milligrams per kilogram as the determining factor. From our observations we are able to support their findings, with certain reservations. It has repeatedly been demonstrated in our study of vasoconstrictor agents that a low concentration administered in a series of successive injections could produce changes of the same extent as those following a single injection of a high concentration, but that for a given dosage greater alterations and more marked neurological symptoms occur following use of a high than of a low concentration.

From clinical observations Romberger in 1943 (6), Prickett and his associates in 1945 (8), Potter and Whitacre in 1946 (9), Bray and his associates in 1949 (14), Rubin and his co-workers in 1948 (18), Crawford and Ausherman in 1950 (16), Brockmeyer and McGowan in 1949 (15), Rooney and Karp in 1949 (11), and many others reported that the intrathecal administration of epinephrine, ephedrine or neosynephrine in conjunction with spinal anesthetics produces no sig-

nificant changes in blood pressure and pulse. Clinically, our findings support this conclusion. In our experimental studies vasoconstrictors alone were injected intrathecally in doses ten to 100 times greater than the clinical dose. Systemic changes in blood pressure and heart rate were almost always detectable. Howarth in 1949 (25) (26), using the radioactive isotope, dibromoprocaine, injected into the subarachnoid space, reported that the drug was immediately detectable in the thoracic lymph but not in the venous blood draining away from the spinal cord. It is highly probable that since the dose employed in this study was large, a considerable concentration may have reached the venous blood through the lymph channel and produced the systemic changes. The clinical dose is small, however, and when the drug reaches the venous blood its concentration is so low that it produces no perceptible clinical signs.

In the present study two monkeys were given 0.3 mg. per kilogram of a 1 per cent solution of epinephrine hydrochloride subcutaneously, intramuscularly, intravenously and intrathecally (lumbar route), respectively, and subsequent changes of blood pressure were observed. The time of onset of systemic effects by the intrathecal route was much slower than by the intravenous or intramuscular routes but more or less the same as by subcutaneous injection. The increase in blood pressure by the intrathecal route was much less drastic than by the intravenous or intramuscular routes and slightly less severe than by the subcutaneous routes.

It was found that the three agents, epinephrine, ephedrine, and neosynephrine, produced both motor and sensory involvement, depending upon the concentration, dosage, frequency and the duration of injection. In most animals epinephrine hydrochloride in 0.1 per cent solution produced spinal anesthesia only when a continuous injection of two to four hours was made. However, no animal recovered after an injection of this magnitude. A dose of 15 mg. per kilogram of ephedrine sulfate in 2.5 per cent solution was sufficient to produce spinal anesthesia with both sensory and motor involvement, and the recovery after such a single injection was complete. Administration of 6.0 to 15 mg. per kilogram of neosynephrine in 1 to 2.5 per cent solution resulted chiefly in general depression, dulled sensory perception and muscular weakness for a period of several hours, while 20 mg. per kilogram in 5 per cent solution produced total spinal anesthesia. The doses used in this study are far greater than the doses used clinically.

Epinephrine

Van Harreveld, in 1939, 1940, 1944 and 1946 (27, 28, 29, 30), ligated the spinal cord of the cat at a low thoracic level and perfused the subarachnoid space below the ligature with a pressure greater than

the systolic pressure. With such a preparation he found hyperalgesia and hyperexcitability followed by depression with acute anoxia of the spinal cord. Histological preparations revealed degeneration of the anterior horn cells. The neurological signs described in his reports are similar to those we obtained following the intrathecal injection of epinephrine.**

Krogh in 1945 (31) and 1950 (32) studied the blood supply of the lower segments of the spinal cord in the rabbit by clamping the abdominal aorta for approximately thirty minutes. His descriptions of "spastic paresis with recovery" coincide with our results following the continuous intrathecal injection of epinephrine of two to four hours duration.

Many early workers, including Montgomery and Luckhardt in 1929 (33), King, Garrey, and Bryan in 1932 (34), Porter, Blair, and Bohmfalk in 1938 (35), Gellhorn, Cortell, and Carlson in 1942 (36), and Tureen in 1936 (37), studied the asphyxial changes of the spinal cord produced either by occlusion of its blood supply or by reduction of its oxygen tension. All of these workers demonstrated a short period of hyperexcitation with a hyperreactive knee jerk, rigidity, hyperextension and tremors preceding a period of depression. These findings, as in the case of those of Van Harrevald and Krogh, lend further support to the possibility that the neurological signs which occur following intrathecal administration of epinephrine are due to anoxic changes following a reduction in the blood supply to the cord through the vasoconstrictor action of the drug. However, until more conclusive evidence is available, the possibility that epinephrine produces these effects, in part at least, through a direct action on the nervous tissues of the cord or higher centers cannot be disregarded.

In most cases intrathecal injection of epinephrine in doses of less than 0.51 mg. per kilogram did not produce significant neurological signs.

Ephedrine

Intrathecal injection of ephedrine produces spinal anesthesia comparable to that produced by the common spinal anesthetic agents. The minimal effective concentration and dose of ephedrine which will consistently produce such spinal anesthesia in monkeys is 15 mg. per kilogram in 2.5 per cent solution. When the concentration and dose of ephedrine is reduced to 6 to 8 mg. per kilogram in 1 per cent solution analgesia occurs without distinct motor involvement. If the concentration and dose of the drug are further reduced, it becomes ineffective. When the concentration and dose of ephedrine are increased to 30 mg. per kilogram in 5 per cent solution spinal anesthesia may persist for four or more hours. Recovery from a dose of 30 mg.

** Study in progress.

per kilogram in 5 per cent solution is complete but some residual muscular weakness persists for a few days. This appears to be very similar to the effects obtained by giving common spinal anesthetics in high concentrations and large doses, as reported by Lundy in 1933 (38) and Co Tui in 1944 (24). The symptoms and signs obtained in this study indicate that ephedrine acts as a spinal anesthetic agent. As reported by Ruben and his co-workers in 1947, 1948 and 1949 (17, 18, 19) in man and Schultz in 1940 (39) in the frog, ephedrine produces nerve block and spinal anesthesia. In view of the anesthetic properties of the drug, Ruben cautioned against the use of large doses of ephedrine in combination with spinal anesthetic agents.

Ephedrine by oral or subcutaneous administration is known to be a central stimulant. In our experiments with 20 monkeys which were given ephedrine intrathecally, any excitatory symptoms other than a slightly hyperreactive knee jerk did not develop. The use of sodium pentothal as the anesthetic might be the factor obscuring such excitement. At the time of the intrathecal injections, however, many active reflexes could be elicited in all animals.

Neosynephrine

The pharmacological properties and therapeutic values of neosynephrine were first reported by Tainter and Stockton in 1933 (40). Lorhan and Lalich in 1940 (41) studied in detail the circulatory and electrocardiographic changes produced by neosynephrine. The effect of neosynephrine upon the nervous system has not been carefully investigated. In our studies, a generalized depression developed in monkeys which received doses greater than 6 mg. per kilogram intrathecally. Further investigation is needed to determine the factors responsible for this condition. Clinically neosynephrine is said to be a central stimulant rather than a depressant, but it is a well established fact that a central stimulant may become a depressant when administered in doses of sufficient magnitude.

Vasoconstriction should be considered as one of the factors in intrathecal administration of neosynephrine. The character of the tremors and the hyperreactive knee jerks noted following the intrathecal injection of neosynephrine are suggestive of the hypoxic state.

Doses of 15 mg. per kilogram of neosynephrine in 2.5 per cent solution produce spinal anesthesia differing from that produced by the common spinal anesthetic agents in that motor paralysis was not complete. When the concentration and dose of neosynephrine were increased to 30 mg. per kilogram in 5 per cent solution a profound spinal anesthesia with motor and sensory involvement developed. Although no attempt has been made to determine the mechanism operating to produce this reaction, we are inclined to view these symptoms as a result of a toxic action of the drug in the nerve tissues.

SUMMARY

Intrathecal injections of epinephrine, ephedrine and neosynephrine were given to medium sized Rhesus monkeys. The lethal dose and the maximal tolerated dose for each drug were determined, although not statistically. Neurological signs, systemic effects and the general condition of the animals were recorded after each injection. The doses used in this study were ten to several hundred times the clinical dose.

Following small doses of epinephrine (less than 0.3 mg. per kilogram, 0.1 per cent solution) excitation developed which was characterized by hyperextension, rigidity and hyperreactive tendon reflexes. Larger doses (0.6 to 1.0 mg. per kilogram) produced excitation followed by depression. The latter was characterized by dulled sensory perception and paresis. With a further increase in dosage, excitation was reduced in duration but not in intensity and the depression became more profound. The clinical picture and neurological signs were similar to those of acute anoxia or hypoxia of the spinal cord.

Intrathecal injection of ephedrine produced spinal anesthesia which did not differ from that produced by common spinal anesthetic agents. The minimal effective concentration of ephedrine which would produce spinal anesthesia in monkeys was 2.5 per cent and the dose was 15 mg. per kilogram. When the concentration of ephedrine was reduced to 1 per cent and the dose to 6 or 8 mg. per kilogram, analgesia without motor disturbance occurred. When the concentration and dose of ephedrine were further reduced, it became ineffective. A dose of 30 mg. per kilogram of a 5 per cent solution produced spinal anesthesia for four hours or more. Recovery from this dosage was complete although some muscular weakness persisted for a few days. No distinct excitation was noticed after intrathecal injections of ephedrine except a slight hyperactive knee jerk. The clinical picture and neurological signs were quite different from those described following acute anoxia of the spinal cord and therefore vasoconstriction was considered to be an unimportant factor in this connection.

Intrathecal injection of 3.0 mg. per kilogram of 1 per cent neosynephrine resulted in slight muscular weakness of short duration, while 6.0 to 9.0 mg. per kilogram resulted in tremors, hyperreactive knee jerks and general depression. The duration and intensity of general depression were further increased in proportion to the concentration and dose. A dosage of 15 mg. per kilogram in 2.5 per cent solution produced spinal anesthesia which, however, was different from that produced by the common spinal anesthetic agents in that there was not complete motor paralysis. A dosage of 30 mg. per kilogram in 5 per cent solution produced profound spinal anesthesia without complete recovery.

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