THE PHARMACOLOGY OF LOCAL ANESTHETIC AGENTS,
WITH SPECIAL REFERENCE TO THEIR USE
IN SPINAL ANESTHESIA

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The pharmacology of local anesthetic agents deserves special consideration in relation to spinal anesthesia. The physiological effects of spinal anesthesia on the organism as a whole are profound, yet they are entirely secondary to the action of the local drug within the subarachnoid space. Unless both the mode of action of such agents and the various modifying factors which may be present are appreciated, neither a clear understanding of the over-all effects of spinal anesthesia, nor a true clinical proficiency with the technique can be attained. Events which occur in the subarachnoid space following induction of spinal anesthesia are so important that they should be emphasized and considered anew, from an academic as well as from a practical point of view, in the light of recent investigations.

ACTION OF LOCAL ANESTHETIC AGENTS

Normal Transmission of Nerve Impulses. Before discussing the mode of action of local anesthetic agents and the various modifying factors, the normal transmission of nerve impulses should be considered (1, 2). Two main functions or attributes of nerve tissue are excitability and the ability to transmit impulses. Three phenomena, associated with these functions, are germane to an understanding of the mode of action of local anesthetic agents, namely, depolarization, alteration in membrane permeability, and oxygen consumption.

The surface membrane of a resting nerve is electrically charged so that there is a difference in potential of 60 to 100 mv. on its two sides (3, 4). The initiation or transmission of impulses along a nerve fiber is associated with alterations in this membrane potential. The changes in membrane potential are characterized by a removal of the polarity which, in turn, causes depolarization of the adjacent normal membrane, and thus a wave of transient depolarization (that is, activity) spreads along the nerve fiber. This transient wave of negativity, known as the action potential, not only removes the polarity of the membrane but actually "overshoots" or reverses the polarity. This membrane potential normally depends on oxidative metabolism and can be maintained only by the performance of metabolic work.

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The alterations in membrane potential during conduction are associated with changes in membrane permeability. The membrane permeability normally varies with increasing axon diameter (4). The product (permeability times axon diameter), however, is a constant for all types of nerves. Thus the flow of ions across the membrane remains constant per unit volume of axon regardless of its size (ergo, function) or the membrane resistance. The membrane of resting nerve is normally more permeable to potassium than to sodium ions, the latter being in a greater concentration in the extracellular than in the intracellular fluid where potassium ions predominate. During the depolarization of action potential the resistance of the membrane drops to about 2 per cent of its resting level. There is then a sudden migration of sodium ions across the membrane to the extent that the "overshoot" of the action potential is produced. An equal and almost simultaneous movement in the opposite direction of intracellular potassium ions across the membrane restores the membrane potential, and the excitation stops. During the refractory period a more gradual movement of ions back across the membrane restores the concentrations of intracellular and extracellular sodium and potassium to normal. The active state probably results from a great increase in permeability to sodium, which produces an action potential exceeding the resting membrane potential, thus reversing the polarity of the membrane (5).

In addition to changes in membrane potential and permeability, the conduction of nerve impulses has been demonstrated to be associated with increased oxygen utilization and the production of carbon dioxide. There is normally about a 20 per cent increase in oxidative metabolism during propagation of action potentials (4). There is no fixed relation, however, between this rate of oxygen uptake and capacity for nerve tissue function (6).

Mode of Action of Local Anesthetic Agents. The assumption has been made in the past that local anesthetic agents produce their effect by interference with utilization of nerve tissue oxygen. This theory assumes that the normally observed increase in rate of oxygen uptake during transmission of impulses is prevented by the local anesthetic; the theory further assumes that there is a direct relationship between oxygen consumption and capacity for function by nerve tissue. Superficially, this theory receives support from the observations that there is a decrease in oxygen consumption by the brain during general anesthesia (7, 8, 9), and that various aerobic cellular enzyme systems are depressed during anesthesia. Narcotics have been reported as selectively inhibiting the dehydrogenases of glucose, lactate, and pyruvate (10), and depressing acetylcholine synthesis (11). The relationship between anesthetic action and the rate of metabolism, however, is an inconsistent one (12, 13, 14). At a concentration of 20 mM., potassium chloride blocks nerve conduction, yet there is actually a concurrent
increase in rate of oxygen uptake. The opposite condition may also pertain, namely, decreased oxygen consumption without impairment of conduction, as occurs following application of sodium azide, yohimbine, or hydroxylamine to a nerve fiber (13, 14). Furthermore, two effective local anesthetic agents, cocaine and chloretone®, have opposite effects on oxygen consumption at concentrations that block conduction: the latter decreases oxygen uptake, while the former does not (15). The concept that local anesthetic agents produce their effect through interference with enzyme action or oxygen utilization is inadequate as the sole explanation for their action. The fact that decreased oxygen uptake by nervous tissue has been reported during certain types of anesthesia does not prove that anesthesia is due to, or even associated with, impaired metabolism of nerve tissue. The decrease in oxygen utilization could be the result, and not the cause, of decreased nerve activity.

It has also been hypothesized that local anesthetic agents exert their effect by interference with depolarization or prevention of repolarization of nerves. High concentrations of potassium chloride apparently do block chiefly by production of depolarization. Although high concentrations of procaine and cocaine may influence membrane potential, at usual clinical concentrations they have no effect on it (4, 16). Similarly, anesthetic concentrations of chloretone do not produce depolarization. The action of various alcohols which block conduction is of interest; there is depolarization but apparently it is a minor factor, since the degree of depolarization is insignificant when compared to the degree present with high concentrations of potassium chloride (which blocks by depolarization); further, the higher alcohols produce less or even no depolarization and yet they are as effective blocking agents as the lower alcohols (12). It is the current opinion that depolarization of nerve tissue is not always the cause of, nor does it always accompany, conduction block (4, 17).

One of the older theories of the mode of action of anesthetics, first advanced in 1907 by Höber (18) and now also associated with the names of Lillie (19) and Winterstein (20), postulates that anesthesia is produced by alterations in cell membrane permeability. That anesthetics produce their primary effect on the cell surface and not on the interior of the cell is now generally accepted (21). That anesthetics decrease membrane permeability has also been demonstrated repeatedly (19, 20). The permeability of nerve membranes to potassium and, especially, sodium ions is vitally concerned with the origin of the action potential, and it can readily be visualized how alteration in membrane permeability would affect the excitability or conductivity, or both, of nerve tissue. Factors other than alteration in cell membrane permeability are undoubtedly also concerned: for example, the affinity of anesthetics for nerve tissue, which is related to their solubility in lipoids and lipoid-like materials (Meyer-Overton lipoid theory of anes-
themia), and the relationship between anesthetic potency and adsorption onto cellular surfaces (the Traube-Lillie-Warburg adsorption theory). Although the type of lipoid present influences the amount and site of adsorption, and although such adsorption may affect cellular metabolism to some degree, the primary action of local anesthetic agents in effecting alterations in nerve excitability and conductivity is probably produced through changes in membrane permeability. This is probably accomplished by polar association between the amino group of the local anesthetic agent and suitable polar groups in the lipoprotein “film” of the nerve membrane (4, 22). [Although all true local anesthetics probably have the same mode of action, general anesthetic agents may well act through a “multiplicity of causes” (12).]

Role of Concentration of Anesthetic Agent. In 1929 Gasser and Erlanger (23), in work later confirmed and extended by Heinbecker et al. (24, 25), demonstrated that different types of nerve fibers are blocked by different concentrations of anesthetic agents, depending

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>ANESTHETIC BLOCKING OF NERVE FIBERS IN ORDER OF DECREASING SENSITIVITY</td>
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<tr>
<td>1. Sympathetic and parasympathetic fibers</td>
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<td>2. Fibers transmitting temperature modalities (sensation of cold is obtunded before that of warmth)</td>
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<tr>
<td>3. Pinprick</td>
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<td>4. Pain, other than pinprick</td>
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<td>5. Touch</td>
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<td>6. Deep pressure</td>
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<td>7. Somatic motor fibers</td>
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<td>8. Fibers conducting vibratory sense and proprioceptive impulses</td>
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on size of the nerve fiber. Smaller fibers have a greater surface per unit volume on which the local anesthetic agent can act and so are more sensitive to the effects of local anesthetics than are fibers with larger diameters. Small, thinly myelinated or nonmyelinated autonomic fibers are most easily affected by local anesthetics. Sensory fibers from 1 to 5 microns in diameter which conduct temperature and pain impulses are more resistant than autonomic fibers, but are more sensitive to local anesthetics than the larger sensory fibers with diameters of 5 to 15 microns which mediate tactile and pressure sensations. Still more resistant are large, myelinated somatic motor fibers.

If a concentration of local anesthetic that is strong enough to block all fibers is applied to a mixed peripheral nerve, there is a definite order in which the various types of fibers are blocked. This sequence, in order of decreasing sensitivity to local anesthetics, is shown in table 1. The same sequence occurs with spinal anesthesia, since it is primarily nerve roots that are affected by the subarachnoid injection of local anesthetics [the significance of dorsal root ganglia paralysis (26) has
not yet been fully evaluated]. Recovery of function following a complete block is in the reverse order because of the relatively greater penetration of drug into small fibers as compared with large fibers. On recovery, the differential effect is more noticeable because it is spread out over a greater period of time.

This basic principle of different types of nerve fibers having different sensitivities to local anesthetic agents has proved of considerable investigative value. Sarnoff and Arrowood (27) found that by infusing sufficient quantities of dilute procaine (0.2 per cent) into the subarachnoid space, they were able to produce a differential spinal anesthesia. Sympathetic fibers and pinprick sensations were blocked. Pain, touch, motor, and proprioceptive fibers remained intact. Using this technique, they demonstrated that the hypotension of spinal anesthesia is not related to concurrent skeletal muscular paralysis: when the sympathetics alone are extensively blocked the blood pressure falls even though somatic motor function is unimpaired. They also obtained evidence suggesting that although some autonomic fibers are morphologically very similar, as evidenced by their simultaneous paralysis by dilute procaine (namely, preganglionic sudomotor and vasoconstrictor fibers) (28), there may be significant differences; block of cardiac accelerator fibers, as measured by the development of bradycardia, occurs at concentrations of procaine that do not block vasoconstrictor fibers, as determined by absence of vasomotor changes in the upper extremity (27). This same technique has also contributed to the knowledge of nerve function and pathways by the demonstration that visceromotor fibers to the intestinal tract are about the same size as other efferent sympathetic fibers, but that visceral sensory fibers are relatively larger (11). Contrary to much of the previous teaching, position sense and the stretch afferents (for example, knee kick and ankle jerk) are mediated by separate nerve fibers (29). Such a technique of differential sympathetic block has also been shown to be of prognostic and diagnostic value in the pain not only of phantom limbs but also of atypical abdominal conditions (30, 31).

This factor of differential concentrations of local anesthetic agents used to block different types of nerve fibers has many clinical applications. For example, the technique of hypotensive spinal anesthesia to reduce bleeding in selected cases during operation and anesthesia (32-35) relies in part on this principle. Using the hypotensive spinal technique, a complete sympathetic block to the first thoracic level can be obtained with a less extensive sensory block and an even more limited motor block. Patients made hypotensive by this technique not only may have their first five or six intercostal muscles active but, even though there is a complete sympathetic block, there is little danger of concentrations of local anesthetic agent being reached in the cervical subarachnoid space great enough to block the motor roots of the phrenic nerves.
During every spinal anesthesia the local anesthetic agent is diluted to varying degrees in the cerebrospinal fluid. When the amount of procaine in the cerebrospinal fluid is measured at various levels above its site of injection into the lumbar subarachnoid space, the concentration is found to decrease as the distance from the site of injection increases (fig. 1). At the site of greatest concentration, all the nerve fibers traversing the subarachnoid space are blocked. A level will be reached, however, at which dilution has occurred, so that motor fibers are no longer blocked, although the touch, pain, pressure, pinprick, temperature, and sympathetic fibers are blocked. Finally, a level will be attained where the concentration will be sufficient to block only the smallest fibers, namely the autonomic. This dilution is clinically most apparent in the cephalad direction when hyperbaric solutions are used. It can be demonstrated readily by testing the level on the skin of the abdomen made anesthetic to painful stimuli and comparing

![Graph](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931681/

**Fig. 1.** Concentration of procaine in spinal fluid at varying distances from site of injection [from Helfrich *et al.* (38)].

it to the level at which loss of ability to detect cold is present, the latter usually being two to three segments higher. This zone of "differential spinal" which must occur with every clinical spinal anesthesia explains how a spinal anesthetic can be administered which will provide adequate anesthesia for surgical incision, but which may not be associated with adequate muscular relaxation. Although, because of technical difficulties, no objective measurements on the trunk have been made of the extent of the sympathetic block above the area made anesthetic to pinprick, in many cases the sympathetic block probably extends several segments above the level of sensory anesthesia. This may explain certain instances of severe hypotension during a relatively low spinal anesthesia; even though the sensory level is, for example, at the tenth thoracic level, above this level more dilute procaine may block the sympathetics to the fifth thoracic level. In such instances, testing for the level made anesthetic to cold by applying a sponge soaked in ether to the skin will give some indication of the extent of sympathetic block, which may prove surprisingly high.
It is difficult to obtain exact information on the minimal concentrations of local anesthetic agents in the cerebrospinal fluid which are required to block different types of nerve fibers. Many of the figures quoted in the literature are inaccurate, as, for example, the widely cited figure of 0.9 per cent procaine as its minimal sensory anesthetic concentration. Some investigators have failed to specify the function of the individual nerve fiber being studied; for example, the concentration necessary to block excitability is less than that required to block conduction. Although only 0.5 to 1.0 mM. of chloretone will block the excitability threshold of a frog’s sensory nerve, the same fiber requires 6 mM. to block conduction (12). In other work, the type of nerve fiber being investigated has not been specified and, as already discussed, this is essential, because different types of nerve fibers, and hence different modalities, are blocked by different concentrations of local anesthetic agents. This is the major objection to results obtained from studies done on mixed peripheral nerves. For example, in Bennett and Chinburg’s interesting work (16) it was found that during stimulation of the distal end of a frog’s cut sciatic nerve, the action potentials were 90 per cent blocked by 4 mM. (0.12 per cent) of cocaine, 86 per cent blocked by 10 mM. (0.23 per cent) of procaine, 78 per cent blocked by 0.1 mM. (0.0026 per cent) of tetracaine (pontocaine®), 90 per cent blocked by 5 mM. (0.13 per cent) of piperocaine (metycaine®), and 90 per cent blocked by 1 mM. (0.034 per cent) of dibucaine (nupercaine®). It cannot be said from such work what concentrations will block, for example, sympathetic fibers, and the blocking action of the local drug on retrograde transmission of impulses along somatic motor fibers is impossible to evaluate.

It is known, however, that approximately twice the concentration of procaine needed to block sensory (pinprick) fibers will block somatic motor fibers (36). The validity of this ratio is substantiated by the observation that as a procaine spinal anesthesia wears off, at the time voluntary motor activity in the anesthetized area is possible there is an average level of 0.5 mg. of procaine per cubic centimeter of spinal fluid (0.05 per cent) (37). At the time pinprick can first be felt, there is an average of 0.2 mg. of procaine per cubic centimeter (0.02 per cent) (38). These figures cannot, of course, be taken as the minimal motor or sensory blocking concentrations, but merely represent the ratio between the blocking concentrations for the two types of fibers. This ratio is 2 to 1 for procaine, but varies with different drugs; it is 4 to 1 for eucaine and cocaine, and 8 to 1 for alypin® (36). At the other extreme, Rudin et al. (39) have demonstrated that 0.1 mg. of procaine per cubic centimeter of spinal fluid (0.01 per cent) does not affect any sensory or even the sympathetic fibers. The fact that Sarnoff and Arrowood obtained sympathetic paralysis and block of pinprick sensation following the injection of 0.2 per cent procaine, although it shows the inaccuracy of the figure of 0.9 per cent procaine as its
minimal sensory anesthetic concentration, in itself cannot be considered as the minimal sensory anesthetic concentration of procaine. The procaine that they injected was diluted at least half: the "priming" dose of 10 cc. of 0.2 per cent procaine and the "maintenance" dose of 0.6 cc. per minute, injected through an indwelling catheter, was diluted by the approximately 20 cc. of spinal fluid distal to the first thoracic level, the point to which the block was carried.

It is most likely that the minimal concentration of procaine required to block sympathetic fibers and the sensation of pinprick in nerve roots in the subarachnoid space is about 0.1 per cent. That other authors have quoted higher figures (40, 41) is probably owing to poorly controlled animal experimentation, failure to include the factor of dilution of the anesthetic agent by spinal fluid, the assumption that peripheral somatic nerves are as sensitive as spinal nerves in the subarachnoid space, or lack of definition of specific type of nerve fiber being studied. Other figures quoted as lower than this [from 0.01 to 0.07 per cent procaine (42)] result mainly from testing with skin wheals the minimal intracutaneous concentration, which is a function of excitability threshold depression, not conduction block. Since the minimal concentration required to block somatic motor fibers is approximately double the minimal sensory anesthetic concentration, 0.2 per cent procaine in a large enough volume would block conduction of motor impulses. Since tetraacaine is approximately fifteen times more potent than procaine (43), similar figures for it would be 0.0066 per cent and 0.013 per cent. When such low concentrations are employed, very large volumes must, of course, be used.

Other Factors Influencing Action of Local Anesthetic Agents. In addition to the size of the nerve fiber, other factors influence the action of local anesthetic agents. Some of these factors deserve special evaluation when the local anesthetic agent is being used to produce spinal anesthesia. For example, it has been shown that the presence of a nerve sheath or epineurium increases the resistance of the nerve to local anesthetic agents. When the sciatic nerve of a bullfrog is stripped of its epineurium the nerve is eight to ten times more responsive to the blocking action of local agents, and, when the sheath has regenerated, the nerve regains its normal sensitivity (44). There are no nerve sheaths surrounding spinal nerves as they traverse the subarachnoid space, and so the action of local anesthetic agents on the nerves at this point is more intense than their action on the same nerve in the periphery. This constitutes one reason why it is not valid to apply characteristics of local anesthetic agents, especially their minimal anesthetic concentrations, as determined on peripheral nerves, to spinal nerves in the subarachnoid space. The myelin sheath also influences the action of local anesthetics on nerve tissue by increasing the minimal blocking concentration. This is best illustrated by the fact that very dilute solutions of a local agent will block an isolated axon.
only at the node of Ranvier (45). The sympathetic fibers traversing the subarachnoid space in the anterior roots are especially sensitive to local agents, not only because of their small size but also because of their paucity of myelin.

There is also evidence to suggest that the function of an axon influences the action of local anesthetic agents independently of the role of size. Heinbecker et al. (25) found that fibers of equal size but of different function are affected by different concentrations of local anesthetic agents. The axon diameters of myelinated autonomic and slow somatic afferent fibers are equal, but the former are blocked by a more dilute solution than the latter. That function alone can modify the minimal effective anesthetic concentration may be the explanation for the observation (27) that preganglionic cardiac accelerator fibers are more sensitive than preganglionic vasoconstrictor fibers to local anesthetics, even though the two are in all probability the same size. Clinically, this is borne out by the observation that during high spinal anesthesia, especially so-called "hypotensive spinal," vasoconstrictor fibers regain function, as shown by rising systolic pressure, before the cardiac accelerator fibers, as determined by continued bradycardia.

The environmental acidity about a nerve fiber also influences the action of local anesthetic agents on nerves. The vast majority of local anesthetics are salts of amines. When brought into contact with an alkali, ionization takes place and free anesthetic base is liberated. In an acid medium there is decreased ionization, with consequent decrease in anesthetic potency. Clinically, this is apparent in the decreased efficacy of local anesthetics in the presence of inflammation or pus. The action of local anesthetic agents, therefore, is potentiated by an alkaline environment. Gerlough (46) showed that the duration of anesthesia with 1 per cent procaine instilled into the cornea of a rabbit increased with rise in pH from 6.0 to 8.9. Fosdick et al. (47) showed that increasing the pH of procaine solutions also speeded the onset of anesthesia. On the basis of the above, it has been assumed that the hydrogen ion concentration of abnormal cerebrospinal fluid causes inadequate or absent sensory anesthesia following an apparently normal subarachnoid injection. The pH of the cerebrospinal fluid, normally 7.4 to 7.6, changes to some degree with alterations in the hydrogen ion concentration of blood, although it is somewhat more stable (48). It does not fall below 7.10 except in the presence of inflammation in the spinal canal, a condition which, by itself, should contraindicate spinal anesthesia. Acidity of the spinal fluid cannot be accepted as an explanation of failure of spinal anesthesia to develop.

On the other hand, it has been argued that in excessively alkaline solutions the separation of free anesthetic base is so extensive that precipitation occurs, with a resultant decrease in effectiveness of anesthetic action. This phenomenon of precipitation of free base in an excessively alkaline medium has been described as being clinically
evident by the appearance of cloudiness when the anesthetic agent is mixed with the spinal fluid. The precipitation has been offered not only as a cause of inadequate anesthesia but also as a possible etiological factor in postspinal neurological sequelae, the crystals so formed coming in contact with nerve roots in toxic concentrations (21). Pharmacologists, however, have not noted such precipitation, even at a pH of 8.0. Cloudiness may rarely occur when local agents are mixed with spinal fluid, but that this cloudiness represents precipitation of the local anesthetic has not been proved, nor has the appearance of this reaction been correlated with the hydrogen ion concentration. In view of published reports (48) on the observed narrow range of the hydrogen ion concentration of spinal fluid, with not only failure of such small changes to impair local anesthesia elsewhere in the body but even to potentiate it when an alkaline medium is present, it is extremely unlikely that either excess alkalinity or acidity of spinal fluid could become sufficient to interfere with the development of properly performed spinal anesthesia. The most frequent explanation for the failure of adequate spinal anesthesia to develop is that the local agent was not injected entirely into the subarachnoid space. In the case of tetracaine, its unrecognized gradual hydrolysis into nontoxic but equally nonpotent 4-N-butylnaminobenzoic acid (49) may be another reason.

*Conditions Influencing Spread of Local Agents in the Spinal Fluid.* Many factors determine the extent to which anesthetic concentrations of local anesthetic drugs will spread in the subarachnoid space. Unless these factors are taken into consideration, a predictable level of anesthesia will be difficult to obtain with any consistency. The first, and probably the most important, factor influencing the level of anesthetic block is the effect of gravity, which, in turn, depends upon two other factors: the specific gravity of the solution being injected in relation to the specific gravity of spinal fluid, and the position of the patient at the time of, and immediately after, the injection. The specific gravity of normal spinal fluid is about 1.007, but there is considerable individual variation, so that the normal range extends from 1.004 to 1.009 (50). Even in the same individual there is variation, depending on the site from which the cerebrospinal fluid is obtained. The specific gravity of ventricular fluid (1.004) is less than that of cisternal fluid, which is less than that of lumbar fluid (51). This increase in specific gravity with descent in the cerebrospinal fluid system is directly related to an increasing protein concentration. Thus, clinically, when a hyperbaric solution is used in Trendelenburg position, it may become increasingly hyperbaric as it ascends in the subarachnoid space. The specific gravity also varies with age, being significantly elevated in older persons (43), and with various systemic diseases. It is increased in uremia and hyperglycemia, although
in the presence of jaundice of a degree sufficient to color the spinal fluid it has been reported to be decreased (52).

Because there is normally such a wide individual range of the specific gravity of spinal fluid, agents considered hyperbaric, if they are actually to prove heavier than spinal fluid in most, or all, patients, should have a specific gravity greater than 1.011. It is because of this wide range in baricity of normal spinal fluid that so-called "isobaric" solutions (about 1.006) are often difficult to control in clinical practice, being actually hyperbaric or hypobaric in certain patients. Hypobaric solutions used to produce spinal anesthesia should have a specific gravity less than 1.003 to be consistently lighter than spinal fluid. The clinical usefulness of hypobaric solutions is impaired because some local anesthetic agents (for example, procaine) in a solution of specific gravity less than 1.003 are so dilute that anesthesia is inadequate or of very brief duration. Actually, the effectiveness of true hypobaric solutions (for example, 1:1500 nupercaine) may well be attributable to the large volumes used, rather than to the specific gravity (50). There is no place in modern practice for the addition of alcohol to make the solution hypobaric.

Reports of accurate measurements of specific gravities of solutions commonly used for spinal anesthesia are infrequent. Any solution consisting of a crystalline agent dissolved in spinal fluid is, of itself, heavier than spinal fluid. But beyond this, figures given in the literature are often conflicting and misleading. Reasons for this include the use of inaccurate methods and the fact that the conditions, especially the temperature, under which the determinations were made, were uncontrolled. The specific gravity of solutions varies inversely with the temperature, the degree of change in specific gravity depending to some extent on the chemical composition of the solute: the specific gravity of spinal fluid decreases 0.001 for each rise in temperature of 4.4 to 5.0 C. (52), while the specific gravity of urine falls a similar amount with each rise in temperature of 3.0 C. Since spinal anesthetic solutions attain body temperature before fixation to the spinal roots (53), the specific gravity of the spinal fluid at body temperature will determine whether the solution is hyperbaric, isobaric, or hypobaric. Determination of specific gravity of solutions of spinal anesthetic agents at room temperature may provide inaccurate information. Specific gravities at body temperature of some commonly used spinal anesthetic solutions, as determined by Davis and King (53), are listed in table 2.

When the specific gravity of the solution being injected is known, its distribution can be controlled after intrathecal injection by altering the position of the patient. A hyperbaric solution injected with the patient in the sitting position will descend so as to affect only the cauda equina, while a similar solution may ascend to high thoracic levels if injected with the patient in the head-down position. If only
the position of the patient is varied while the specific gravity of the solution and the other variables listed below are kept as constant as possible, safer and more predictable levels of anesthesia will result in a large series of cases. Altering other factors simultaneously with the gravitational effect is dangerous for the neophyte, and will result in undesirable spread sufficiently frequently, even in the hands of the experienced anesthetist, to make the results unreliable.

After the effect of gravity, the next most important factors influencing the level of block are volume and concentration. The effect of volume on spread of anesthetic agents is the result of displacement of spinal fluid and is independent of concentration and specific gravity. On a purely physical basis, a large volume of anesthetic solution, when injected into an area of fixed volume, will produce a greater area of anesthesia than will a lesser volume of solution having the same specific gravity and concentration. Similarly, the concentration of anesthetic agent in the solution injected will influence the level of anesthesia independently of effects of volume and specific gravity. For example, if 2 cc. of a solution of 10 mg. of tetracaine in 5 per cent dextrose, with a specific gravity of 1.020, is injected and a level of anesthesia is obtained to the tenth thoracic level, 2 cc. of a similar solution containing 15 mg. of tetracaine and adjusted to a specific gravity of 1.020 would give a higher anesthetic level, to about the sixth thoracic level.

The speed and force of injection also influence the level of a block because of the production of turbulence. Turbulence is easily initiated in a long, narrow, relatively rigid tube such as the spinal subarachnoid space, and it will cause greater spread of an anesthetic solution. If a hyperbaric solution is injected very slowly with the patient in a sitting position, there is no turbulence and anesthetic concentrations of the agent will be obtained only in the distal portion of the subarachnoid space. With the patient in the same position, if the same volume of the same agent is injected as rapidly as possible, enough turbulence will be created to produce a wider range of anesthetic action. Actually, under these circumstances, the force applied while injecting through a needle is of greater importance in causing turbulence than

<table>
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<tr>
<th>Agents</th>
<th>Specific Gravity</th>
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<tr>
<td>Procaine hydrochloride, 2.5 per cent in water</td>
<td>1.0052</td>
</tr>
<tr>
<td>Tetracaine hydrochloride, 0.5 per cent in 0.45 per cent saline and 5 per cent dextrose solution</td>
<td>1.0204</td>
</tr>
<tr>
<td>Tetracaine hydrochloride, 0.1 per cent in 0.09 per cent saline solution</td>
<td>1.0019</td>
</tr>
<tr>
<td>Dilucaine hydrochloride, 0.25 per cent in 5 per cent dextrose solution</td>
<td>1.0178</td>
</tr>
<tr>
<td>Dilucaine hydrochloride, 0.066 per cent in 0.5 per cent saline solution</td>
<td>1.0033</td>
</tr>
<tr>
<td>Piperocaine hydrochloride, 5 per cent in Ringer’s solution</td>
<td>1.0113</td>
</tr>
<tr>
<td>Piperocaine hydrochloride, 1.5 per cent in Ringer’s solution</td>
<td>1.0090</td>
</tr>
</tbody>
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is the rate of injection. Rapid injection through a small gauge needle will, of course, cause more turbulence than the same rate of injection through a larger needle. The skilled anesthetist, therefore, will always try to inject spinal anesthetic solutions with the same force, or, if possible, always use the same size needle and inject at the same rate to control the factor of turbulence. Deliberate use of turbulence caused by barbotage is to be condemned.

The site of injection of the anesthetic agent into the subarachnoid space will also influence the level of block. Clinically, injection can be done in sites other than the usual lumbar interspaces, but above the second lumbar vertebra there is danger of trauma to the spinal cord, while in the thoracic and cervical areas injection is not only technically more difficult, but also, especially in the cervical area, subsequent spread of the agent may involve vital nerve centers.

The direction of the bevel at the time of injection probably plays little or no role in determining level of block: if water is ejected from a syringe through a needle into the air, the water always goes straight regardless of the direction in which the bevel is pointed. The pressure of the cerebrospinal fluid also bears little, if any, relation to the level of block; ranges in pressure encountered clinically do not influence the effects of gravity, turbulence formation, or the effects of volume and concentration. Diffusion, a term often loosely applied to spinal anesthesia, also is of little, if any, clinical import. True diffusion consists of the intermingling of different types of molecules uninfluenced by turbulence or difference in specific gravity. It is a slow process, requiring hours or even days to cover a distance of inches. Circulation of spinal fluid is also of no significance in clinical spinal anesthesia.

**Duration of Action of Spinal Anesthetic Agents.** The different local anesthetic agents have characteristic durations of action, but the period over which any given agent exerts its effect may vary under different circumstances. Since it has been demonstrated that detoxification of spinal agents does not occur within the subarachnoid space, but rather that they are removed by vascular absorption (38, 54, 55), the single determining factor for duration of action of an agent is the rate at which this absorption takes place. Concentration has a role here, for the more dilute a given amount of agent is (that is, the greater vascular absorbing surface to which it is exposed), the shorter its duration of action. Clinically, this is apparent from the observation that 100 mg. of procaine will provide anesthesia of greater duration if used to produce saddle anesthesia than if a level to the tenth thoracic segment were obtained with the same dose. Duration of anesthesia is prolonged also by decreasing the vascular absorbing surface (namely, by producing vasoconstriction), and it is probable that this is the method by which intrathecal vasoconstrictors increase the anesthetic time of spinal anesthetic agents (56). Similarly, decreased blood flow to the vessels surrounding the subarachnoid space may ex-
plain the longer duration of anesthesia in elderly, arteriosclerotic patients, as well as in patients in whom hypotensive spinal anesthesia has been induced.

**Effect of Spinal Anesthetic Agents on the Spinal Cord**

Although the primary site of action of local anesthetic agents introduced into the subarachnoid space is on the nerve roots, such agents also affect the spinal cord itself. This does not consist of a temporarily complete chemical transection of the cord, as once postulated, since during segmental spinal anesthesia some impulses that arise distal to the completely anesthetized area (for example, pain, proprioception) are transmitted by intrachordal fibers past areas in which subarachnoid nerve roots are completely blocked. That the finer sensations of light touch and temperature discrimination are not conducted past such a segmental spinal anesthesia, suggests that transmission of nerve impulses within the cord is impaired. Histologically, it is known that when spinal agents are used in high concentrations, pathological changes are produced within the substance of the cord itself (57, 58), and intrachordal procaine is chemically demonstrable following its subarachnoid injection (59). The extremely small concentrations of procaine which are necessary to depress the cord were demonstrated by Rudin and co-workers (39) during a study of spinal fluid levels of procaine following its epidural injection. They showed not only that up to 10 per cent of such

![Diagram of Spinal Cord](image-url)
epidural procaine could be recovered from the spinal fluid, but also that when the procaine concentration in the spinal fluid was as little as 0.1 mg. per cubic centimeter, there was depression of the cord. Oscillating cord potentials, probably generated by cord gray matter, were suppressed, and this occurred at such minimal concentrations that the most sensitive subarachnoid nerve fibers, namely, the sympathetics, were not affected. The practical, clinical applications of the effects of spinal agents on the cord itself have not received the attention they deserve, and are largely undetermined.

The mechanism by which a local anesthetic agent can influence nerve structures in the substance of the spinal cord is readily explained. Blood vessels penetrating the central nervous system from the pia mater are surrounded by extensions of the subarachnoid space known as the spaces of Virchow-Robin (fig. 2). These spaces ultimately connect with the perineuronal clefts which surround the bodies of nerve cells. Local anesthetic agents dissolved in the spinal fluid may thus have a direct action on intrachordal nerve cells by diffusing into these spaces of Virchow-Robin. As already discussed, different types as well as different functions of nerve tissue have varying sensitivities to local anesthetic agents. Anesthetic concentrations sufficient to impair synaptic transmission within the cord may be inadequate to block, for example, conduction along a sympathetic nerve fiber.

Effects of Spinal Anesthetic Agents on the Brain Stem

That the deleterious effects of high spinal anesthesia are attributable to the direct action of the local anesthetic agent on the respiratory and vasomotor centers of the brain stem is an old theory (61, 62). Drugs injected into the lumbar subarachnoid space may have some subtle effects on the brain stem, but there is no proof that the respiratory failure and peripheral vascular collapse which may occur with high spinal anesthesia are due to direct paralysis of vital centers in the central nervous system. Patients given doses of a spinal agent large enough to produce total sympathetic block to the first thoracic level do not show evidence of impaired function of the respiratory or vasomotor centers (34, 35). Similarly, sensory anesthesia of the entire body, including most cranial nerves, has been obtained repeatedly by Koster (63), Wright (64), Jonneseo (65) and others without the appearance of respiratory arrest or vasomotor paralysis. Experimentally, the injection of 1 cc. of 5 per cent or 0.5 cc. of 10 per cent procaine into the fourth ventricle of dogs has no significant effect on respiration or blood pressure (66). Furthermore, cisternal fluid removed from a dog in respiratory failure after lumbar subarachnoid injection of 150 mg. of procaine does not produce any effect when injected into the lateral ventricle of another, normal dog (67). In human beings (68, 69), the concentration of procaine in the cisternal
fluid after injection of 150 mg. of procaine into the lumbar subarachnoid space, even with the patient in the Trendelenburg position, is below that concentration which is required to depress directly the brain stem. Any local anesthetic agent which might actually reach the cisterna magna is, of course, more likely to spread laterally into the cerebral subarachnoid space than to go against the flow of cerebrospinal fluid through the foramina of Magendie and Luschka to the fourth ventricle (50).

Respiratory arrest and peripheral vascular collapse do occur with high spinal anesthesia, but they are not attributable to the direct action of the spinal drug on the brain stem. These adverse reactions are the result of inadequate medullary blood flow secondary to extreme hypotension. The commonest cause of decreased cerebral flow under these conditions is peripheral hypotension associated with the head-up position. If a normal patient is given a spinal anesthesia high enough to produce a total sympathetic block, the systolic pressure usually will not fall below 90 mm. of mercury if he is in slight head-down position, and the respirations will remain adequate (34). In this position, the venous return to the heart is sufficient to maintain adequate cardiac output, and hence, adequate cerebral blood flow. If such a patient were put in a slight head-up position, however, or even if his lower extremities were dropped, there would be peripheral pooling of blood, decreased venous return to the heart with decreased cardiac output, extreme hypotension, and possible respiratory arrest owing to inadequate medullary blood flow.

Effect of Spinal Anesthetic Agents on the Cerebral Cortex

The only evidence suggesting that spinal anesthetic agents have an effect on the cerebral cortex is based on the observation of two phenomena: first, patients given a high spinal anesthesia frequently lapse into what appears to be normal sleep (63, 70), and, second, if such patients are lightly narcotized with an inhalation anesthetic such as nitrous oxide-oxygen, very low concentrations of anesthetic gases are required to maintain unconsciousness (34). A discussion of the effects of spinal anesthetic agents on the cerebral cortex, therefore, becomes a discussion of the etiology of this clinically observed depression of cerebral cortical activity during high spinal anesthesia.

Theoretically, during high spinal block, the local anesthetic agent could appear in the cerebral subarachnoid space, and such has been offered as the reason for the somnolence. There is considerable uncertainty, however, concerning the effects of local anesthetic agents directly applied to the cerebral cortex. Certainly, most of them appear to irritate rather than to depress the cerebral cortex. Hyperexcitability progressing to convulsions is characteristic of most reactions to local anesthetics, this presumably being the result of the direct action of the agent on the cortex after it is absorbed by the blood
stream. Convulsions are also reported when high concentrations of procaine come in contact with the cerebral cortex (71). The fact that cortical activity probably bears little relationship to consciousness, however, makes it most unlikely that this sleep is produced by the direct action of the local agent on the cortex. Dandy (72) has shown that neither bilateral removal of cerebral cortices in dogs nor unilateral resection in man affects consciousness. Even bilateral ligation of the anterior cerebral arteries of man does not alter consciousness, providing the blood supply to the corpus callosum is not damaged. Penfield (73) and Jefferson (74), among other investigators, agree with Dandy that normal cerebral cortical activity is not a prerequisite of consciousness, which is more likely a function of the brain stem or diencephalon. Even though it is unlikely that the somnolence of high spinal anesthesia is the result of the direct action of the local agent on the cerebral cortex, it could be due to its effect on the brain stem. As already discussed, some very dilute local anesthetic agent may be found in the cisternal fluid during a high spinal anesthesia (68, 69), and although, as mentioned, it is highly unlikely that such could appear in the ventricular system in concentrations great enough to depress the vasomotor or respiratory centers, enough could be present to depress the "consciousness center." That such is possible is demonstrated by the fact that 2.5 per cent procaine applied directly by a pledget to the brain stem of a guinea pig produces no effect on the vital centers but does result in general anesthesia (63). Similarly, injection of 1 to 2 cc. of 3.33 per cent procaine into the cisterna magna of man produces unconsciousness without medullary paralysis (75). In view of the fact that the various functions of peripheral nerves are blocked by different concentrations of local anesthetics, it is not unlikely that, similarly, the various functions of the brain stem also are affected by different concentrations of local drugs, and that consciousness could be impaired without depression of the respiratory and vasomotor centers.

It has also been suggested that total sensory deafferentation resulting from high spinal block produces alterations in consciousness. This theory is based on the hypothesis that wakefulness is the result of bombardment of the central nervous system by afferent stimuli. Complete removal of all afferent impulses, then, would theoretically result in sleep (50). There is no evidence, however, of complete deafferentation of the brain with high spinal anesthesia. The optic and auditory nerves are still functional, as are various afferent visceral reflexes. This theory also assumes, with questionable validity, that there is no intrinsic activity of the central nervous system independent of afferent stimuli. The most significant argument against this "deafferentation" hypothesis is the observation that during differential spinal block, patients become somnolent despite absence of significant sensory impairment (27).
High spinal anesthesia could also produce somnolence secondary to alterations in cerebral blood flow. It has long been recognized (76, 77) that arterial hypotension can produce alterations in electroencephalographic activity. Beecher et al. (76) found that the electroencephalographic changes with hypotension produced by hemorrhage or cardiac tamponade were "indistinguishable from those caused by an increase in depth of anesthesia," and that if the blood pressure were lowered sufficiently, the recorded activity of the cortex disappeared. During high spinal block, actual measurements of cerebral blood flow in man have shown a significant decrease from 52 to 46 cc. per 100 gm. per minute (78). It seems likely that alterations in blood flow to the brain may contribute to the appearance of somnolence during high spinal anesthesia. This is also suggested by the personal clinical observation that somnolence is less common and less profound in such patients when the arterial blood pressure has been maintained with vasopressors. It is also possible, however, that very dilute concentrations of the local agent may appear in the ventricular fluid and affect the state of consciousness.

**Summary**

The pharmacology of local anesthetic agents as used to produce spinal anesthesia is reviewed. The mode of action of such agents acting in the subarachnoid space differs somewhat from that of similar agents used on peripheral nerves. The reasons for this and their clinical significance are discussed. The various factors that may influence the action of local anesthetic agents, especially as used in spinal anesthesia, are considered. The effects of local anesthetic agents on the spinal cord, the brain stem, and the cerebral cortex are reviewed.

**REFERENCES**

PHARMACOLOGY OF LOCAL ANESTHETIC AGENTS


