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A COMPARISON OF THE ACTIONS ON NERVE FIBERS OF CERTAIN ANESTHETIC MIXTURES AND SUBSTANCES IN OIL *

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THE term "oil anesthetic" has been used to denote a mixture of locally anesthetic materials dissolved in one of the vegetable oils, usually oil of sweet almonds. All of the numerous preparations of this type are said to produce a local anesthesia lasting for days or weeks, in contrast to the minutes or, at best, a few hours obtained with most aqueous solutions. The usual explanation given for the prolonged action is a gradual release of the anesthetic materials from the oil with a resultant continuous block of the nerve fibers in the injected region. This hypothesis was advanced by Yeomans, Gorsch and Mathesheimer (1), when they introduced the use of these preparations and their explanation of the effects obtained has appeared in nearly every subsequent report. Of all writers on the clinical use of the "oil anesthetics," Steinberg (2) alone seems to have believed that the prolonged action was the result of destruction of nerve fibers. In 1939 the question was studied experimentally and it was found that the long-lasting effects were invariably accompanied by extensive degeneration of the nerve fibers in the injected area (3). On the basis of these experiments it was concluded that injection of anesthetic mixtures in oil caused prolonged anesthesia by killing nerve fibers and not by a gradual release of the potent materials, with their consequent depression of functional activity.

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During the initial experiments, three different mixtures were tried. They were (1) nupercaine hydrochloride 0.5 per cent, phenol 1.0 per cent and benzyl alcohol 10.0 per cent; (2) eucupin base 0.1 per cent, ethyl aminobenzoate 3.0 per cent and benzyl alcohol 5.0 per cent; (3) procaine base 1.5 per cent, butesin 6.0 per cent, and benzyl alcohol 5.0 per cent, each dissolved in U.S.P. oil of sweet almonds.* The present report deals with a further series of experiments designed to test the activity of the separate ingredients of these mixtures and the effects of their repeated injection into the same region.

METHODS

The peripheral motor branches of the facial nerve in the cat were used in testing the effects of individual anesthetic substances and various combinations of them. In all cases, sterilized oil of sweet almonds was used as the solvent. In making each test, a 21 gage needle was introduced slightly in front and below the external auditory meatus, and a measured amount of the solution was injected into the lateral aspect of the face. After piercing the skin, the needle was pushed forward in the subcutaneous layer for about 2 cm.; it was then withdrawn slowly and at the same time the oil solution was gradually expressed from the syringe. When the needle point had been returned to the starting point it was pushed forward again, but in a slightly different direction, and once more withdrawn while oil was expelled. In this manner 1 to 3 cc. of the solution was widely distributed to one side of the face. Usually four or five needle tracks were used during the injection of 3 cc., the amount used in nearly all of the experiments. Following the injection, the area was massaged gently for a few minutes to disseminate further the injected material. In order to prevent struggling and excitement, all injections were done under general anesthesia with ether.

The effect of each injection was determined by noting its action on the orbicularis oculi. Closure of the eyelids is impossible when this muscle is paralyzed, and as a cat invariably responds to a gentle puff of air directed against the eyes by blinking, the state of the muscles was easily determined by blowing in the cat's face. As long as no movements of the lids were observed, the block was considered complete. Recovery was recorded as soon as the space between the lids could be obliterated. Obviously, this did not represent restoration of the muscle to its original level, but further recovery after attainment of complete closure of the lid was difficult to evaluate in equivalent terms for each animal. For this reason, recovery time was taken as the interval between injection and return of ability to obliterate the palpebral aperture. However, if sufficient time was permitted, the once paralyzed

* The nupercaine preparations used in these and subsequent experiments were donated by the Ciba Company and the eucupin preparations were likewise contributed by Rare Chemicals, Inc.

muscle attained a strength equal to that of the uninjured muscle of the opposite side. Most of the animals used were sacrificed and the nerves were examined for histologic changes. The interval between injection and examination of the nerves varied between ten days and three months, dependent in part upon the action of the drug used. When block was not obtained, the animal was killed ten to fourteen days after the injection and a search was made for degenerating fibers. The same interval was used for some animals in which a long-lasting block was obtained; with others of this group, examination was deferred until recovery took place. In the latter cases evidence of degeneration could be detected by marked reduction in the number or by the complete absence of medium and large calibered fibers in the treated nerves.

The branches of the facial nerve were carefully isolated and prepared for histologic examination by immersion in 1 per cent osmic acid for twelve hours. Portions of each nerve were subsequently embedded in paraffin and sectioned, while other portions were teased in glycerine. The latter method has the advantage of permitting certain identification of a few normal fibers among a mass of degenerated fibers and vice versa. In a few instances, thick, frozen sections of skin taken from the injected area and treated with osmic acid were examined for degenerating sensory fibers.

RESULTS

Most of the results are summarized in table 1. Inspection of this table will show immediately the great difference between the effects of solutions containing 10 per cent benzyl alcohol and all of the others tested. Twenty-one trials with the nupercaine mixture which contained 10 per cent benzyl alcohol were followed by complete block in every case. The average duration of complete paralysis of the orbicularis oculi was sixteen days and varied in individual cases between two and twenty-two days. The effects of 10 per cent benzyl alcohol alone were very little different. All eighteen trials with this solution were followed by complete paralysis of the orbicularis oculi which lasted on the average for fifteen days and varied in duration between four and twenty-one days.

In animals with complete inability to move the lids persisting for ten days or longer, all of the nerve fibers in the facial branches to the orbicularis oculi were found to be in a state of degeneration when examined at a suitable interval following injection. If the nerves were examined later after regeneration had occurred, fibers which had survived the injection, that is, large and medium sized fibers, were not seen. When some contraction occurred earlier than ten days after injection, a few surviving fibers could be found among the numerous degenerating ones. Complete closure of the lid eventually returned after each injection, and in the few animals permitted to survive for several weeks longer, differences between the two eyes could not be detected.

TABLE 1

RESULTS FOLLOWING INJECTION OF ANESTHETIC SUBSTANCES DISSOLVED IN OIL INTO BRANCHES OF THE FACIAL NERVE TO THE ORBICULARIS OCULI

Substances injected	No. of trials	Duration of complete block in days			Time for recovery (complete lid closure)			Histologic evidence of nerve degeneration
		max.	min.	av.	max.	min.	av.	
Nupercaine mixture (Ciba)	21	22	2	16	36	4	27	Complete or nearly so in every case
Benzyl alcohol, 10%	18	21	4	15	41	15	21	Complete or nearly so in every case
Phenol, 1%	1	0	0	0	0	0	0	None
Nupercaine hydrochloride, 1%	3	0	0	0	0	0	0	None to a few fibers
Nupercaine hydrochloride, 1% with phenol, 1%	1	0	0	0	0	0	0	None
Almond oil	6	0	0	0	0	0	0	None
Eucupin mixture (Rare Chemicals)	5	5	0	1	—	—	—	A few fibers to very marked; never complete
Benzyl alcohol, 5%	14	0	0	0	5	0	2	A few fibers to very marked; never complete
Ethyl aminobenzoate, 3%	1	0	0	0	0	0	0	A few fibers
Eucupin base, 0.2%	2	0	0	0	0	0	0	None to a few fibers
Eucupin base, 0.2% plus ethyl aminobenzoate, 3%	2	1	0	—	5	4	—	None to very few fibers
Procaine mixture (after Morgan)	17	3	3 hrs.	6 hrs.	6	1	3	Numerous in each case but never complete
Procaine base								
2%	3	12 hrs.	0	4 hrs.	5	0	2	None to a few fibers
5%	2	0	0	0	0	0	0	None
10%	9	5	1	3	10	5	7	None to more than 50%, usually the latter

Tests for possible cumulative effects, resulting in permanent damage, were made by infiltrating the same area repeatedly. One cat was treated nine times with the nupercaine mixture and another animal received seven successive injections of 10 per cent benzyl alcohol alone. As shown in table 2, each injection was followed by recovery, and the final recovery was complete as judged by the following tests. Three

TABLE 2

RESULTS OF REPEATED INJECTIONS OF ANESTHETICS IN OIL

Cat No.	Intervals between injection and recovery (complete lid closure)									
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	Average
6–40 Nupercaine mixture	28	19	21	30	32	17	34	36	28	27
12–40 10% benzyl alcohol	18	16	19	15	41	12	31			22

months after the last injection, the strength of the lid muscles was tested by forcibly opening the eyes with the fingers, by causing closure every two seconds for thirty minutes by means of intermittent air blasts and by kymographic recordings of the strength of contraction in response to electrical stimulation of the facial nerves. None of these procedures revealed differences between the injected and the normal sides.

Trials with the other components of the nupercaine preparation, that is, nupercaine hydrochloride when used in 1.0 per cent concentration and phenol, 1.0 per cent, were without effect when the materials were used either separately or in combination. Likewise, the oil alone had no observable effect upon the function and structure of the nerve fibers. In two animals, one in which oil alone was used and the other in which 1.0 per cent nupercaine hydrochloride was employed, a few degenerating fibers were seen in one of the smaller branches of the facial nerve. This was considered to be caused by the needle striking or piercing the branch involved. In five instances, an effort was made to produce lasting block with 3 cc. of a 5.0 per cent solution of nupercaine base in oil. Death resulted within thirty minutes in all instances. A 1.0 per cent solution in oil produced complete block for two days in one instance and for four hours in another. The nerves in these cases were not examined.

The eucupin-containing mixture and its separate ingredients were much less effective in producing complete block of the branches of the facial nerve (table 1). Only once in five trials was a complete block obtained. It lasted for five days as compared with averages of fifteen and sixteen days obtained with the preparations containing 10 per cent benzyl alcohol. Nevertheless, both eucupin mixture and 5.0 per cent benzyl alcohol alone always caused some degeneration of nerve fibers. At least one-half the fibers were destroyed in the case of five day block; in the others the number was less and quite variable. A transient weakness of the muscle was observed after most of these injections.

The mixture containing procaine base never produced a paralysis which lasted more than three days, but in seventeen trials it never failed to cause a complete block lasting for three hours or longer. Considerable numbers of degenerating nerve fibers were found as a result

of each of these injections. Procaine base alone in 2.0 per cent and 5.0 per cent concentrations was without observable effects except in one case in which a block lasted twelve hours and in another in which there was a slight weakness for one-half hour. A few degenerating fibers were present in the blocked nerve and none were seen in the others. Procaine base, 10 per cent, in oil was effective in each of nine trials, producing blocks lasting between one and five days. In one of these cases no degenerating fibers were seen; in the others, only about half of the fibers were intact.

In addition to the records on paralysis of the orbicularis oculi and the presence or absence of degeneration of nerve fibers, a number of incidental observations that should be recorded were made. Small abscesses were occasionally encountered at necropsy and in one of the first experiments, a sloughing of a portion of the skin occurred. These reactions were attributed to pooling of the oil, a complication which is warned against in practically all papers on the clinical use of the oil solutions. On the other hand, comparatively large amounts of the oil were absorbed if properly distributed. For example, the cats in which repeated injections were given received a total of 25 to 30 cc. of oil into an area not over 4 cm. in diameter during a period of nine months. Three months after the last injection, the subcutaneous tissues contained no macroscopic drops of oil and there was no detectable increase in the thickness or consistency of the skin and subcutaneous tissues, but deep in the subcutaneous tissue a very thin layer of soft, orange-colored material was noticed. Upon microscopic examination this was found to be composed largely of fat-laden macrophages.

In the numerous sections examined, droplets of oil were never seen within the perineural sheaths, although large droplets just outside the sheath, as shown in figure 1, were characteristic. From this finding it is believed that the potent materials must leave the oil solvent and pass through the perineurium to reach the nerve fibers.

Delayed reactions did not occur. The injected substances were either effective immediately or not at all. Likewise, the stage of degeneration was always similar to that which would have occurred if the fibers had been crushed or cut at the time of injection. In other words, the maximal effect was exerted at the time of injection and no signs of a prolonged functional block and subsequent degeneration were noted.

COMMENT

The results demonstrate clearly the effects of three anesthetic mixtures in oil and of their individual components when applied to motor fibers in nerves of small caliber. Because of the low penetrating power of the oil solutions, even the strongest substance used, 10 per cent benzyl alcohol in oil, will not destroy all of the fibers in nerves as large as the sciatic nerve in the cat. Attempts to block this nerve completely were unsuccessful even when it was exposed and surrounded by 10 per

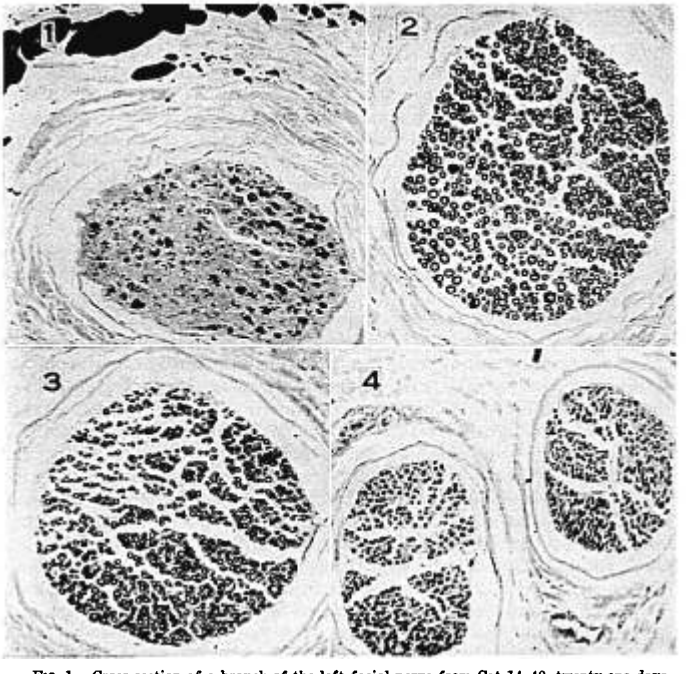

FIG. 1. Cross section of a branch of the left facial nerve from Cat 14–40, twenty-one days after injection of 3.0 cc. of 10 per cent benzyl alcohol in oil into the left face. The nerve was fixed in osmic acid. This nerve contains no normal fibers but much disintegrating myelin, seen as black-staining droplets in the section. On the left side of the figure, large droplets of the injected oil may be seen in the connective tissue outside the perineural sheath. (× 150.)

FIG. 2. Cross section of a branch of the left facial nerve from Cat 11–40, removed fifty days after injection of 3 cc. of 10 per cent benzyl alcohol in oil. This section was taken from near the posterior margin of the injected area. The fibers in the left side of the figure are much larger than those at the right, indicating incomplete penetration of a destructive concentration of benzyl alcohol. The fibers at the left are normal, those at the right are regenerated fibers. (× 200.)

FIG. 3. Cross section of the same nerve shown in figure 2, but taken from near the center of the injected area and approximately 1 cm. distal to figure 2. At this point only a few fibers survived the injection; the rest degenerated and subsequently regenerated. (× 200.)

FIG. 4. The same nerve shown in figures 2 and 3 but with the section taken about 1 cm. distal to that shown in figure 2. No large fibers remain at this point, indicating complete destruction of all fibers at the time of injection. This and the two preceding figures illustrate the complete regeneration that occurs following the injection of benzyl alcohol in oil. (×200.)

cent benzyl alcohol or by nupercaine mixture. Nerves the size of the main facial branches, that is, 1 mm. or slightly less in diameter, often were penetrated incompletely, and centrally placed fibers survived (figs. 2, 3 and 4). The low penetrating qualities of the oil solutions and their necessarily haphazard distribution despite the most careful injection are regarded as explaining in a large measure the variation in the results obtained with any one of the materials. From these observations it seems reasonable to conclude that "oil anesthetics" act principally on externally placed fibers in large nerve trunks, and practical uniformity of action on all component fibers is attained only when the branches are less than 1 mm. in diameter.

Although the majority of the observations were made on motor fibers, there is reason to believe that the substances tested almost certainly have a more potent action on the sensory fibers. This conclusion is based in part upon the well known refractoriness of motor fibers to local anesthetics in aqueous solutions, and upon clinical reports which stress the marked diminution of sensation and the mild degree of motor weakness caused by injection of oil solutions around the inferior hemorrhoidal nerves. In addition, during this series of experiments several examinations of frozen sections of skin, fixed in osmic acid, from the areas of injection revealed numerous degenerating fibers. In two instances when the nupercaine mixture was injected into the subcutaneous tissues of the thigh all fibers in the saphenous nerve degenerated. For these reasons it seemed safe to assume that the prolonged sensory loss reported to follow injection of anesthetics in oil is caused for the most part by degeneration of nerve fibers. In this connection it should be remembered that regeneration sets in promptly and is complete, or nearly so, not only after a single injection, but also after repeated injections.

In addition to their denervating effect, anesthetics in oil can produce a functional block of fibers that remain intact. This was particularly noticeable when procaine mixture was used. With this material, a complete block was obtained every time it was employed, but each of them was of comparatively short duration, that is, three hours to three days. During these intervals activity of the orbicularis oculi could not be elicited and this presumably means that all or nearly all nerve fibers to the muscle were not conducting during the period of paralysis. Following each of these blocks, weakness of the muscle was observed which varied considerably in extent and duration. The weakness was accounted for by finding many degenerating fibers in the blocked nerves. Because of the unquestionable functional block produced by the procaine mixture and less certain occasional results from the other substances, it cannot be concluded that the entire effect of the oil anesthetics is the result of destruction of nerve fibers. The destructive action certainly accounts for the more prolonged effects obtained, but blocks of shorter duration must be caused in part by temporary cessation of

function without degeneration. Exactly how much of the paralysis lasting for three days or less was caused by functional block and how much by degeneration of fibers could not be determined from the present experiments. Procaine base alone was used in attempts to block the facial nerve for a few days without causing degeneration of the nerve fibers. These trials were unsuccessful and the problem of the limits of duration of anesthesia without fiber degeneration was not solved.

The fact that the prolonged effects of local anesthetics in oil are accompanied by and in all probability largely the result of degeneration of nerve fibers is not regarded as a contraindication to their use. On the contrary, the demonstration of prompt and complete regeneration invites further experimentation with temporary denervation by chemical means as a method to relieve pain and to produce muscular relaxation. It is the opinion of the authors that the oil in itself constitutes more of a barrier to an extended use of these nerve-destroying materials than the destruction itself. Perhaps at best the oil can be regarded only as a necessary source of annoyance because of its slow absorption and the danger of improper injection.

SUMMARY AND CONCLUSION

A study was made of the functional and histologic effects of anesthetic mixtures and their constituent compounds dissolved in oil by injecting the solutions so as to reach the motor branches of the facial nerve. Three mixtures were tried; one contained nupercaine hydrochloride 0.5 per cent, phenol 1.0 per cent and benzyl alcohol 10.0 per cent; another contained eucupin base 0.1 per cent, ethylamine benzoate 3.0 per cent and benzyl alcohol 5.0 per cent and the third contained procaine base 1.5 per cent, butesin 6.0 per cent and benzyl alcohol 0.5 per cent. The solvent for these and for the individual substances was U.S.P. oil of sweet almonds. The nupercaine mixture caused degeneration of all or nearly all of the nerve fibers in the injected area with each application and return of function was dependent upon regeneration. The same results were obtained with 10.0 per cent benzyl alcohol alone, while the other ingredients, separately and together, were without effects. The eucupin mixture seldom produced more than transient weakness of muscles supplied by the facial nerve, but it always caused the degeneration of a considerable number of nerve fibers. Practically identical results were obtained with 5.0 per cent benzyl alcohol alone; neither eucupin base nor ethyl aminobenzoate had much effect and they caused very little degeneration. The procaine mixture regularly caused a nerve block of several hours' duration, and in one case it lasted for three days. Extensive degeneration of nerve fibers similar to that caused by 5.0 per cent benzyl alcohol resulted from each injection.

It is concluded that the prolonged effects of the anesthetic mixtures in oil were caused almost entirely by the benzyl alcohol content, and that this substance in 10.0 per cent concentration will destroy all of the fibers

in small nerves and a considerable number of them when it is used in 5.0 per cent concentration.

REFERENCES

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2. Steinberg, N.: Recent Advances in Treatment of Rectal Diseases by Injection Methods in Ambulatory Patients; Pruritis Ani, New England J. Med. 215: 1019–1021 (Nov. 26) 1936.
3. Duncan, Donald: Some Effects of Anesthetic Mixtures Dissolved in Oil on Motor Nerves in the Cat, Proc. Soc. Exper. Biol. & Med. 42: 405–407 (Nov.) 1939.

REGULAR MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS, INC.

NEW YORK MEDICAL COLLEGE AUDITORIUM
5th Ave. and 105th St.

Thursday, October 14, 1943

BUSINESS SESSION: 7:30 p.m.

Active and Life members are requested to bring membership cards. Only those presenting membership cards will be entitled to vote for the proposed changes in Constitution and By-Laws.

SCIENTIFIC SESSION: 8:00 p.m.

1. "The Survival of Preserved Red Cells After Transfusion," by O. F. Denstedt, Ph.D., Assistant Professor of Biochemistry, McGill University, Montreal, Quebec.
   Discussant: Ralph Stillman, M.D., New York, N. Y.
2. "Anesthesia in Children," by M. Digby Leigh, M.D., Lecturer on Anesthesia, McGill University, Montreal, Quebec.
   Discussant: Sydney S. Lyons, M.D., New York, N. Y.
3. "Circulatory Effects from Cyclopropane Administered After Hemorrhage," By S. G. Hershey, M.D., Resident Anesthetist, Bellevue Hospital, New York, N. Y.
   Discussant: Louis Porter, M.D., New York, N. Y.