ROLE OF ANTIHISTAMINIC DRUGS IN REGIONAL AND SPINAL ANALGESIA * † ‡

C. R. Stephen, M.D., W. K. Nowill, M.D., H. Hall, M.D., R. Martin, M.D., and G. Margolis, M.D.

Durham, North Carolina

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Within the last ten years considerable progress has been made in the synthesis of drugs that appear to counteract the undesirable effects of histamine or histamine-like substances within the body. As pharmacological knowledge has increased with reference to these "antihistaminic" compounds, it has become apparent that their properties also include the production of specific effects on other tissues or organ systems. Drugs that fall within this chemical grouping have been found to prolong the refractory period of the heart as does quinidine, to produce cerebral depression and cholinergic-blocking action as does scopolamine, to exert analgesia and narcotic actions similar to demerol®, and to possess topical and local anesthetic properties similar to cocaine and procaine (1).

Since the accidental discovery that tripelennamine hydrochloride (pyribenzamine) exhibits anesthetic activity when applied to mucous membranes (2), laboratory and clinical data have corroborated that this is possible when low concentrations are employed. Applied to the cornea of the rabbit and man, representative drugs of this series, in concentrations of 0.5 and 1 per cent, consistently produced anesthesia of the conjunctiva (3). In clinical practice sensory reflexes of the buccal and pharyngeal mucosae have been obtunded successfully by the topical application of 1 and 4 per cent solutions (4–6). Surface anesthesia of the urethral canal has proved satisfactory both to patient and surgeon after the application of tripelennamine in 2 per cent solution (7). Undesirable systemic reactions have not been observed in patients in whom the compounds have been utilized for topical anesthesia. Their widespread adoption has been limited possibly by the bitter taste they engender in the mouth and the burning sensation which the higher concentrations (4 per cent) may produce.

Experimental investigation has demonstrated that the antihistaminic drugs may block the transmission of impulses along nerves with an end result similar to that of procaine. In the classical sciatic nerve

* From the Division of Anesthesia and the Department of Pathology, Duke University Hospital and School of Medicine.

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preparation of the frog, application of tripelennamine, 2 per cent solution, to the nerve blocked completely both ipsilateral and contralateral motor responses to electric current (3). Utilizing the intradermal skin wheal technique of evaluation in human beings, Landau and associates (8) found that the local anesthetic activity of dimenhydrinate (dramamine®), diphenhydramine hydrochloride (benadryl®) and tripelennamine was 2.4 times more potent than procaine. They deduced that antihistaminic drugs have potent local anesthetic properties.

Animal and clinical studies of these compounds for local, regional and subarachnoid effectiveness and toxicity have not been attempted heretofore to our knowledge. In such an assessment, it is necessary to keep in mind the ideal attributes of a local anesthetic drug. These may be enumerated as follows: (1) Nerve blocking should be complete and capable of attainment in low concentrations. (2) The process of blocking should be completely reversible, so that full physiological action will return to the nerves involved in a predictable time. This implies functional but not histological alteration of nervous tissues. (3) Furthermore, the drug injected into the region of the nerves should be nonirritating to any other tissues with which it comes into contact. These include meninges, connective tissue, muscle fibers and subcutaneous tissue. (4) The total amount of drug required for injection, or its rate of absorption, should not be such as to induce undesirable systemic reactions in the patient.

In order to determine to what extent representative antihistaminic drugs approached the "ideal," the investigation was conducted both in the laboratory and in the operating room. Regional and subarachnoid injections were performed in rabbits, and this was followed by similar injections in patients. Careful histological studies by one of us (G. M.) were carried out on all animal tissues exposed to the drug at various time intervals after the injection. Tripelennamine (pyribenzamine®)§ was chosen as the pilot drug, and laboratory evaluation was attempted also with antistine and methapyrilene hydrochloride.‖

ANIMAL STUDIES

Tests

The following agents were tested in the concentrations listed, and at the indicated sites: (1) tripelennamine, 0.5 to 5 per cent, in regional (brachial plexus and sciatic nerve) and spinal analgesia; (2) antistine, 1 and 3 per cent, in regional analgesia; (3) methapyrilene, 1 and 3 per cent, in regional analgesia, and (4) procaine hydrochloride, as a control material, 0.5 to 5 per cent, in regional and spinal analgesia.

Rabbits were used as the test animals.

§ Tripelennamine (pyribenzamine®) and antistine supplied through courtesy of Dr. J. L. Graeme, Ciba Pharmaceutical Products.

‖ Methapyrilene hydrochloride supplied through courtesy of Dr. W. E. Askue, Sharpe and Dohme, Inc., West Point, Pennsylvania.

In the tests of regional analgesia a total of 141 nerves were studied histologically in 36 rabbits. Fifty-three histologic studies were made following tripelennamine; 44 at two to fourteen days and 9 at thirty to 240 days after injections. Twelve nerves were studied after methapyrilene, 10 after antistine, and 66 following procaine hydro-

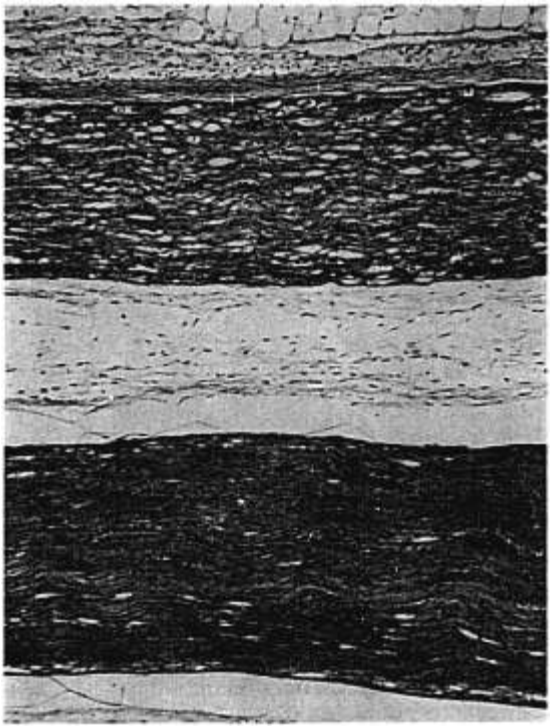

FIG. 1. Second degree nerve injury, severe (above) and minimal (below) in adjacent nerve trunks four days after injection of 5 per cent tripelennamine. (Hematoxylin and eosin, ×99; rabbit.)

chloride; all of these nerves were examined from two to fourteen days after the injections. In the spinal analgesia tests 22 rabbits were studied histologically. The findings in 6 of these were invalidated because of the presence of trauma in 2 and of a spontaneous meningo-

encephalitis in 4. In the tripelennamine series 4 cords were studied from four to eight days following injection, and 6 specimens from forty-five to 240 days after injection. In the procaine hydrochloride group 2 animals were sacrificed four to five days after injection, and 4 from forty-five to 240 days after injection.

Methods

Regional Analgesia.—Tests for regional analgesic effect consisted of the transcutaneous injection of 0.5 cc. of the test solution into the region of the sciatic nerve and the brachial plexus on one side and

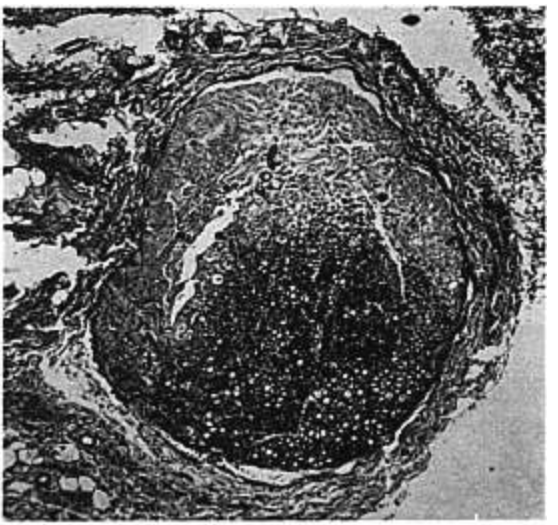

FIG. 2. Second and third degree nerve injury four days after injection of 5 per cent tripelennamine. In the upper prtion of the nerve bundle both axons and supporting tissues are necrotic. (Hematoxylin and eosin, × 114; rabbit.)

matching contralateral injections of procaine hydrochloride. A 22 gauge, ¾ inch needle was used and the solutions deposited in a pool about the nerves. The animal was then observed for the degree and duration of motor paralysis. At the termination of the study each animal was tested for residual motor weakness, and then sacrificed. The nerves were examined grossly, the regions encompassing the injections were removed, allowed to adhere to slips of cardboard, fixed and embedded in paraffin. The proximal and distal ends were sec-

tioned transversely and the intermediate portion longitudinally. Baker's formal-calcium solution was used as the fixative for all tissues in this study. The routine staining techniques consisted of the hematoxylin-eosin method and the Holmes (9) method for axis cylinders. Selected specimens were stained by the Crimbring (10) technique for myelin.

The anatomic effects on nerves were indexed according to the following modification of the classification of Sunderland (11):

1. First degree injury, in which the block of nerve function is not accompanied by anatomic changes.
2. Second degree injury, defined as the destruction of axons with preservation of supporting structures. This category was subclassified for our purposes as follows:
   a. Minimal, when but a few axons in a nerve are destroyed (fig. 1);
   b. Moderate, when several scattered axons are destroyed;
   c. Severe, when all, or virtually all axons are destroyed in a nerve bundle (fig. 1).
3. Third degree injury, when the destruction involves supporting structures in addition to axons (fig. 2).
4. Fourth degree injury, when extensive stretches of nerve are completely destroyed.
5. Fifth degree injury, when there is complete anatomic transection of a nerve.

Any nerve lesion graded as second degree, severe, or more advanced may be considered to be a complete transverse lesion of the nerve, and the only major differences between these higher grades of injury is the manner of repair (11).

Spinal Analgesia.—Spinal analgesia was produced by a method designed to eliminate traumatic effects associated with injections by previously described techniques into the limited lumbar subarachnoid space available in rabbits. Considerations leading to the development of this method are to be presented elsewhere (12). With the rabbit under ether anesthesia, a midline incision was made over the last lumbar interspace and the interlaminar area was exposed by blunt dissection. The test solution was thereupon injected into the subarachnoid space using a 25 gauge, ½ inch needle with the distal ¼ inch bent at a 90 degree angle. The volume of the injected material was calculated on the basis of 0.02 cc. per inch of spinal length, and usually amounted to 0.3 cc. This volume produced satisfactory anesthesia to a mid-thoracic or low cervical level. During closure of the incision the inhalation anesthesia was discontinued, so that the animal was fully awake within a few minutes after termination of the procedure. The effect and duration of action of the tested agent were thereupon determined. At the conclusion of the study each animal was tested for

residual effects and then sacrificed. The vertebral column was dissected and fixed according to the method of Trowell (13) designed to insure proper fixation and elimination of traumatic artefacts. The entire vertebral column was fixed with the cord *in situ* and completely

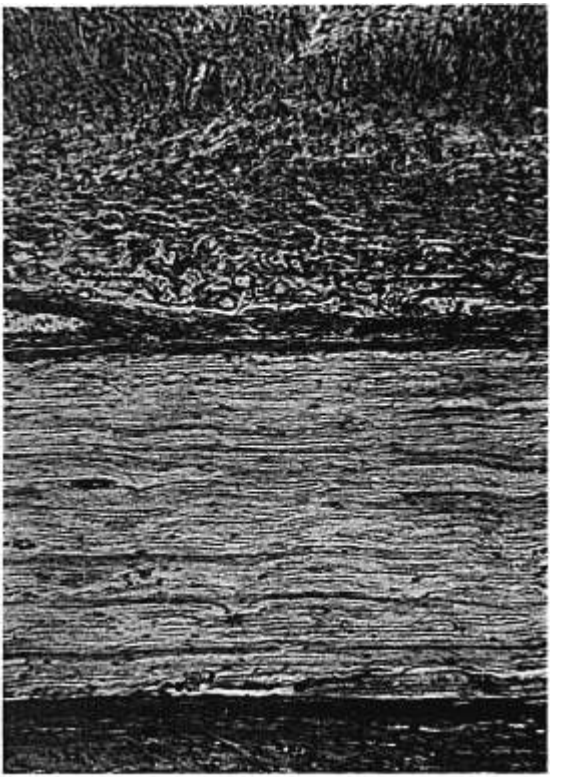

FIG. 3. Perineural granulation tissue six days after injection of 2 per cent tripelennamine. (Hematoxylin and eosin, × 119; rabbit.)

exposed from the dorsal surface. After initial fixation the entire lumbosacral cord was sectioned transversely at 4 mm. levels, and the cauda equina was cut longitudinally; samples of the thoracic and cervical cord were also selected. The fixative and the embedding and

staining methods used in the nerve studies were employed for these tissues.

The anatomic effects on the parenchyma of the cord were classified on the basis of the categories of Sunderland (11) with certain modifications. These were based on the considerations that the mass of nervous tissue exposed to the agents was so much larger in diameter and that by virtue of their location partial lesions of large extent had to be graded as severe. This modified classification again involves a subclassification of second degree injury, as follows: (a) minimal, when but a few axons are destroyed; (b) moderate, when axonal

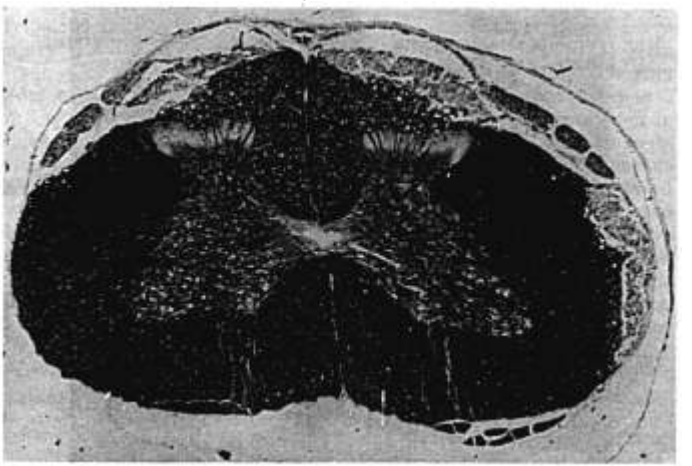

FIG. 4. Cord and nerve root injury five days after injection of 3 per cent tripelennamine. The posterior roots are completely degenerated, and there are extensive bilateral zones of destruction in the superficial regions of the posterior columns, and in the lateral column on the right. (Crimbring myelin, × 34; rabbit.)

destruction is scattered but more extensive; (c) severe, when complete axonal destruction involves areas of functionally significant extent (fig. 4), and (d) complete transverse cord or root lesions produced by axonal destruction (Figs. 4, 5).

Results of Animal Studies

Regional Analgesia.—In 12 rabbits the intensity and duration of sensory and motor analgesia produced by brachial and sciatic injections of tripelennamine (24 injections) were compared to the effects of matched contralateral injections of procaine hydrochloride. The

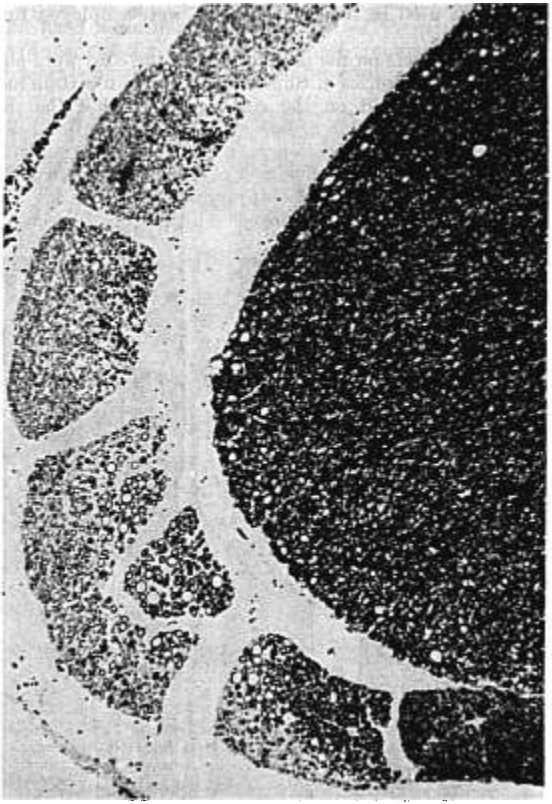

FIG. 5. Nerve root injury five days after injection of 3 per cent tripelennamine. Proceeding from the anterior roots laterally and posteriorly there is a gradation of injury from first degree through second degree complete. No cellular inflammatory reaction is present. (Crimbring myelin, × 100; rabbit.)

average duration of motor paralysis is indicated in table 1. The slightly longer effect of tripelennamine was not considered significant, since the standard deviation in these results was greater than 100 per cent. The degree of sensory analgesia produced by tripelennamine was less profound than with procaine hydrochloride. In one rabbit injected with tripelennamine paralysis of nerve function lasted until the time of sacrifice forty-eight hours later.

TABLE 1

AVERAGE DURATION OF MOTOR PARALYSIS PRODUCED IN 12 RABBITS BY REGIONAL ANALGESIA WITH TRIPELENNAMINE AND PROCAINE HYDROCHLORIDE

Concentration, per cent	Agent and Duration, minutes	
	Tripelennamine	Procaine Hydrochloride
2.0	45	35
3.0	55	40
4.0	135	130

The tabulation of the anatomic effects on nerves produced by the tested agents is presented in table 2. This classification is an index of the maximal nerve injury observed in each specimen studied. Tripelennamine in 1 and 2 per cent concentrations produced nerve injury classified as second degree, severe, in 3 of 38 nerves. With 5 per cent solutions of tripelennamine, severe nerve injury ranging from second degree, severe, to fourth degree were encountered in 5 of 8 nerves. Tests with methapyrilene and antistine were limited in number but it was clear from these preliminary trials that these agents were capable of producing severe nerve injury at concentrations as low as 1 per cent. Antistine, which in 3 per cent solution produced complete necrosis of a 22 mm. segment of one nerve, was considered the most toxic of these agents. With procaine hydrochloride, nerve changes were minimal except in a single nerve graded as second degree, moderate. Increasing the concentration of procaine hydrochloride from 1 to 5 per cent did not produce potentiation of its toxic effect.

Whether or not nerve injury was produced by the antihistamines,

TABLE 2

CLASSIFICATION OF NERVE LESIONS PRODUCED BY PERINEURAL INJECTION OF TRIPELENNAMINE, METHAPYRILENE, ANTISTINE AND PROCAINE HYDROCHLORIDE IN 36 RABBITS

Agent and Concentration, per cent		Nerve Injury, degree							
		I	IIa*	IIb*	IIc*	III	IV	V	Total
Tripelennamine	1	4	4	1	1	0	0	0	10
	2	17	9	0	2	0	0	0	28
	3	4	1	0	0	0	0	0	5
	4	1	1	0	0	0	0	0	2
	5	2	1	0	3	0	2	0	8
Methapyrilene	1	3	2	0	1	0	0	0	6
	3	2	3	0	1	0	0	0	6
Antistine	1	2	1	0	2	0	0	0	5
	3	2	0	0	2	0	1	0	5
Procaine Hydrochloride	1	19	8	0	0	0	0	0	27
	2	10	3	1	0	0	0	0	14
	3	8	5	0	0	0	0	0	13
	5	10	2	0	0	0	0	0	12

*a = minimal, b = moderate, c = severe.

all specimens studied within the first fourteen days following injections of these agents showed a severe injurious effect on the perineural connective tissue. This consisted of a necrotizing action, accompanied by a scant inflammatory exudation and succeeded by a striking vascular and fibroblastic proliferation that proceeded through all the stages common to the history of granulation tissue (fig. 3). This reaction was followed in the tripelennamine studies of extended duration. It slowly subsided, and was inconspicuous in most specimens studied thirty days or longer following the injections. The effect of these agents on other tissues was not studied directly, but chance injections into perineural muscles gave opportunity to observe a comparable necrotizing effect on this tissue. The mildness of the effect of procaine hydrochloride on connective tissues contrasted sharply with the changes produced by the antihistamines.

No studies were designed to determine the relative systemic toxicity of the tested agents, but during the tests it was observed that tripelennamine exerted a powerful convulsant activity in the rabbit. Total

TABLE 3

AVERAGE DURATION OF MOTOR PARALYSIS PRODUCED IN 12 RABBITS BY SPINAL ANALGESIA WITH TRIPELENNAMINE AND PROCAINE HYDROCHLORIDE

	Agent and Duration, minutes	
Concentration, per cent	Tripelennamine	Procaine Hydrochloride
0.5	10	15
1.0	28	15
2.0	75	25
3.0	75	—
4.0	240	80

doses in excess of 10 mg. per kilogram produced generalized convulsions, followed by irreversible and subsequently fatal respiratory and circulatory depression. The maximal test of tripelennamine (0.5 cc. of 5 per cent solution) approached this toxic level. A few tests in dogs indicated that they, too, were sensitive to this convulsant effect.

Spinal Analgesia.—The degree and duration of spinal analgesia was recorded in 6 rabbits after subarachnoid injection of tripelennamine and in 6 rabbits following procaine hydrochloride. Although difficult to measure, sensory paralysis appeared to be less profound than motor, a finding noted also with regional analgesia. Upon cutaneous electrical stimulation of the hind legs during the height of the motor paralysis a pain response could frequently be elicited in an animal. Sensory analgesia disappeared in a cephalad-caudad manner and preceded motor recovery. Since motor recovery had a more definite end point, the duration of spinal analgesia was measured by this modality (table 3). Tripelennamine exerted an effect of significantly longer duration at every concentration, except for 0.5 per cent, the lowest level tested. However, the intensity of depression

of both motor and sensory function was observed to be less profound with tripelennamine than with procaine hydrochloride. All animals appeared to make a complete functional recovery from the anesthesia.

The anatomic effects of the subarachnoid injections on spinal cord and nerve roots are tabulated in table 4. Cord and root injury occurred in 3 of 10 rabbits following injection of tripelennamine. In one animal the injury to these structures was of severe degree (figs. 4, 5). In one of 6 rabbits injected with procaine hydrochloride a few scattered degenerating axons were observed in the cord; no instance of root injury was encountered.

The lesions were confined to the lumbosacral region of the cord, and characteristically affected the posterior roots and the peripheral zones of the posterior and lateral columns of the cord (figs. 4, 5). Except for the lesion which was encountered forty-five days after the injection

TABLE 4

CLASSIFICATION OF SPINAL CORD AND NERVE ROOT LESIONS PRODUCED BY SUBARACHNOID INJECTION OF TRIPELENNAMINE AND PROCAINE HYDROCHLORIDE IN 16 RABBITS

Agent and Concentration, per cent		Injury, degree										Total
		I		IIa*		IIb*		IIc*		IId*		
		Cord	Root	Cord	Root	Cord	Root	Cord	Root	Cord	Root	
Tripelennamine	2	3	3	0	0	0	0	0	0	0	0	3
	3	3	4	0	0	1	0	1	0	0	1	5
	5	1	1	1	1	0	0	0	0	0	0	2
Procaine Hydrochloride	3	3	4	1	0	0	0	0	0	0	0	4
	5	2	2	0	0	0	0	0	0	0	0	2

* a = minimal, b = moderate, c = severe, d = complete.

of procaine hydrochloride, all the degenerative changes were observed during the first four to eight days. In none of the animals studied during the early period after injection was there a significant cellular exudative reaction. At no stage of the observations was there evidence of a proliferative meningeal reaction.

Discussion

These experiments demonstrate that tripelennamine, methapyrilene and antistine are effective agents for the production of regional and spinal analgesia in rabbits. However, their injurious effect on tissue at therapeutic concentrations renders them undesirable analgesic agents in man.

These experiments present ample evidence of the difficulties attached to the interpretation of animal tests of agents used for regional nerve block or spinal analgesia. Despite the development of painstaking

techniques for the production of nontraumatic spinal analgesia, and the use of large numbers of animals for the study of regional analgesia, recognizable residual changes in nerve function in the injected animals were deceptively meager, and even relatively elaborate and expensive histopathologic techniques failed to demonstrate noxious effects on nervous tissue in a large majority of the material studied. Yet, all of the drugs in the antihistamine group subjected to these tests exerted a consistent injurious effect on connective tissues, consisting essentially of necrosis and a reparative hyperplasia. When this potential necrotizing effect was realized on nervous tissue a most severe grade of injury resulted. Manifestly, it is by this potential necrotizing action that these drugs must be evaluated rather than by the negative findings obtained on the majority of the nervous tissue studied.

The quantitatively insignificant degree of cellular inflammatory response accompanying tissue injury is another deceptive feature in the experimental evaluation of these drugs. The measurement of this response would appear to have no validity in the estimation of noxious effects of subarachnoid injections (fig. 5). This lack of correlation between tissue injury and inflammatory exudation has previously been documented in the case of muscle and connective tissue injury in the investigation of another agent proposed for regional analgesia (14).

The above considerations indicate that the investigation of experimental drugs designed for regional analgesia is expensive, time-consuming, and uncertain. Yet the testing of these proposed agents by methods encompassed in this paper should be a prerequisite for their clinical use in man. This problem can be greatly simplified by the adoption of a simple preliminary screening method based upon the requirement set forth as item (3) of the ideal attributes of a local anesthetic drug. This requirement is that the therapeutically effective concentration of a drug should exert no significant noxious local effect on tissue when injected into a restricted area. This standard for therapeutic safety reduces the problem to the proposition that any agent capable of producing local injury of tissue is capable of injuring nerve. By disregarding considerations balancing the known greater susceptibility of specialized nerve tissue to toxic injury against the possible protective action of the perineurium, the problem perhaps, is oversimplified. On the basis of this prerequisite, however, the drugs tested in this study could have been quickly screened out as being too irritant for trial long before the stage of clinical testing was reached. Experiments of this nature demonstrating even more clearly the positive correlation of a necrotizing effect on tissue and a noxious effect on nerves of a drug already being used clinically have been presented in detail in another report from these laboratories (14). The rapidity of healing of animal tissues (14) dictates that the most sensitive tests are those of short duration, before repair processes obscure the initial

injurious effect, a factor also favoring quick, economical preliminary screening tests.

CLINICAL STUDIES

Intradermal skin wheal tests employing tripelennamine were conducted on 3 volunteers, with procaine serving as a control (table 5). The onset of anesthesia was rapid with all the concentrations injected. The analgesia conferred by the antihistaminic drug tended to be of longer duration than that by procaine. Injections of tripelennamine in 3 to 5 per cent concentrations were definitely painful and produced an erythematous reaction about the wheal. These findings were not seen with procaine. When 4 and 5 per cent concentrations of the test drug were used, postanesthetic tenderness developed in the areas injected, followed by necrosis and sloughing of the overlying skin in

TABLE 5

INTRADERMAL SKIN WHEAL ANESTHESIA IN HUMAN VOLUNTEERS

Solution, per cent	Time in Minutes					
	Tripelennamine			Procaine		
	Subject No. 1	No. 2	No. 3	No. 1	No. 2	No. 3
0.1	5	9	10	8	9	10
0.25	15	11	27	8	13	12
0.5	20	13	29	15	14	13
1.0	25	14	29	15	17	24
2.0	43	21	36	17	29	32
4.0	60	34	46	43	33	41
5.0	70			45		

three to four days. These areas did not heal completely for ten to thirty days. Similar wheals made with procaine did not exhibit evidence of such irritation.

REGIONAL NERVE BLOCK

Regional blocks of the radial nerve between the brachioradialis and biceps muscles, about 1½ inches (4 cm.) above the elbow, were performed on the above volunteers. Two cubic centimeters of solution were injected, 1 per cent tripelennamine in one arm and 1 per cent procaine in the other. The onset of anesthesia was rapid with both drugs, but appeared more profound and of longer duration with the antihistaminic. Some discomfort was noted during the injection of the test drug, and a residual localized tenderness was present in the arm for several hours following the return of normal nerve function.

Approximately fifty regional nerve blocks, using a 1 per cent solution of tripelennamine, have been performed on 35 patients during the past

eight months for diagnostic and therapeutic purposes and for surgical analgesia. These have included stellate ganglion blocks, lumbar sympathetic blocks, cervical paravertebral blocks, intercostal nerve blocks and various nerve blocks of the upper extremity. The amount of drug injected varied from 40 to 200 mg. This upper limit of dosage was chosen arbitrarily in order to avoid effects of overdosage (9). All the blocks were effective, and anesthesia began within five minutes of the time of injection. The duration of effects varied from a minimum of two hours for an intercostal nerve block to a maximum of ten hours for a stellate ganglion block. Several patients had nerve blocks at other times with xylocaine®, 1 per cent solution. When the results were compared subjectively and objectively, it was indicated that more profound effects were obtained for somewhat longer periods with tripelennamine.

The course of these patients was followed carefully and none complained of any discomfort during the actual injection, nor was any history of residual pain elicited following the block. Two patients had three consecutive stellate ganglion blocks and a third patient had nine similar blocks over a period of three days without any subsequent pain or tenderness over the injected area. Lumbar sympathectomy was done on one patient who had had a sympathetic block of this region a few days previously. Histological examination of the lumbar chain revealed no abnormal tissue changes.

Most patients became somewhat drowsy following the injection of the antihistamine. However, they could be roused easily and always responded rapidly to their name. This development was considered more beneficial than detrimental to the patient. Systemic complications occurred in one patient.

A 75 year old white woman was suffering from severe, long-standing pain over the distribution of the sciatic nerve. This was believed to be the result of a herpes zoster syndrome. She was receiving deep x-ray therapy in an effort to relieve the pain. A sympathetic block at the first, second and third lumbar interspaces was performed. A total of 100 mg. of tripelennamine was employed. Ten minutes after the injection the patient became nauseated and vomited, and hypotension, bradycardia and cold, clammy skin developed. Spontaneous recovery occurred during the next ten to fifteen minutes and there were no permanent sequelae. This resembled a vagotonic response, but could have been a drug reaction.

SUBARACHNOID ANALGESIA

The decision to employ tripelennamine to produce subarachnoid analgesia was not undertaken lightly. However, animal investigation indicated that regional and spinal analgesia initiated by low concentrations of this drug was reversible and left no permanent, functional

TABLE 6

TRIPELENNAMINE SPINAL ANALGESIA IN PATIENTS

Patients	67
Spinal anesthesias administered	100
Patients with more than one spinal anesthesia	27
Continuous spinal anesthesia	1

residual effects. The antihistaminic drugs represented a new chemical grouping for local anesthetic agents. One of these might conceivably have some advantage over spinal anesthetic drugs in use at the present time. Therefore, mindful of the present antipathy in many circles regarding this method of pain relief (6), a cautious approach was made clinically.

The first 6 patients selected for subarachnoid injection had far advanced metastatic carcinoma of the cervix with severe abdominal, pelvic and thigh pain. In 3, the sacral plexus and nerve trunks to the lower extremities were involved. Spinal anesthesia was established by injecting through the third lumbar interspace 50 to 150 mg. of tripelennamine dissolved in distilled water in 3 to 5 per cent solution. As these patients were febrile, dehydrated, anemic and cachectic, severe systemic reactions might have been anticipated. On the contrary, anesthesia developed in a period of three to ten minutes, varying in level from the ninth to the fourth thoracic dermatomes, without untoward effect. Pain was completely relieved in each case. Motor and sensory anesthesia lasted from one and a half to two and a half hours for the 50 mg. dose, and as long as six hours for the 150 mg. injections. Postanesthetic neurological abnormalities were not increased or more diversified than those present before injection. One patient with partial bowel obstruction and under treatment with Wangensteen suction and parenteral fluids was noted to have generalized weakness of all extremities in the forty-eight hour period following spinal block. This symptom created apprehension until the serum potassium was found to be extremely low. The asthenia cleared completely with adequate potassium therapy.

Following this preliminary work, the scope of the clinical investigation was extended. A total of 100 spinal anesthetics have been admin-

TABLE 7

TRIPELENNAMINE SPINAL ANALGESIA: CLINICAL EVALUATION 67 PATIENTS

Sex	No.	Age		Anesthetic Risk	
		Years	No.	Grade	No.
Male	5	20–39	10	I	28
Female	62	40–49	17	II	27
		50–59	13	III	10
		60–69	19	IV	2
		70–79	8		

istered to 67 patients (table 6). The sex, age distribution and estimated anesthetic risk of these patients are detailed in table 7. It will be noted that a number were in the older age group. This was in keeping with the continued policy to select only the poorer risk patients for this investigative work. The primary and secondary diagnoses (table 8 and 9) of the

TABLE 8

PRIMARY DIAGNOSIS OF 67 PATIENTS RECEIVING TRIPELENNAMINE SPINAL ANALGESIA

	Patients
Carcinoma of cervix	49
Carcinoma of bladder	5
Carcinoma of uterus	4
Carcinoma of vagina	3
Peripheral vascular disease	3
Renal failure	1
Benign hypertrophy of prostate	1
Carcinoma of prostate	1

TABLE 9

SECONDARY DIAGNOSIS OF 67 PATIENTS RECEIVING TRIPELENNAMINE SPINAL ANALGESIA

	Patients
Anemia	20
Hypertensive cardiovascular disease	18
Metastatic carcinoma	10
Congestive heart disease	7
Diabetes	4
Pulmonary disease (moderate to severe)	3
Urinary tract infection	2
Residual hemiparesis	1
Addison's disease	1

TABLE 10

INDICATIONS FOR ADMINISTRATION OF TRIPELENNAMINE SPINAL ANALGESIA

	Cases
Radium implantation	66
Relief of pain (causalgia (?))	10
Dilatation and curettage, biopsy of cervix	7
Prostatic resection	6
Vasospastic disease	3
Skin grafting	2
Radical groin dissection	1
Anuria	1
Cystoscopy	1

patients selected tend to substantiate this policy. The reasons for anesthesia or operation are listed in table 10. Patients who had radium implantations came to the operating room twice as a rule, and this presented an opportunity to investigate the cerebrospinal fluid after the first anesthesia and to determine the effect of a second block with tripelennamine forty-eight hours after the first block.

The dosages of tripelennamine administered, the sensory dermatome levels attained, and the duration of anesthesia are noted in table 11. All injections were made with the patient in the lateral position. Originally, a 15 per cent solution of the antihistamine in distilled water was used, this being diluted with spinal fluid to make a 2.5 to

TABLE 11

IMMEDIATE RESULTS OF TRIPELENNAMINE SPINAL ANALGESIA IN 100 ADMINISTRATIONS

Patients	Dosage, mg.	Level (Sensory)	Duration, minutes
8	30-50	D 1 to L 2	30-90 (av. 70)
85	50-60	Saddle to C 4 (av. D 6)	30-195 (av. 130)
5	75-100	D 6 to D 1	Up to 6 hours
1	150	D 2	

3.5 per cent mixture. Later, the drug was supplied by the manufacturer in ampules containing 100 mg. of a dry, lyophilized preparation. In the majority of patients, the drug was mixed as required with spinal fluid. In 4 patients, equal amounts of 10 per cent dextrose and spinal fluid were mixed in order to inject a hyperbaric solution. In only 2 patients was a 5 per cent solution employed. Continuous spinal anesthesia was instituted for twelve hours in one patient with anuria and terminal renal disease.

Satisfactory analgesia was obtained in all but 2 cases. The one instance of failure was a 268 pound woman in whom the spinal tap and subarachnoid injection appeared to be satisfactory technically. Two days previously spinal anesthesia with tripelennamine had given good results in this patient. A second patient required supplemental general anesthesia because analgesia was incomplete with a dosage of 30 mg.

TABLE 12

SYMPTOMS IMMEDIATELY FOLLOWING TRIPELENNAMINE SUBARACHNOID INJECTION

	Cases
Drowsiness	11
Nausea	7
"Hot" in anesthesized area	4
"Pain" in foot	3
Vomiting	2
"Itching" in feet	2
Discomfort on injection	1

The dermatome level of analgesia was quite variable and not proportional to the amount of drug injected (table 11). Except in the few instances in which glucose was used, the solution injected was estimated to be isobaric. The level of analgesia attained was higher than that usually seen with equivalent doses of procaine. The level continued

to rise in most patients for fifteen to twenty minutes after the injection before it became stabilized. Excessively high levels were encountered seventeen times, once to the fourth cervical dermatome. In these patients there were no subjective sensations of shortness of breath and respiratory activity did not appear to be impaired; therefore it was considered that the thoracic analgesia was primarily sensory.

Initially, preanesthetic subcutaneous injection of a vasopressor was omitted. When higher levels of analgesia were obtained, however, there was an associated fall in blood pressure, as is found with the more conventional spinal anesthetic drugs. This was to be expected physiologically, and therefore in the later group of patients a vasopressor drug was injected before the subarachnoid tap. The blood pressure in this series appeared to vary with the amount and type of vasopressor, the height of anesthesia and the general condition of the patient. No instances of disturbing or profound hypotension were observed.

TABLE 13

CEREBROSPINAL FLUID FINDINGS IN 30 PATIENTS 24 TO 48 HOURS AFTER TRIPELENNAMINE SPINAL ANALGESIA

Specimens analyzed		30
No abnormalities		14
Pandy reaction	Neg.	20
	Trace	2
	+	4
	++	1
	+++	1
	++++	2
White blood cells (per c. mm.)		
Normal (less than 5)		22
Between 5 and 10		7
Over 10 (32 per c. mm.)		1

The duration of anesthesia correlated well with the amount of drug injected (table 11), increasing with greater dosage. On a comparative basis, analgesia with tripelennamine lasted one and a half to two times longer than that expected with procaine.

Most of the side effects which were observed during anesthesia occurred a short time after the injection (table 12). Drowsiness was evident in 11 patients and became obvious ten to fifteen minutes after deposition of the drug. This sleepiness was not associated with apprehension, and was considered a favorable reaction under the circumstances. It probably was an indication of the central sedative action of antihistaminic drugs. Nausea occurred in 7 patients, in 2 of whom it progressed to frank emesis. These symptoms were of short duration and usually associated with a fall in blood pressure. The paresthesias which were noted all disappeared with the development of complete anesthesia. One patient complained of discomfort during the actual injection.

In 30 patients specimens of cerebrospinal fluid were obtained twenty-four to forty-eight hours after subarachnoid block with tripelennamine (table 13). Fourteen of the specimens showed no abnormalities. Various degrees of positive Pandy reaction were seen in eight samples and greater than normal lymphocyte cell counts were present in eight analyses. The presence of a positive reaction for protein did not necessarily coincide with an abnormal number of lymphocytes (table 14).

TABLE 14

CEREBROSPINAL FLUID FINDINGS IN 30 PATIENTS 24 TO 48 HOURS AFTER TRIPELENNAMINE SPINAL ANALGESIA

Patient	Tripelennamine Dose in mg.	Dermatome Level (Sensory)	Pandy Reaction	Cells per c.mm.
1. D 66522	65	D 11	0	2-3
2. D 60513	50	D 5	0	2
3. D 57122	50	D 7	0	2
4. B 61214	50	D 7	0	7
5. D 57004	50	D 10	0	5
6. D 51839	90	D 1	0	0
7. D 61214	50	D 7	0	7
8. D 57211	60	D 6	+	1
9. D 57532	80	D 3	0	7
10. D 59902	50	D 9	0	2
11. D 57298	50	D 12	+	0
12. D 60513	50	D 5	0	2
13. D 12690	100	D 7	0	7
14. D 49752	60	D 9	Sl. Tr.	0
15. D 43864	25	D 8	0	0
16. D 48613	50	D 8	++++	8-10
17. D 52531	60	D 4	0	0
18. D 44622	60	D 7	0	0
19. 62166	50	D 11	Tr.	0
20. D 50914	30	D 4	0	2
21. D 44579	50	D 11	++++	32
22. D 44579	75	D 8	+++	?
23. C 69748	60	D 9	Tr.	2
24. D 54420	60	D 4	0	0
25. B 12913	50	D 10	0	0
26. D 47724	60	D 2	0	0
27. D 47724	60	D 3	Sl. Tr.	5
28. D 55656	50	D 2	+	1
29. D 50272	60	D 11	+	0
30. A 56044	50	D 12	++	2

The increases in cell counts were considered minimal. Analyses of spinal fluid after analgesia with other local anesthetic drugs were not made, but Kamsler (17) reported that 9 of 12 patients showed no increase in cerebrospinal fluid cell count after a single subarachnoid injection with the conventional drugs. On the other hand, Merritt and Fremont-Smith (18) indicated that spinal anesthesia is almost regularly followed by an inflammatory reaction in the cerebrospinal fluid. The cellular reaction is usually lymphocytic.

Careful neurological examinations were carried out on 42 patients before and after anesthesia.¶ Neurological changes noted in the preanesthetic period were not increased or altered after anesthesia. No recent abnormal findings were noted in the postanesthetic period by these two examiners. No major complications such as paraplegia, peroneal palsy, extensive areas of anesthesia, hypesthesia, hypalgesia or paresthesia occurred in this series.

Symptoms noted in the postanesthetic period are listed in table 15. Five patients with extensive carcinoma who had a radicular type of pain before anesthesia complained that the pain was more severe after analgesia had worn off. This finding was difficult to evaluate since all these patients were addicted to narcotics. Postanesthetic radicular pain was not seen in any other patients. Two patients not examined neurologically in the preoperative period exhibited small areas of hypesthesia on the medial and dorsal areas of one foot. A second spinal anesthesia with tripelennamine in these patients did not aggravate or alter these findings. Postspinal headache was observed in 4 patients. This incidence is not considered excessive. There were no known late neurological sequelae in this series.

TABLE 15

POSTANESTHETIC SYMPTOMS IN 14 PATIENTS AFTER RECOVERY FROM TRIPELENNAMINE SPINAL ANALGESIA

Radicular type pain accentuated	5
Headache	4
Nausea and vomiting	3
Numbness (localized areas on feet)	2

DISCUSSION OF CLINICAL STUDIES

The clinical investigations show that at least one of the antihistaminic group of drugs is capable of producing intradermal anesthesia, regional nerve block analgesia and subarachnoid analgesia. That this can be done as safely and as efficiently as with the time-tested local anesthetic drugs is doubtful in the light of present limited knowledge. One hesitates to endorse the unlimited clinical application of tripelennamine for the following reasons: (1) Intradermal wheals with 4 and 5 per cent concentrations produced irritative reactions and necrosis of the area injected. Such reactions were not seen with procaine. This indicates that the margin of safety, the therapeutic-toxicity ratio, at least for dermal tissues, is less for the antihistaminic drug than for procaine. (2) The abnormal findings in the cerebrospinal fluid of 53 per cent of the patients who had spinal anesthesia indicate a degree of reaction that does not fulfill the requisites of an "ideal" local anesthetic. (3) With one possible exception, severe systemic reactions

¶ We are indebted to Drs. F. L. Merritt and C. McClure for the neurological examinations.

were not observed clinically, perhaps because the total injected dosage was limited to 200 mg. This limitation is a handicap in the use of any drug, and particularly in this instance when higher dosages may be indicated for certain regional and local anesthetic procedures. The potential systemic toxicity of tripelennamine runs contrary to the concept of the "ideal" local anesthetic drug.

CONCLUSIONS

As a result of the animal and clinical studies presented, the following conclusions are reached:

1. The antihistaminic drugs, tripelennamine, antistine and methapyrilene, interrupt successfully sensory and motor nerve impulses when used for regional nerve block and subarachnoid injection. When they are employed in low concentrations, this is a functionally reversible process.

2. These drugs may exert a noxious effect on tissues at therapeutic concentrations. Frequently this action is productive of severe injury to nervous tissue.

3. The therapeutic-toxicity ratio of these antihistaminic drugs is less than that of procaine. This applies both to local and systemic manifestations.

4. If the clinical studies herein presented are considered without reference to the animal investigations, relatively optimistic conclusions could be drawn regarding the efficacy and safety of these drugs. It is suggested, therefore, that deductions based on clinical work only may be unwarranted and hazardous.

5. This inquiry into the local anesthetic properties of antihistaminic drugs has been limited and exploratory in nature. It is hoped that some stimulus may have been given to examine more closely the rapidly increasing number of drugs in this chemical grouping. One may be found with such a wide therapeutic-toxicity ratio that it will prove a valuable addition to clinical pharmacology.

6. With new drugs designed for local anesthesia, the use of a simplified and rapid screening test is advocated. Acceptability of a drug for more intensive experimental work would depend on its lack of significant noxious effects when injected in therapeutic concentrations into intradermal, subcutaneous and intramuscular sites.

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