NUPERCAINE-GLUCOSE FOR SPINAL ANESTHESIA: RESULTS OF OVER 5000 CLINICAL ADMINISTRATIONS *

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IT is needless to indicate to anesthesiologists the relative merits and demerits of spinal anesthesia induced by the continuous spinal and the single injection technics. Anesthesia is induced and maintained with greater ease by the latter. The feature which most limits the usefulness of the single injection technic is that often the operation outlasts the anesthesia. Although many drugs have been employed for spinal anesthesia, few yield prolonged action by the single injection method. Pontocaine and nupercaine are the two currently available agents most useful in this respect. Pontocaine has enjoyed popularity since Sise (1) advocated its administration in a solution made hyperbaric by glucose. The effects of gravity are utilized to extend anesthesia to the desired spinal segments by tilting the patient during the induction period. Exact localization of the drug is possible because cephalad diffusion of the pontocaine is minimized by the glucose. When employed in suitable subjects by capable individuals, the pontocaine-glucose technic yields excellent results and is entirely satisfactory. Although pontocaine is suitable for most operations, anesthesia does not last more than one and a half to two hours. For longer procedures nupercaine is preferred.

The various methods which have been advocated for the administration of nupercaine are not as simple as is the technic described by Sise for pontocaine. The method described by Jones (2) has been the most popular until recently. In this technic a relatively large volume of a hypobaric solution of nupercaine is employed. During the induction period the subject must be placed face downward and the table is tilted so that the head remains dependent for approximately ten minutes. The prone position is absolutely necessary to allow the posterior root filaments to come in contact with the solution so that satisfactory sensory anesthesia may be secured. The results obtained by Jones's technic are frequently disappointing because diffusion of the nupercaine is an uncontrollable factor. Localization of anesthesia at the desired

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spinal segment is secured with difficulty because there is no logical basis for determining the volume of solution required. Severe circulatory disturbances usually follow the change from the prone to the supine position after anesthesia is established. In addition, the induction is time-consuming. The technic described by Wilson (3) also requires the use of a large volume of nupercaine solution. The subject remains in the sitting position during injection of the solution so that upward diffusion is insured. This technic is characterized by lack of controllability and is hazardous even when employed by capable individuals.

In the view of the success obtained with pontocaine-glucose, we wondered at the possibility of extending the method to the use of nupercaine. There appeared to be no reason why nupercaine could not be substituted for pontocaine in the glucose technic. Pontocaine and nupercaine behave similarly as far as solubility, stability and hydrogen ion concentration of the aqueous solution is concerned. The prolonged action of nupercaine could thus be secured with the precision and simplicity allowed by the pontocaine-glucose technic.

The use of hyperbaric solutions of nupercaine has been described previously. Silverton (4) employed an 0.5 per cent solution in 6 per cent glucose. Sankey and Whitacre (5) have used the concentration of nupercaine recommended by Jones (1:1500) which was made hyperbaric by glucose. The height of anesthesia is largely controlled by displacement afforded by the large volume of fluid injected, but may be further controlled by gravity should the need arise.

The technic we have developed is simpler than any previously described for nupercaine. Furthermore, it is rapidly executed and reasonably controllable. The results are little influenced by wide variations in the intrinsic factors such as length and diameter of the cord, size of the subarachnoid space, or body weight. In this technic the only variable factor is the position of the patient during the induction period. The other intrinsic factors such as site of injection, dosage volume of solution, rate of injection and specific gravity of the solution remain constant for a given extent of anesthesia. The patient is tilted immediately after injection of the solution and progress of anesthesia is followed from moment to moment until it is at the desired spinal segment, at which time cephalad ascent is terminated by leveling the table. For "low" spinal anesthesia there is no need to tilt the table. If "saddle" anesthesia is desired, the puncture is performed with the subject in the upright sitting position. In this manner, anesthesia may be so localized as to involve the perineum and not the legs and thigh.

Nupercaine (also known as percaine and dibucaine) differs in a number of respects from procaine, pontocaine and related drugs. The majority of local anesthetics are esters of complex alcohols. Nupercaine, on the other hand, is a substituted amide and not an ester. It

is a weak base that forms salts when neutralized by mineral acids. The base is easily precipitated from aqueous solutions of its salts by alkalies and basic salts. It is advisable to rinse glassware with water acidified by dilute hydrochloric acid used for preparing the solution.

TECHNIC

The preparation employed for this technic consists of 0.5 per cent (1–200) nupercaine hydrochloride dissolved in a phosphate buffer and saline solution. Each cubic centimeter contains 5 mg. of the drug. The volume of solution containing the estimated dose is mixed with an equal volume of 10 per cent glucose in distilled water or physiologic saline solution. The resulting volume of solution, even when the maximum dose is employed, is relatively small. The mixture is injected into the subarachnoid space through a 20 or 22 gauge needle as rapidly as gentle pressure on the plunger permits without barbotage. The lateral prone position is preferred when "medium" and "high" spinal anesthesia are desired. The upright sitting position is mandatory for saddle anesthesia. The puncture is performed at the third interspace for anesthesia above the costal margin and at the fourth lumbar interspace when less extensive anesthesia is desired. Immediately following the injection the patient is placed in the supine position and the table is tilted in the Trendelenburg position. The angle varies with the height of anesthesia desired. For high spinal anesthesia for upper abdominal operations it may be as much as 20 degrees. The head is flexed as sharply as possible upon the thorax by supporting it on a pillow which has been doubled upon itself. Unless this precaution is rigidly observed, the mixture may ascend into the cervical region and cause respiratory failure by paralyzing the phrenic nerves. Generally, within fifteen to twenty seconds the subject notes a feeling of warmth or numbness or both in the lower extremities. In contrast to the behavior of the short-acting drugs, the onset of anesthesia is delayed when nupercaine or pontocaine is used. Occasionally, ten minutes may be required for establishment of complete anesthesia when nupercaine is introduced intrathecally. However, hypalgesia, which always precedes anesthesia, ensues immediately. Consequently, when performing the sensory examination to establish the level of anesthesia, one does not seek the areas of complete insensibility, but instead those of hypalgesia, or diminished sensation. The line of demarcation between the hypalgesic and the unanesthetized area is reasonably sharp and well defined. One should always test sensation gently with a sharp instrument. When the line of demarcation lies at the desired spinal segment the ascent of the drug is terminated by promptly readjusting the table to the horizontal position. The hypalgesic areas in due time become completely anesthetic. There is little or no tendency for anesthesia to creep beyond a given segment once it has been established at that level.

This is not the case with pontocaine. In this respect nupercaine is more controllable than pontocaine.

The time the patient remains in the inclined position varies for each individual case. As few as thirty seconds or as long as three minutes may be required for hypalgesia to appear in the desired segment. So many variable factors influence the cephalad progress of the drug that no fixed time interval can be stated. The degree of inclination of the operating table, likewise, cannot be standardized but must be adjusted to suit the needs of each individual patient. For the sake of safety the progress of the drug in the cephalad direction must be followed by almost continuous sensory examinations as long as the patient is in the inclined position. If the drug appears to involve the upper thoracic or lower cervical segments, the operating table should be restored immediately to the horizontal position or placed in the reverse Trendelenburg position at an angle of 5 to 10 degrees. The reverse Trendelenburg position not only terminates the cephalad advance of the drug, but favors a caudad regression of the solution. For best results it is imperative that there be as little delay as possible in inclining the operating table when the intrathecal injection is completed. Failure to obtain satisfactory anesthesia for upper abdominal surgical procedures is frequently due to delays in inclining the table promptly. Trendelenburg position is not necessary to obtain "low" spinal anesthesia. For "saddle" anesthesia the puncture should be performed with the patient in the upright sitting position and this position should be maintained for thirty to sixty seconds after the drug is injected.

It is a well-established pharmacologic fact that the smaller and unmyelinated nerve fibers are affected first and to a greater extent by local anesthetic drugs. The sensory and autonomic fibers, therefore, since they are the smallest in a mixed nerve, are the first to be affected. The motor fibers are affected later. For several minutes after establishment of sensory anesthesia by this technic, motor power remains unchanged or is mildly depressed. Motor paralysis is rarely completely established in less than five minutes. The degree of motor paralysis varies in the different spinal segments, depending upon the concentration of drug in each segment. In the thoracic region where the concentration of the drug is obviously less than at the site of puncture, more sensory fibers are involved than motor. Muscular relaxation, therefore, is incomplete or absent. At the site of injection and throughout the lumbar region, the concentration of the drug is greater and all fibers are affected. Anesthesia, therefore, is complete. Both anesthesia and motor paralysis are present. The concentration of the drug in the upper spinal segments may be increased by increasing the total amount of the drug injected. It is obvious, then, that muscle relaxation is controlled by varying the quantity of the drug. Intensity and extent of anesthesia desired, therefore, depend upon dosage. For upper abdominal operations, 12 to 15 mg. of nupercaine yield satis-

factory sensory and motor anesthesia. For anesthesia below the costal margin, 7 to 10 mg. are ample. For "saddle" anesthesia 2.5 mg. suffice. In the upper age group the lower dose range should be employed.

The time-honored custom of mixing the drug with cerebrospinal fluid is dispensed with in this technic for two reasons: First, spinal fluid, which has a pH 7.4, is sufficiently alkaline to cause a precipitation of the nupercaine base from aqueous solutions of the hydrochloride. Unsatisfactory anesthesia results if one employs solutions in which flocculation has appeared. Laboratory studies suggest that glucose prevents precipitation of the free base when solutions of salts of local anesthetic agents are injected into the subarachnoid space. Second, the solution may be prepared before the lumbar puncture is performed and injected immediately upon completion of the puncture. Failures owing to dislodgment of the needle or shifting of the patient's position while the solutions are being prepared are thus averted.

Fifteen to twenty minutes should be allowed to elapse after injection of the solution before changes in posture are attempted. Trendelenburg prone, lithotomy and other positions necessary for completing the operation may then be employed with safety.

RESULTS

Anesthesia induced by this technic was employed for 5453 surgical and obstetrical procedures of all types. In 21 per cent of the cases, anesthesia was "high" and extended to or beyond the seventh thoracic segment. In 30.1 per cent of the cases it was "medium" and extended between the tenth and seventh thoracic segment; and in the remainder of the cases, it was low and confined below the tenth thoracic segment. Most of the low spinal anesthesias were saddle blocks. Satisfactory anesthesia was obtained in all but 5.7 per cent of the "high" spinals; 4.9 per cent of the "medium," and 2 per cent of the "low" and "saddle" blocks. Inhalation or intravenous anesthesia was necessary in these cases because of complete or partial failure of the block or because of extreme apprehension of the patient. Seventy per cent of the patients who had upper abdominal surgical procedures were given morphine intravenously because they were restless or complained of pain upon traction on the upper abdominal viscera.

Records on duration of anesthesia were difficult to maintain because in most instances anesthesia outlasted the operation and the end point was difficult to determine after the patients had been returned to their beds. One must emphasize that duration of anesthesia may vary widely with a given drug from patient to patient and even in the same patient when the same technic and dosage are employed two or more consecutive times. However, the average duration of anesthesia with nupercaine is two to three hours in upper abdominal surgery. In low spinal anesthesia and saddle block the duration is considerably longer. At times six and seven hours' duration have been recorded. The addi-

TABLE 1-A

COMPLICATIONS DURING HIGH SPINAL ANESTHESIA

	Nupercaine	Pontocaine
Total cases	1252	836
Hypotension	72%	71%
Vasoconstrictor administered once	71%	82%
Vasoconstrictor twice or more	29%	18%
Nausea and vomiting	4.3%	4%
Unsatisfactory anesthesia	5.7%	5%
Intravenous morphine and scopolamine	30%	20.4%

TABLE 1-B

POSTOPERATIVE COMPLICATIONS WITH HIGH SPINAL ANESTHESIA

	Nupercaine, Per Cent	Pontocaine, Per Cent
Atelectasis	3.7	2
Dyspnea	0.01	0
Sore throat	0.06	0
Cough and upper respiratory infection	1.8	2.3
Shock	1.1	0.2
Distention	23.3	13.0
Nausea and vomiting	8.2	9
Evisceration	0.02	0
Urinary retention	2.8	3.7
Headaches of all kinds	7.3	7.7

TABLE 2-A

COMPLICATIONS WITH MEDIUM AND LOW SPINAL WITH NUPERCAINE-GLUCOSE

	Medium	Low and Saddle
Total cases	1205	2524
Hypotension	75.3%	39%
Vasoconstrictor used once	81%	94%
Vasoconstrictor twice or more	19	6
Nausea and vomiting	3	1.8
Unsatisfactory anesthesia	4.3	1.1

TABLE 2-B

POSTOPERATIVE COMPLICATIONS WITH MEDIUM AND LOW SPINAL ANESTHESIA

	Medium, Per Cent	Low and Saddle, Per Cent
Atelectasis	1.6	0
Cough or upper respiratory infection	5.7	0.8
Shock	0	0
Distention	4.1	0.1
Urinary retention	4.6	6
Cystitis	1.8	?
Headaches of all kinds	4.6	8

tion of 1 mg. of epinephrine to nupercaine prolongs the duration of anesthesia an average of 40 per cent. Ephedrine does not appear to affect the duration appreciably (6). Although it is difficult to compare accurately and evaluate complications encountered with different agents, a study of 836 "high" spinal anesthesias induced with pontocaine-glucose suggests that the variety and nature of complications do not differ materially with other drugs. Hypotension was the most annoying and serious complication common to both drugs (table 1A). No. significant differences were noted in the time of onset, severity or duration and response to therapy between the hypotension observed with nupercaine and that occurring following induction of anesthesia and pontocaine. No remarkable differences were noted in the incidence of nausea, vomiting, restlessness, urinary retention or headache. The incidence of headaches appears greater in the low spinal or saddle block anesthesia. Exactly why this occurs is unexplainable. Premedication consisted of a short-acting barbiturate, morphine and scopolamine in adequate dosage, one to one and one-half hours prior to anesthesia.

DISCUSSION

In evaluating a local anesthetic drug for intrathecal administration, one must base its merits upon potency, systemic toxicity and local toxicity. The comment is frequently made by many clinicians that nupercaine is more toxic than other currently employed local anesthetic drugs. Nupercaine is both more toxic and more potent than procaine and similar agents. However, it must be emphasized that observers frequently confuse toxicity with potency. Data on the systemic toxicity of local anesthetic drugs for man are meager and difficult to estimate. Studies in animals indicate that nupercaine is approximately fifteen to twenty times more toxic than procaine. On the other hand, it is twenty times more potent. One milligram of nupercaine, then, is theoretically equivalent to 20 mg. of procaine. The amount of nupercaine necessary to obtain the same extent of anesthesia yielded by procaine is considerably less, approximately one-twentieth. Therefore, although nupercaine possesses a greater absolute toxicity, its relative toxicity approximates that of procaine.

The more potent a drug is, the greater the intensity of anesthesia it will cause when used in equivalent amounts. The severity of physiologic disturbances which accompany spinal anesthesia depends upon the intensity and extent of anesthesia. Intensity of anesthesia depends upon the number of dermatomes affected by the drug. The greater the number of sensory, motor and autonomic components affected in a spinal segment, the more intense will be the anesthesia. Physiologic disturbances appear during spinal block, regardless of the drug employed, if the amount injected is sufficient to produce extensive, intense anesthesia. It is common knowledge that the most distressing physiologic disturbance accompanying spinal anesthesia is hypotension.

Relatively small amounts of nupercaine, by yielding intense anesthesia, may cause marked physiologic disturbances, particularly circulatory disturbances. These are more frequent when anesthesia affects many spinal segments. Hypotension is erroneously described as a manifestation of toxicity. Hypotension is not a symptom of toxicity but rather of potency. Toxic reactions are caused by a rapid accumulation of a high concentration of the drug in the blood or to intolerance to the drug. Such reactions may be the result of accidental intravascular injection or rapid absorption of the drug from the site of injection. Excitement, nausea, vomiting, convulsions, and ultimately respiratory and circulatory failure are the usual symptoms of toxicity. Toxic reactions are not benefited by vasopressor substances, oxygen and other supportive measures so useful for the relief of hypotension. Fortunately, toxic reactions are rare in spinal anesthesia. In no instance were any manifestations of toxicity or intolerance to the drug noted in this study.

Considerable disagreement exists concerning the reversibility or "local toxicity" of various anesthetic drugs when administered intrathecally. Neurologic complications ascribable to changes produced in the intraspinal elements by the local action of the drug have been reported following the use of most of the currently employed local anesthetic drugs. It is almost impossible to draw any conclusions regarding the relative merits of one agent over another from the isolated case reports which appear in the literature. Systematic studies of this problem have not been attempted because of the difficulty of studying the spinal cord in routine autopsies. A considerable amount of data of an experimental nature exists, however. Recently Co Tui (7) and his co-workers, in comparing the effects of procaine, nupercaine and monocaine in cats and rabbits, found that slight transitory changes occur in the cords of these animals when therapeutically equivalent doses of drugs are employed. The quantity of nupercaine required to produce the same anesthetic effect as the pharmacologic equivalent of procaine produced the same degree of histologic change as procaine.

The changes lasted for the same period of time with each drug. On this basis one would assume that the "local toxicity" of nupercaine is no greater than a therapeutic equivalent of procaine.

The feeling that nupercaine will cause degenerative changes in the cord more frequently than the currently employed local anesthetic agents is not founded upon factual data. In the 5453 cases studied, no neurologic complications were noted during the period of hospitalization, which averaged fourteen to sixteen days. In this series, 209 patients received two injections of nupercaine and 38 received three or more. One patient received sixteen intrathecal administrations of nupercaine over a period of two years without any untoward reactions.

A good deal of discussion has been stimulated from time to time concerning the concentration of the nupercaine solutions. The impres-

sion popularized by the older clinicians that 1:200 or 1:400 nupercaine solutions will often produce neurologic changes seems unfounded from the experiences gained in this series and also from results of other workers, particularly those who have employed the drug for saddle block for obstetrics (8, 9, 10). The number of cases reported in these series, as in this one, has been in the thousands. It must be emphasized that this technic utilizes the same dosage as technics using dilute solutions. Instead of displacing a large volume of spinal fluid, as in the Jones technic, in this technic nupercaine becomes diluted with spinal fluid intrathecally over a given segment of cord. Ultimately, the same concentration of drug is used as in the technic employing a dilute solution.

A review of the literature from 1938 to 1946 has failed to reveal cases of spinal cord damage attributable to local toxicity of nupercaine. Twelve cases of paralysis of the abducens nerve with diplopia following spinal anesthesia with nupercaine have been reported. The etiology of this complication is not definitely established. It is reasonable to assume that it is not due to local toxicity of the drug upon the nerve itself, inasmuch as the solution injected obviously does not come in contact with this nerve (table 3).

TABLE 3

REVIEW OF LITERATURE (INDEX MEDICUS UNDER "ANESTHESIA") 1936-1948

Drug	Complications	No. of Cases	Recovery
Nupercaine	Paralysis of abducens and diplopia	12	Full recovery 23 days to 15 months postoperatively
Pontocaine	Flaccid crural paraplegia	1	None
	Hysterical gait	1	Complete after electrocerebral therapy
	Cervical arachnoiditis	1	Complete after laminectomy
	Paralysis of abducens, diplopia	1	Complete after 21 days
Pontocaine-Procaine Mixture	Neurogenic dysfunction of the urinary bladder	1	Recovery partial after presacral neurotomy
Procaine	Paralysis of abducens, diplopia	1	Complete after 4 months
	Paralysis of hypoglossal	1	Complete after 4 months
	Arachnoiditis and paralysis of bladder and lower limbs	1	Still disabled after 7 years.
	Spastic paraparesis	1	None
	Spastic myelitic syndrome	1	None
	Hysterical crural paresis	1	Complete
	Paralysis of diaphragm	1	None. Death on 28th postoperative day
Metycaine	Arachnoiditis with paralysis of both extremities	2	None
Spinocaine	Toxic myelopathy and/or cauda equina neuropathy	4	Complete recovery in one case. Partial recovery in the rest

Obviously, the same criteria for selection of patients, contraindications, conduct and precautions employed for spinal anesthesia with other drugs are applicable to this technic.

SUMMARY

Nupercaine mixed with glucose has been employed for spinal anesthesia by the single injection technic. The technic described is simpler than previously described technics for nupercaine. Clinical results indicate that complications and hazards differ little, if any, from those of other currently employed spinal anesthetic agents.

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