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THE EFFECTS UPON THE DURATION OF SPINAL ANESTHESIA OF COMBINING NONANESTHETIC SUBSTANCES WITH THE AGENT * †

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IT has become common practice for anesthesiologists to combine various substances, many of them nonanesthetic, with the spinal anesthetic agent for the purpose of intensifying and prolonging the action or controlling the extent of the block. Glucose, for example, is added to make the solution hyperbaric and to assist in confining the drug to the desired spinal segments. Vasoconstrictors are added to intensify the drug's action. Procaine, although an anesthetic substance, is often added to increase the specific gravity of the solution and to shorten the latent period of longer lasting drugs. Whether or not these substances are of value is based to a large extent upon clinical impression rather than upon factual evidence. Inasmuch as there is presently considerable discussion concerning neurologic sequelae to spinal anesthesia the question arises as to whether these substances contribute any additional hazard. It is desirable to know whether or not they actually are of service or should be omitted. This study was instituted to obtain factual data on the value of these substances as adjuncts to the agent.

METHOD OF STUDY

We are fortunate in having access to a group of patients each of whom requires several spinal anesthesias at two, three or four day

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intervals. Repeated anesthesia in the same patient utilizing the same technic is thus possible. These patients are all women who require anesthesia for implantation of radium for carcinoma of the cervix. Inasmuch as this procedure is innocuous, brief, accompanied by little or no trauma or blood loss and is performed on subjects whose disease is in the incipient stage, who are of the same sex, in about the same age group, in good physical condition, who need the same extent of anesthesia without benefit of preanesthetic medication or medication of any sort, these subjects have been ideal for study of finer details and controversial issues concerning spinal anesthesia. In a previous issue of this journal we reported the results of a study of various vasoconstrictors combined with nupercaine and pontocaine (1) in some of these patients. The methods of induction and conduct of anesthesia used in the following study are identical to those described in that report.

RESULTS

Effects of Glucose.—It has been our impression for some time that glucose not only is useful for increasing the specific gravity of the anesthetic solution but also has a potentiating effect when combined with the anesthetic agent. Furthermore, we have had the impression that the induction time, that is, the latent period from moment of injection of the solution until anesthesia is established, is prolonged when glucose is used. In order to study these impressions, saddle block anesthesia was induced in 12 controls with 50 mg. of procaine in saline solution. Several days later the same dose of procaine was administered in the same volume of 10 per cent glucose to these same patients. The results are summarized in table 1. The average induction time was shortened from 2 minutes, 38 seconds in the controls to 1 minute, 10 seconds. The duration of anesthesia was changed little, however, averaging 80 minutes in the control and 78 minutes when glucose was used. Different results were obtained when pontocaine was used. The average

TABLE 1

Pt.	Procaine-Saline		Procaine-Glucose	
	Induction Time, seconds	Duration, minutes	Induction Time, seconds	Duration, minutes
1	290	80	140	118
2	155	72	120	72
3	125	68	170	50
4	105	109	120	53
5	210	68	140	77
6	110	57	90	62
7	150	56	80	49
8	145	117	120	115
9	107	115	75	90
10	95	85	105	87
11	95	71	75	91
12	145	65	75	70
Av.	158	80	70	78

induction time was 2 minutes, 7 seconds when 5 mg. of pontocaine was dissolved in physiologic saline solution and 2 minutes, 9 seconds when 10 per cent dextrose was the solvent. Without glucose, the average duration was 146 minutes and with glucose, 188 minutes, or an average increase in duration of 28 per cent. These results are summarized in table 2. We are not able to explain exactly why glucose appears to prolong the action of pontocaine and not that of procaine but it may be that the acidifying effect of the glucose solution prevents partial precipitation of the pontocaine. This particular point is discussed later in this paper. Attempts to study nupercaine in saline solution were not successful because the anesthesia was "spotty" and could not be localized. The glucose was of definite benefit when combined with nupercaine because it permitted exact localization and yielded uniform anesthesia.

TABLE 2

	Pontocaine-Saline		Pontocaine-Glucose	
Pt.	Induction Time, seconds	Duration, minutes	Induction Time, seconds	Duration, minutes
1	110	140	70	195
2	160	75	135	215
3	135	105	145	140
4	160	170	190	160
5	150	290	165	260
6	300	95	135	165
7	195	135	75	140
8	110	125	60	130
9	105	175	120	220
10	95	185	110	305
11	124	180	150	155
12	190	130	85	175
13	100	160	130	225
14	205	135	145	180
15	270	90	123	150
Av.	127	146	129	188

On a number of occasions the agent has been inadvertently omitted from the solution and glucose alone was injected. It has been our impression in these instances that hypalgesia was present. In order to confirm or dispel this impression, 10 subjects were deliberately given intrathecal injections of 2 cc. of 10 per cent glucose. They were tested for hypalgesia, anesthesia, reflex changes, two point discrimination and changes in motor power. Eight showed hypalgesia tested by the pin prick method with a definite line of demarcation between the hypalgesic and the normal area. The duration of this hypalgesia varied from 15 to 660 seconds, averaging approximately 200 seconds. No other sensory changes were noted. Vibratory sense, two point discrimination and motor power were not disturbed. These injections were then followed after 10 minutes by the injection of 5 mg. of pontocaine in 10 per cent glucose. In all instances there was a tendency for anesthesia

to "creep" and be "spotty." The localizing effect that glucose ordinarily affords apparently was no longer present.

Some anesthesiologists are reluctant to use glucose for spinal anesthesia on the premise that it predisposes to a high incidence of neurologic sequelae. No factual data are available to back their contention. Spinal anesthesia has been induced 15,000 times at Charity Hospital during the past ten years. The agents used were metycaine, procaine, pontocaine, lucaine, cylaine, xylocaine or nupercaine dissolved in glucose solution. No instance of a well-defined neurologic complication was observed in this group of patients during their stay in the hospital.

Effects of Alkalis.—Another impression occasionally encountered among anesthesiologists is that the alkalinity of the cerebrospinal fluid in some way is responsible for variable results obtained in spinal anesthetic technics. Local anesthetics are weak organic bases. They are ordinarily dispensed as salts of strong acids, such as sulfuric, hydro-

TABLE 3

Pt.	Procaine-Glucose Induction Time, seconds	Procaine-Glucose Duration, minutes	Alk. Procaine-Glucose Induction Time, seconds	Alk. Procaine-Glucose Duration, minutes
1	110	95	100	115
2	150	120	155	105
3	110	80	135	65
4	60	180	90	165
5	115	100	115	110
6	105	60	75	60
7	130	95	105	85
8	100	90	160	75
9	135	100	70	90
10	65	80	80	75
11	135	165	110	145
12	120	115	100	160
Av.	70	106.8	70	104.2

chloric and others. The salts are more soluble in water than the base. Consequently, when solutions are alkalinized, a precipitate of the free base forms. The hydrogen ion concentration or precipitation point varies with each drug. Nupercaine and pontocaine precipitate at a pH between 7.2 and 7.5. Procaine precipitates above a pH of 8.0. In order to study the effects of alkalinity, procaine hydrochloride dissolved in glucose was alkalinized with sodium bicarbonate until the pH was 8.0. Spinal anesthesia was induced, using the saddle block technic, with 50 mg. of procaine. The duration of action and plane of anesthesia were identical to that obtained with procaine and glucose without alkalinization (pH 6.4). The data are summarized in table 3.

A comparative study between alkaline solutions of pontocaine and nupercaine could not be made because attempts at alkalinization of these agents invariably yielded clouding or precipitation. Solutions of glucose are acid, the pH varying from 6.4 to 6.8 depending upon the source of the specimen. Unbuffered solutions of pontocaine or nuper-

caine yield a faint white precipitate when combined with cerebrospinal fluid, presumably owing to the effect of the sodium bicarbonate normally present in the cerebrospinal fluid. Pontocaine, 20 mg. in 4 cc. of 10 per cent glucose, added to 20 cc. of spinal fluid, yields no such precipitate. The hydrogen ion concentration of such a mixture remains on the acid side. This may explain the discrepancy between the effects of glucose upon the action of procaine and of pontocaine. Procaine does not

TABLE 4

Pt.	Pontocaine		Pontocaine-Procaine	
	Induction Time, seconds	Duration, minutes	Induction Time, seconds	Duration, minutes
1	160	97	175	96
2	215	54	185	129
3	105	59	110	241
4	145	71	210	116
5	145	85	110	215
6	160	136	160	156
7	200	137	170	152
8	80	98	75	90
9	110	126	127	217
10	155	168	110	201
11	160	103	205	105
12	200	84	130	122
13	125	104	140	146
14	120	144	80	106
15	260	64	205	112
16	75	121	150	197
17	160	91	165	82
18	115	119	95	157
19	110	178	105	237
20	155	78	130	89
21	220	95	200	103
22	280	156	195	140
23	280	110	250	120
24	120	156	115	145
25	230	185	230	185
26	115	122	150	185
27	235	70	70	192
28	315	184	170	133
29	215	41	195	101
30	170	124	275	165
31	140	76	95	148
32	110	93	170	88
33	195	69	185	135
Av.	169	109	155	146

precipitate in spinal fluid; pontocaine may precipitate and thereby cause a partial reduction in concentration of the agent. The glucose is sufficiently acid to prevent any of the pontocaine from precipitating and, therefore, no reduction in concentration results.

Effects of Combining Procaine with Longer Lasting Drugs.—Many anesthetists combine procaine with the longer lasting local anesthetic drugs to secure a hyperbaric solution and to shorten the latent or induction period of anesthesia. Pontocaine is often combined with procaine

with these views in mind. Whether or not any additive effect and shortening of the latent period actually occurs has never been demonstrated in a controlled study. In a series of controls, utilizing 5 mg. of pontocaine in 10 per cent glucose solution by the saddle block technic, the average induction time was 2 minutes, 49 seconds and the duration of anesthesia 109 minutes. When the pontocaine was fortified with 75 mg. of procaine, the average induction time was shortened to 2 minutes, 35 seconds and the average duration of anesthesia was lengthened to 146 minutes. In other words, procaine causes an average increase in duration of 28 per cent. The data are summarized in table 4. Similar results were obtained when the effects of nupercaine-procaine mixtures were studied in 32 subjects. The effects of 2.5 mg. of nupercaine in 10 per cent glucose solution were compared to those of an equivalent amount fortified with 75 mg. of procaine. The average induction time was 4 minutes and 5 seconds and average duration of anesthesia 89 minutes when nupercaine in glucose was used alone. When nupercaine was combined with procaine, the average induction time was shortened to 3 minutes and 3 seconds and the duration increased to 115 minutes. Here again the average increase in duration was approximately 27 per cent. These results are summarized in table 5. Although the duration of anesthesia obtained with various spinal anesthetic agents depends largely upon the chemical nature rather than the concentration of the drug, concentration does play a role in prolonging anesthesia. The latent period is shortened and the total duration of sensory anesthesia prolonged. The duration is not prolonged, however, in direct proportion to concentration of drug. The longer latent period of nupercaine in comparison to that of pontocaine when each drug was used alone and in combination with procaine is worthy of note. The clinical impression that longer lasting drugs are characterized by a slower onset of anesthesia and motor paralysis is borne out by these observations. The prolongation obtained by adding procaine to these agents is not as pronounced as that obtained by adding epinephrine. Epinephrine causes an increase averaging 65 per cent, procaine an average increase of 27 per cent.

Effects of Vasoconstrictors Upon the Duration of Action of Procaine.—In previous studies reported from this department utilizing these same patients and the same technic, it was observed that vasoconstrictors significantly prolonged the action of pontocaine and nupercaine (1). These results are in agreement with the observation of others (3, 4). In reiteration it appears that epinephrine is superior to other vasoconstrictors in prolonging the action of both nupercaine and pontocaine. Procaine, however, was not studied at that time. In view of the fact that procaine is one of the most widely used and the most serviceable local anesthetic drugs, a study utilizing the same technic appeared desirable. The preliminary results of this study have been reported elsewhere (2) but for the sake of completeness are

summarized as follows: epinephrine, 0.375 mg. combined with 75 mg. of procaine yielded an average duration of anesthesia of 95 minutes while when it was used alone the average was 58 minutes. The average increase in duration was 65 per cent. Pituitrin, 10 international units combined with procaine, 75 mg., yielded an average increase of 24 minutes or 54 per cent increase over the control. Norepinephrine (arterenol), 0.038 mg., combined with procaine, 75 mg., yielded an aver-

TABLE 5

Pt.	Nupercaine		Nupercaine-Procaine	
	Induction Time, seconds	Duration, minutes	Induction Time, seconds	Duration, minutes
1	347	55	145	137
2	165	146	125	224
3	347	50	208	68
4	240	80	195	88
5	167	88	79	85
6	230	52	225	55
7	350	59	180	142
8	200	43	105	77
9	225	63	340	110
10	155	85	165	159
11	285	105	165	150
12	220	156	165	243
13	390	66	435	75
14	310	79	185	94
15	310	77	150	94
16	250	90	410	106
17	170	103	115	175
18	225	112	195	99
19	260	110	140	173
20	365	68	160	92
21	275	62	212	60
22	345	40	185	127
23	260	141	196	147
24	230	40	194	75
25	200	125	260	140
26	370	54	245	87
27	165	123	226	80
28	325	101	150	108
29	148	117	208	110
30	255	61	252	64
31	253	65	152	131
32	627	119	125	95
Av.		85.5		114.7
	245	85.5	183	114.7

age increase of 24 minutes or 49 per cent over the control. Ephedrine, 50 mg. combined with procaine, 75 mg., yielded an average increase of 5.4 minutes or a 10 per cent prolongation over the control. The behavior of vasoconstrictors in combination with procaine follows the same general pattern observed when pontocaine and nupercaine were studied (1).

Local Anesthetic Effects of Ephedrine and Epinephrine.—It is well known that an overlapping of pharmacologic action exists between

many drugs. Atropine, for example, possesses a mildly stimulating action on the central nervous system, an anticholinergic action, a local anesthetic action and an antihistaminic action. Pyribenzamine likewise possesses a local anesthetic action, an antihistaminic and, in addition, a mild hypnotic action. Some of the vasoconstrictors possess a weak local anesthetic action in addition to the pressor and vasoconstrictor actions. Papers on the anesthetic effect of ephedrine, epinephrine, oenethyl and other vasconstrictors used intradermally and intrathecally have appeared from time to time in the literature (5, 6). The prolongation of spinal anesthesia by vasoconstrictors could possibly be the result of an additive effect of the local anesthetic drug and the vasoconstrictors. In order to test the value of ephedrine as a spinal anesthetic agent 6 patients were given 50 mg. of ephedrine sulfate intrathecally. A well-defined zone of hypalgesia or anesthesia was not demonstrated. Eight patients were given 1 mg. of epinephrine in dextrose intrathecally and again, no area of hypalgesia or anesthesia could be demonstrated. It was obvious that the local anesthetic effect of both these drugs is too feeble to induce spinal anesthesia of a degree necessary to be clinically useful, and no further attempts were made to pursue this aspect of the problem.

Effects of Varying the Dose of Epinephrine.—At the outset 1 mg. of epinephrine was combined with the spinal anesthetic agent to prolong anesthesia. No rational basis was used in adopting this dosage except, perhaps, that it was the content of an ampule of a 1 to 1000 solution and it appeared logical to add it. It occurred to us that smaller dosages might be as effective and, consequently, a study was undertaken to determine the minimal effective dose of epinephrine necessary to yield significant intensification and prolongation of spinal anesthesia. The average duration of anesthesia using 5 mg. of pontocaine with the saddle technic was 140–160 minutes when 1 mg. of epinephrine was used. A comparison was then made in a series in which 0.5 mg. of epinephrine was used for the first, and 0.25 mg. for the second spinal anesthesia. The average duration when a dose of 0.5 mg. was employed was 136 minutes compared with 120 minutes when the dose was 0.25 mg. When 0.125 mg. was used in the first block, the duration was 113 minutes compared with an average of 129 minutes in the second block in which 0.25 mg. was used. The data are summarized in table 6. It is apparent, then, that decreasing the dose of epinephrine has some effect upon duration but that variations are not in direct proportion to the decrease in concentration of epinephrine. Apparently for saddle block anesthesia the minimal effective dose of epinephrine which is clinically satisfactory is between 0.25 and 0.50 mg. There is little to be gained by exceeding 0.5 mg.

Differences in Duration Between "High" and "Low" Spinal Anesthesia.—We have consistently been unable to obtain any significant prolongation or intensification of action by combining neosynephrine

with procaine, pontocaine or nupercaine (1, 7). Any prolongation we have observed is in no way comparable to that reported by other clinicians. It has been suggested to us that inasmuch as we have employed the saddle block technic in these studies, possibly a difference might exist between the susceptibility of sacral segments of the cord and the upper lumbar and thoracic segments. This possibility appeared remote but in order to dispel this doubt, 20 patients were given 50 mg. of procaine combined with 25 mg. of ephedrine in 10 per cent dextrose solution. A saddle block distribution of anesthesia was obtained. At a later date in order to anesthetize a greater segment of the

TABLE 6

Pt.	Pontocaine 5 mg./Epinephrine ¼ mg. Induction Time, seconds	Duration, minutes	Pontocaine 5 mg./Epinephrine ½ mg. Induction Time, seconds	Duration, minutes
1	150	90	105	115
2	120	115	135	105
3	225	129	100	55
4	310	146	105	259
5	90	170	325	86
6	140	137	110	83
7	80	109	90	184
8	105	117	90	175
9	80	204	125	172
10	120	102	200	125
11	280	46	120	143
12	115	129	220	186
13	130	103	165	167
14	110	74	110	84
15	100	84	130	38
16	210	61	105	86
17	100	216	70	251
18	110	161	170	244
19	90	82	100	128
20	105	45	90	92
21	80	185	50	184
22	150	106	100	103
23	70	139	70	61
24	35	137	40	132
Av.	129	120	122	136

cord, 100 mg. of procaine combined with 50 mg. of ephedrine in 10 per cent dextrose was given to these same patients. The level was allowed to extend as near as possible to the tenth thoracic segment. The average duration of sensory anesthesia with the saddle block technic was 68 minutes; with the higher distribution of anesthesia it was 77 minutes. The data are summarized in table 7. It is obvious from these figures that no remarkable difference in susceptibility to these drugs exists in the two parts of the cord.

Systemic Effects.—A total of 882 patients has been used in these studies. Each patient received one block as a control and at least one additional block in which a vasoconstrictor or other agent was studied. The majority of these patients (662) received vasoconstrictors. In

general, no significant systemic elevation in the blood pressure level was noted in any case. The drugs studied and quantities used were: epinephrine 1.0, 0.5, 0.25 and 0.12 mg.; ephedrine 50 mg.; neosynephrine 1.0, 5 and 10 mg.; pituitrin 10 units; oenethyl 100 mg., vasoxyl 10 mg. and arterenol 0.038 mg. Attempts to determine the level of procaine in the blood after intrathecal injection were not successful. A qualitative test using the diazo reaction was positive when procaine alone was administered intrathecally, but the reaction was difficult to elicit when epinephrine was combined with the procaine. This is evidence in support of the suggestion that vasoconstriction is the mechanism by which the action is prolonged when this combination is utilized.

TABLE 7

HIGH-LOW SPINAL SERIES

Pt.	High Spinal		Low Spinal	
	Induction Time, seconds	Duration, minutes	Induction Time, seconds	Duration, minutes
1	180	72	140	73
2	170	87	160	92
3	170	75	165	87
4	220	90	145	94
5	130	86	125	54
6	145	65	105	51
7	190	49	260	35
8	255	76	380	71
9	170	54	170	53
10	160	98	165	73
11	115	74	240	62
12	180	71	155	68
13	190	92	195	66
14	200	66	230	63
15	215	69	130	62
16	195	74	200	78
17	120	104	80	75
18	195	62	255	68
19	275	84	140	71
20	150	84	140	62
Av.		76.6		67.9
	181	76.6	168	67.9

Neurologic Sequelae.—No neurologic sequelae were noted in this series of 882 patients even though each received at least two, and in many instances three or more, intrathecal injections. Obviously, the series is too small to permit any significant conclusions concerning neurologic sequelae. Examination of the cerebrospinal fluid in 100 patients after the first lumbar puncture likewise showed no significant deviation from the normal (8).

SUMMARY

Patients requiring repeated anesthesia with identical technics were used to compare the effects of nonanesthetic substances combined with the agent upon the duration of spinal anesthesia. Glucose did not pro-

long the duration of anesthesia but did shorten the induction period when procaine was studied. The induction period of pontocaine was shortened; the duration was prolonged.

Omitting the glucose when nupercaine was used resulted in "spotty" and unsatisfactory anesthesia. When glucose was added, well demarcated levels of uniform distribution of anesthesia were secured.

Glucose alone intrathecally resulted in a definite distribution of hypalgesia which was evanescent. No definite areas of anesthesia or motor effects were observed.

Alkalinizing the procaine-glucose solution to a pH of 8.0 caused no significant change in duration of anesthesia. Alkalinizing pontocaine and nupercaine caused precipitation of the agents so that no comparison could be made.

Combining procaine with pontocaine shortened the induction time and prolonged anesthetic time 28 per cent. Similar observations were noted with nupercaine.

Combining epinephrine, pituitrin and arterenol with procaine caused significant prolongation of action. The action was not prolonged when ephedrine was used. These drugs may be placed in the following order so far as efficiency is concerned: epinephrine, pituitrin, arterenol and ephedrine.

Epinephrine and ephedrine alone, administered intrathecally, do not produce anesthesia of clinical usefulness.

Varying the dose of epinephrine causes some variation in duration of anesthesia but not in proportion to the dose. A dose exceeding 0.5 mg. appears to prolong the action only little more than when 0.5 mg. is used. Reducing the dose below 0.25 mg. causes a significant reduction in effectiveness. The minimal effective dose for the saddle block technic appears to be between 0.25 and 0.50 mg.

The effect of procaine-ephedrine mixture in the sacral segments appears to be similar to its behavior in the lumbar and lower thoracic segments in regards to duration of anesthesia.

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