PYRIBENZAMINE®: EVALUATION OF EFFECTIVENESS AS AN ANALGESIC AGENT IN REGIONAL ANESTHESIA *

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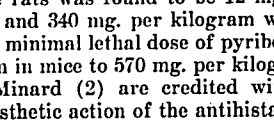
THE introduction of antihistamines for regional anesthesia is warranted if they possess advantages over those known anesthetic agents usually employed. In addition, they should lack the undesirable side effects of the conventional agents. Both laboratory and clinical research must prove their superiority. It is proposed in this preliminary report to review the pharmacology and laboratory reports and to present our observations in a series of cases in which the specific antihistamine, pyribenzamine® ‡, was used in local and regional anesthesia for surgical procedures and in diagnostic and therapeutic nerve blocking.

Pyribenzamine hydrochloride, chemically 2-[Benzyl(2-dimethylaminoethyl) amino] pyridine Hydrochloride, is a white crystalline material which is stable to boiling and autoclaving, nonhygroscopic, and readily soluble in water. The pH of aqueous solutions varies between 6.56 and 6.71. It has a molecular weight of 291.82. The solution remained clear on standing for a period of at least six months in which the clinical study was performed, with no apparent loss of effectiveness.

Its structural formula is



The acute toxicity of pyribenzamine in terms of the minimal lethal dose (LD_{50}) in male rats was found to be 12 mg. per kilogram when given intravenously and 340 mg. per kilogram when given subcutaneously (1). The oral minimal lethal dose of pyribenzamine ranges from 210 mg. per kilogram in mice to 570 mg. per kilogram in male rats.

Rosenthal and Minard (2) are credited with being the first to demonstrate the anesthetic action of the antihistamine drugs. In 1939 they reported that thymoethyldiethylamine, one of the earliest histamine antagonists, when injected intracutaneously in 0.5 per cent solution, produced local anesthesia to the same extent as 1 per cent procaine and the effect lasted longer. In the dog, subcutaneous injections of the

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† Accepted for publication April 6, 1954.

‡ Pyribenzamine was supplied through the courtesy of CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

drug abolished pain response to pinching, pricking or cutting. Similar results were obtained in monkeys and guinea pigs. Burn (3) found that it was three times as effective as procaine when injected into the skin of the guinea pig. In the following years, a large number of antihistamine drugs were developed, all of which apparently had marked local anesthetic properties (4). The anesthetic potency of equimolar concentrations of certain of these drugs in the skin of normal human subjects was determined by Keating and his co-workers (5). They ranked the anesthetic potency of the drugs studied in the following order: phenergan®, pyribenzamine, neo-antergan and benadryl®. Landau, Nelson and Gray (4) compared the efficacy of a 0.05 per cent solution of procaine and the various antihistaminic substances in producing local anesthesia in an intradermal wheal. They found pyribenzamine, dramamine® and benadryl to be about 2.2 times as effective as procaine, while phenergan and antistine® were about 5.2 times as effective as procaine.

The local anesthetic properties of pyribenzamine were discovered accidentally by Yonkmann and his co-workers (6) in the laboratory during early studies on toleration of the drug in appraising its antiallergic potentialities. When the crystals were held between the lips anesthesia of the medicated areas resulted within three to four minutes, and lasted for fifteen to thirty minutes. Further, in exposing the sciatic nerve of the frog, they were able to produce anesthesia by applying pledgets of cotton soaked with 2 per cent solution of pyribenzamine. Moseley (7) used a swab of 1 per cent solution of pyribenzamine applied to the lip and tongue for ten seconds and was able to produce loss of taste in thirty to forty seconds, numbness in two and a half minutes and anesthesia to pinprick in four minutes. He also reported on 30 gastroscopies performed after anesthetization with pyribenzamine used as a gargle. Ten milliliters of a 1 per cent solution were retained in the mouth and pharynx for three minutes, expectorated, and then this process was repeated in four to five minutes. The duration of the anesthetic effect was sufficient for full and complete examination. Reynolds and his co-workers (8) used an average of 30 cc. of a 1 per cent solution of pyribenzamine in 33 of 42 patients, and no recognizable reactions were observed in any of the patients. Kutscher (9) reported on 280 cases in which he used a 4 per cent solution of pyribenzamine as a topical anesthetic agent in dental surgery. His clinical impression was that it was superior to 10 per cent butyn® sulfate solution; he found no instance of local toxicity, systemic reaction or sensitivity. Recently, Fitzpatrick and his co-workers (10) presented 100 cases in which a 2 per cent solution of pyribenzamine was used for urethral manipulation; they found that it was more effective than a 4 per cent solution of metycaine® hydrochloride. As had Reynolds and his group, they reported some burning on application of the drug, which disappeared as anesthesia was produced. Stubbart injected 0.5 to 1.0

per cent solutions of pyribenzamine for routine infiltration anesthesia for minor surgical procedures, with satisfactory results (11).

CLINICAL STUDIES

Experimental Data

Pyribenzamine was first assayed as to its anesthetic potency in 20 volunteers among the house staff and nursing staff. A series of two intradermal wheals was made approximately 5 cm. apart on the volar surface of the right forearm, into each of which 0.2 ml. of a 1 per cent solution of pyribenzamine hydrochloride was injected. The same surface of the opposite forearm was used to make two intradermal wheals, into each of which 0.2 ml. of a 1 per cent solution of procaine hydrochloride was injected. The degree of analgesia was determined in each volunteer at five minute intervals by pressing the tip of a number 25 gauge, one-half inch hypodermic needle against the skin surface of the wheal. The degree of dissipation of analgesia was graded from 4+ to 0; 4+ indicated that the subject felt no pain or sensation of pressure of the needle point; 3+ indicated that the pressure of the point of the needle was barely perceived; 2+ indicated that the subject knew definitely that the needle point was through the skin; 1+ that the needle point produced a sensation of discomfort, and 0 that pain was caused by the entrance of the needle point (fig. 1). None of the volunteers was informed as to the contents of the various solutions. The pyribenzamine solutions were labeled numbers 1 and 2, and the procaine solutions were labeled numbers 3 and 4. The results of our findings are presented in table 1.

TABLE 1

SUMMARY OF INTRACUTANEOUS WHEAL TESTS

Agent	No. of Cases	Duration in Minutes
Procaine 1%	20	35–40
Pyribenzamine 1%	20	140–145
Procaine with epinephrine	10	130–135
Pyribenzamine with epinephrine	10	420 plus

The average duration of anesthesia in the intradermal wheals was 142 minutes when a 1 per cent solution of pyribenzamine was used, and thirty-seven minutes when a 1 per cent solution of procaine was employed (fig. 1). The duration of anesthesia produced by procaine compares with the values reported by other investigators, whereas with pyribenzamine the duration of anesthesia was longer than that produced by other anesthetic agents reported in the literature (12, 13, 14).

It was noted that in at least half of the volunteers tested, some bleeding occurred at the point of entrance of the needle for the production of the wheal into which pyribenzamine was injected. Four volunteers complained of pain during injection, and 2 of some burning around

the wheal at the end of forty minutes. There was an almost characteristic slight erythema around the pyribenzamine wheal in almost all of the cases tested. Later in the study, it was suggested by members of the Plastic Surgery Department that epinephrine be added to the drug used. This solution was first tested on 10 volunteers in the manner described above, except that solutions numbers 2 and 4 contained epinephrine in a concentration of 1:100,000, added to the pyribenzamine or procaine solution.

It can be seen from table 1 that the duration of anesthesia was increased by the addition of epinephrine. When it was combined with pyribenzamine, analgesia was still present after seven hours, and in 2 nurse volunteers, there was still no reaction to the needle prick the

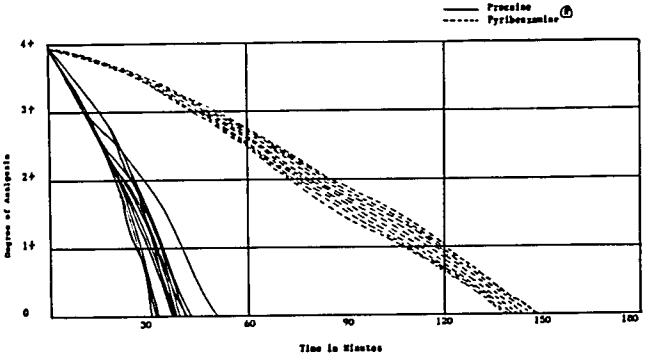

FIG. 1. Experimental data on metric potency in volunteers using procaine and pyribenzamine 1 per cent.

next day. With the exception of one volunteer, no bleeding was noted at the site of injection of the solution containing epinephrine. No other irritating side effects were noted.

Regional Nerve Blocks

Pyribenzamine solution, 1 per cent, was used in the production of 329 diagnostic and therapeutic nerve blocks on 125 patients seen in the Nerve Block Clinic over a period of six months. They are classified in table 2. These nerve blocks were tried on all patients referred from the Out Patient Department, or hospitalized, unless the referring physician refused permission for the use of a "new" drug. In the main, the blocks were performed by the residents who were not informed as to the drug being used. Because of the sedative properties noted by investigators of the antihistamines, no preliminary barbiturate

sedation was given to the patients. No toxic reactions, as evidenced by stimulation of the central nervous system occasionally seen with procaine or other related anesthetic solutions, were present. Several patients who had been having nerve blocks with procaine solution before the study was begun, and who now were given pyribenzamine, were asked whether they noticed any difference in the "injections." Two patients, who had previously reported so-called "jags," stated that they felt drowsy after the injection. New patients also reported this drowsy effect. None had any excitation symptoms. Two cases of stellate ganglion nerve block and 3 of obturator nerve block, were classed as failures because the patients did not obtain relief of pain. It was thought that failure was the result of errors of technique rather than ineffectiveness of the drug used, particularly in the former group

TABLE 2

SUMMARY OF REGIONAL NERVE BLOCKING FOR DIAGNOSTIC AND THERAPEUTIC EFFECT WITH PYRIBENZAMINE (1 PER CENT)

Type of Block	Number of Patients	Number of Blocks	Average Amount of Solution Used, ml.	Analgesic Effectiveness	
				Number	Per Cent
Lingual	2	2	5	2	100
Cervical	3	4	15	4	100
Suprascapular	37	162	8	162	100
Stellate ganglion	22	58	10	56	96
Phrenic	1	2	10	2	100
Brachial plexus	3	3	15	3	100
Intercostal	2	4	6	4	100
Dorsal sympathetic	7	10	20	10	100
Lumbar sympathetic	42	78	15	78	100
Obturator	6	6	10	3	50
Totals	125	329	(av.) 11.4	324	(av.) 94

of patients, since subsequent blocking at a later visit produced therapeutic effects.

The anesthetic effect apparently was immediate, and was indicated in the patients having stellate ganglion blocks by the production of a Horner's syndrome and in those having suprascapular blocks by the immediate increase in range of motion of the extremity. The volume of solution used in these procedures was reduced after the initial use as its marked effectiveness was noted. There was no evidence of local tissue injury in those patients who had repeated blocks.

Surgical Anesthesia

One hundred patients who were scheduled for operative procedures under local anesthesia were given injections of pyribenzamine solution, 1 per cent, at the site of operation. The surgeons were only told

TABLE 3

SUMMARY OF LOCAL INFILTRATION NERVE BLOCK FOR SURGICAL PROCEDURES WITH PYRIBENZAMINE (1 PER CENT)

Surgical Procedures	Number of Patients	Average Amount of Solution Used, ml.	Duration of Operation	
			Range in Minutes	Average in Minutes
Aspiration of knee	2	12	20–30	25
Biopsy	5	10	25–65	35
Excision of ganglion, cyst, tumor of skin or subcutaneous tissue	27	17	25–80	44
Excision of keloid	4	15	20–60	40
Excision of prepatellar bursitis	1	20	35	35
Excision of olecranon bursa	3	20	30–45	36
Excision of calcific deposit of shoulder	3	18	25–50	38
Excision of inclusion cyst of vagina	1	10	25	25
Fulguration for rectal bleeding	1	12	15	15
Insertion Kirschner wire for fracture	2	15	45–60	52
Release of de Quervain's stenosing tenosynovitis, and trigger thumb	34	15	20–90	38
Repair of lacerations	3	24	70–80	73
Removal of wire, healed fracture clavicle	1	10	25	25
Removal of nail, healed fracture hip	2	15	15–35	25
Removal of sutures	1	15	20	20
Skin graft for ulcer	7	24	40–95	50
Separation of pedicle graft	3	28	35–115	70

that it was a new anesthetic drug. The results are summarized in table 3. Anesthesia was successful in every case, and in none were there any toxic signs, sometimes observed with procaine or related drugs. Although no attempt was made to limit the amount of solution employed, the surgeon was advised to use smaller amounts since the drug had greater potency than procaine. Moreover, the surgeons found that smaller amounts than they had been accustomed to use were adequate as shown in Table 4. In only one case was it necessary to supplement with general anesthesia, and it was thought that this was because of the patient's apprehension and the language barrier, rather than the ineffectiveness of the drug. The Plastic Surgical Service reported that in some cases the areas of injection appeared unusually "wet," and in one patient the skin graft had not taken as well as had been expected. The following is a summary of the postoperative records in this cases:

This patient had had the end of the right ring finger amputated

TABLE 4

COMPARISON OF DOSES OF PROCAINE AND PYRIBENZAMINE USED IN LOCAL INFILTRATION FOR SURGICAL PROCEDURES

Surgical Procedures	Procaine 1%. ml.	Pyribenzamine 1%. ml.
Excision of olecranon bursa	35–60	17–25
Excision of prepatellar bursitis	50–100	20
Release of stenosing tenosynovitis	20–30	5–20

On October 20, 1953, a thenar pedicle flap and split skin graft were made from the left thigh. Pyribenzamine solution, 1 per cent, was used, and good anesthesia was produced. For four or five days after operation there was marked serous exudate, which gradually diminished. Fifty per cent of the split skin graft was lost, but the thenar pedicle flap healed satisfactorily.

On October 30, 1953, surgical delay of the thenar flap was carried out. The anesthetic agent was a 1 per cent solution of procaine. The postoperative course was uneventful.

On November 6, 1953, the thenar flap pedicle was severed, the thenar donor site was closed and the pedicle flap was applied to the end of the

TABLE 5

SUMMARY OF REGIONAL NERVE BLOCKING FOR SURGICAL PROCEDURES WITH PYRIBENZAMINE (1 PER CENT)

Surgical Procedures	Number of Patients	Average Amount of Solution Used, ml.	Duration of Surgery	
			Range in Minutes	Average in Minutes
1. Brachial Plexus Block				
Repair of lacerations of skin and tendons	4	30*	75–90	83
Skin graft from forearm to traumatic amputation finger	3	32*	70–100	80
Repair lacerated tendons	4	25*	40–85	71
Tendon graft	1	35*	110	110
Excision ganglion	3	15†	25–40	33
Release tenosynovitis	3	15†	20–40	30
2. Finger Block				
Open reduction fracture	2	10†	20–25	22
Foreign body	1	10†	15	15
Amputation finger	1	10†	55	55
3. Bunion and Toe Block				
Repair hammertoe	4	10†	25–60	47
Repair hallux valgus, unilateral	4	10†	40–70	50

* Fractional doses in continuous block.
† Standard doses per same block.

finger. The anesthetic agent was 1 per cent pyribenzamine combined with epinephrine, 5 minims to the ounce. For two or three days after operation there was marked serous exudate, which gradually decreased. Half of the transferred pedicle flap was lost from the end of the involved finger. On November 27, 1953, a serous bleb formed on the thenar donor site which had been skin grafted; the bleb healed secondarily. The end of the finger showed slow epithelialization.

Because of the result in this case, a brachial plexus regional nerve block was used whenever possible thereafter in cases involving the upper extremity. An explanation for partial failure of the graft to "take" has not as yet been determined.

Regional nerve block for surgical anesthesia was performed in 30 cases. The results are summarized in table 5. These patients were examined in the immediate postoperative period to determine duration of analgesia and to observe any alteration in their general condition. There was complete relief of pain and no sedation was required for at least eight hours after the nerve block.

One severe complication occurred in a patient who had a brachial plexus nerve block.

An 18 year old, well developed negro was admitted for emergency treatment of a partial amputation and compound fractures of the third and fourth fingers of the right hand. Brachial plexus nerve block, using a 1 per cent solution of pyribenzamine, was elected as the method and drug of choice. He was given 100 mg. of demerol® and 0.4 mg. of scopolamine, intramuscularly, at 9:40 p.m.

At 10:00 p.m. the brachial plexus block was performed. Paresthesias down to the fingers were produced, and 15 to 20 ml. of pyribenzamine solution was injected. The needle was left in situ for additional injections of the solution if necessary. The patient stated that numbness was present from the moment the solution was injected. The patient appeared drowsy, but it could not be ascertained whether this was caused by the premedication or the injected solution, or both. The preoperative blood pressure was 122 mm. systolic and 80 mm. diastolic; at 10:10 p.m. it was 160 mm. systolic and 90 mm. diastolic and the pulse was 100. At 10:15 p.m. the tourniquet was placed high on the arm and pumped up after the upper extremity had been milked by the wrapping of an Esmarch's bandage. Both of these procedures he tolerated without pain.

At 10:20 p.m. the patient suddenly had a convulsive seizure which was combated with the use of oxygen. Following this episode, which lasted approximately two to three minutes, operation was attempted, but patient was uncooperative and mentally confused, although he did not complain of pain.

General anesthesia was induced and operation proceeded uneventfully thereafter. He was completely alert and cooperative when seen the next morning, and had no recollection of the convulsive episode.

There was no familial history of epilepsy in this case. It is possible that some of the pyribenzamine solution may have reached the circulation in an amount capable of stimulating the central nervous system. Generally, this reaction is rare unless a patient is hypersensitive to antihistaminics in general. Reactions of this type are more commonly seen in children (15). Another factor suggested is that members of the negro race have a decreased tolerance for anesthetic drugs (16) and may have a peculiar racial idiosyncrasy to scopolamine (15).

Following this occurrence, the standard dose given for brachial plexus anesthesia was 15 ml. of the 1 per cent solution. In cases in which the needle was left in place, taped to the skin, the initial dose was 10 ml., followed by fractional increments of 5 ml. whenever necessary. Another patient, who had been given brachial plexus anesthesia for a complete avulsion of the skin and lacerated tendons of the hand and forearm, complained bitterly of pain whenever a reparative surgi-

cal procedure was done on the ulnar side of the upper extremity, which would suggest that its spreading ability did not include the posterior cord.

Usually, all local and regional injections for surgical procedures resulted in a rapid onset of action, a higher percentage of success than with previously used agents and a smaller amount of systemic reactions. Successful anesthesia was obtained in brachial plexus nerve block even in the absence of paresthesias.

COMMENT

The literature on the antihistaminic substance, pyribenzamine 1 per cent solution, has been reviewed for its local anesthetic action. It was found in the laboratory studies, to have not only marked anesthetic properties but an anesthetic potency about 2.2 times as great as procaine. Our clinical findings corroborated the results of pharmacologic experiments and other clinical studies.

Our studies on human volunteers demonstrated that pyribenzamine produced anesthesia in the intradermal wheal at least four times as long as with procaine solution. When epinephrine, 1:100,000, was added to both solutions, the duration of action was over four times as long. Pyribenzamine has the advantages of rapid onset of anesthesia, profoundness, and apparently low toxicity by virtue of the use of smaller amounts than necessary when procaine is employed. Evidence of stimulation of the central nervous system was detected in only one patient. The frequent finding of drowsiness increased the effectiveness of pyribenzamine as an analgesic agent.

Pyribenzamine was used for local infiltration and regional nerve block for diagnostic, therapeutic and surgical procedures in 459 cases. All injections resulted in a rapid onset of action, longer duration of action, a higher percentage of success in regional nerve blocking and a smaller number of systemic reactions. There were indications of some burning, occasional bleeding, erythema at the site of injection and possibly increased oozing which may be owing to increased vascularity, or "spreading" ability of the drug, or both. Complete recovery was noted in all patients.

Our clinical experience seemingly indicates that pyribenzamine may be a drug of useful local anesthetic action, which is not only more potent but relatively less toxic than procaine. These findings encourage further clinical investigation of this drug for its local anesthetic usefulness.

It is realized, however, that the effects of pyribenzamine injected intraneurally and perineurally in experimental amounts should be studied histologically as was done with long-acting local anesthetics by Mannheimer, Pizzolato and Adriani (17).

SUMMARY

Laboratory and clinical evidence of the local anesthetic action of pyribenzamine is reviewed.

Pyribenzamine solution, 1 per cent, alone or with epinephrine, 1:100,000, was used in intradermal wheal testing on 30 human volunteers, 329 diagnostic and therapeutic nerve blocks, local infiltration for 100 surgical procedures and regional nerve block for 30 surgical procedures.

Its rapid onset of action, longer duration of action, high percentage of success and low incidence of reactions of the central nervous system indicate its suitability as an anesthetic agent.

The observation locally of occasional burning, bleeding, erythema and oozing may be disadvantageous to the common usage of pyribenzamine.

Pyribenzamine, 1 per cent, is apparently more potent and relatively less toxic than an equivalent dose of 1 per cent procaine.

Further clinical testings are indicated.

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