THE DEVELOPMENT OF EFOCAINE, A NEW APPROACH TO PROLONGED LOCAL ANESTHESIA

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The history of local anesthesia is punctuated with attempts to produce a prolonged effect. Generally, the agents described either resulted in a minimal increase in the duration of anesthetic action or caused the destruction of the nerve which produced an effect lasting for a period equal to that necessary for the regeneration of the neurofibril. This report is concerned with the successful production of local anesthesia of from six to eight days' duration without any neurodegenerative effects or local toxic tissue responses.

The approach toward increasing the duration of anesthetic action has been twofold. The first is concerned with the synthesis of structural variants and the second with the development of a means of inhibiting absorption through special solvent formulations. The synthesis of new anesthetic agents was shown to hold little promise in this respect since in most instances the toxicity of the compound increased in a much greater order than did the duration of activity.

Among the earliest methods intended to prolong the anesthetic effect through delayed absorption was the inclusion of a vasoconstricting agent. Although this combination is still widely used, its effect is minimal, since anesthesia is extended for a matter of minutes.

In 1928, Yeomans, Gorsch and Mathesheimer (1) described a method of producing prolonged local anesthesia by dissolving the

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anesthetic agent in oil instead of in water. The rationale for this substitution was that the immiscible solvent would liberate the active agents in small amounts and thus extend the duration of activity. Other investigators (2, 3, 4) reported related formulations all having in common an oil solvent and from 5 to 10 per cent of benzyl alcohol, although different local anesthetic agents were employed.

While the literature abounds with glowing reports (4, 5, 6, 7, 8, 9) of the clinical response of these products, negative opinions (10, 11, 12, 13, 14) have also been presented with equal vigor. Smith (12) protested the use of the term anesthetic with the oil solutions since postoperative anesthesia was not produced at any time. It remained for Duncan and Jarvis (15) and Kelly (16) to supply the experimental evidence that resolved this controversy and conclusively established the general failure of the oil solutions. It was shown (15) that any prolonged effect observed was not the result of any inhibitory solvent action but of the degenerative effect of the benzyl alcohol on the nerve. The extent of anesthetic action, therefore, was limited to the period of regenerative repair rather than pharmacologic activity of the preparation. The neuro-destructive action of benyzl alcohol was observed only with preparations containing at least 10 per cent, which explained the failure to obtain any prolonged effect with preparations containing lesser quantities of benzyl alcohol.

It is indeed surprising that these preparations are still in use since the basic rationale for a prolonged effect due to an oil solvent has also been conclusively disproved by Emery and co-workers (17, 18), Brown *et al.* (19), Bray (20) and Freyberg (21). The status of the oil-solvent has been aptly described by Duncan and Jarvis (15) as "... at best the oil can be regarded only as a ... source of annoyance because of its slow absorption and the danger of improper injection."

A fresh approach to the problem of prolonged effect produced by delayed absorption through solvent action was provided by Duttmann (22). A hypertonic and highly viscous solvent was utilized, which served to limit the diffusion of the active ingredients from the site of injection. Gelatin was first used as the retardant which, because of its relatively limited supply in Europe and intense pain on injection, was soon replaced with polyvinylpyrrolidone (P.V.P.), although the subjective effects were not eliminated.

Although prolonged activity was noted, anesthesia was still of short duration. Thus Starlinger (23) reported an increased duration of from 100 minutes for 1 cc. of 0.5 per cent procaine-epinephrine solution to 240 minutes for the same solution containing 3.5 per cent of polyvinylpyrrolidone. Varying degrees of activity have been reported by other investigators (24, 25, 26, 27, 28, 29, 30), with a maximal duration of approximately 360 minutes. With the wider use of this technic, which required viscosities of about 400 times that of water (31), it was noted that the prolonged distention of the tissue by the highly viscous

solution produced some destruction, as evidenced by continuous pain and slower healing of wounds in the infiltrated area (32). There is still a question concerning the systemic safety of this solvent with regard to hepatic damage and renal toxicity (33). Practically, this latter approach, although only minimally increasing anesthetic duration, caused tissue damage as well as posed a problem of systemic toxicity and was, therefore, discarded.

EXPERIMENTAL DATA

It is well known that drugs which are slightly soluble exert an effect for a greater period of time than their soluble counterparts. Thus, aqueous suspensions of insoluble materials, such as the hormones (34) or procaine-penicillin, exert an effect of greater duration than do its oil or aqueous-soluble counterparts. However, the injection of a suspension has a number of drawbacks. Sedimentation of particles makes accurate dosage impossible. A large bore needle is required to permit passage of the crystals, which causes marked operational trauma and pain. The suspended particles make it difficult to detect contamination by foreign materials and mold growth. With particular reference to the local anesthetics, the bases all hydrolyze on contact with water, thus rendering them unsuitable for the preparation of suspensions.

Monash (35) reported a greatly increased duration of activity of the suspended free base of procaine as compared with the acid salt; however, his experimental product was limited only to extemporaneous preparation and included among its agents, a trace of indicator (phenolphthalein) which is a tissue irritant; a potent suspending agent and alcohol.

These drawbacks of the suspensions were circumvented by forming a saturated solution of the aqueous-insoluble anesthetic base in a water-miscible, nontoxic organic solvent which, when diluted with minimal quantities of the aqueous body fluids, would cause a complete and immediate deposition of the active ingredients to form an *in vivo* drug respository, thus exerting a prolonged effect. Moreover, the organic solvent would exert a protective effect, inhibiting hydrolytic destruction of the active agents.

Propylene glycol was selected as the organic solvent because of its water miscibility and its nontoxicity (36, 37, 38). The use of this agent as an intramuscular and intravenous solvent for drugs has been investigated by McGavack and Vogel (39), Cleghorn and co-workers (40), Senger and co-workers (41) and Gold and co-workers (42). The consensus was that it is a relatively non toxic material which may be injected intramuscularly in relatively large doses without undue local effects. Some transient pain has been noted with these injections, and it has been reported (43) that repeated frequent injections of this material (approximately three times daily for many

TABLE 1

THE CHEMICAL AND PHARMACOLOGIC PROPERTIES OF THE TEST PREPARATIONS STABILITY

No.	Base	Prop. Glycol; Water	Prop. Glycol; P.E.G.; Water	Relative Toxicity*	Relative Potency†	Penetrating Power for Tissue
1	Procaine	8 days	stable‡	1.0	1	poor
2	Butethecaine	7 days	65 days	1.0	1	poor
3	Dibucaine	10 days	60 days	14.2	2½	good
4	Piperocaine	8 days	46 days	1.7	½	good
5	Tetracaine	6 days	38 days	5.8	2.0	poor
6	Benzocaine	stable‡	stable‡	nontoxic§	§	excellent
7	Butyl-*p*-amino-benzoate	stable‡	stable‡	nontoxic§	§	excellent

* Relative toxicity to cats; procaine as 1 (Moore, D. C.: J.A.M.A. 146: 804, 1951).
† Relative anesthetic potency; cocaine as 1.
‡ Stable for 3 months at room temperature.
§ No comparative data available for these agents with control experiments.

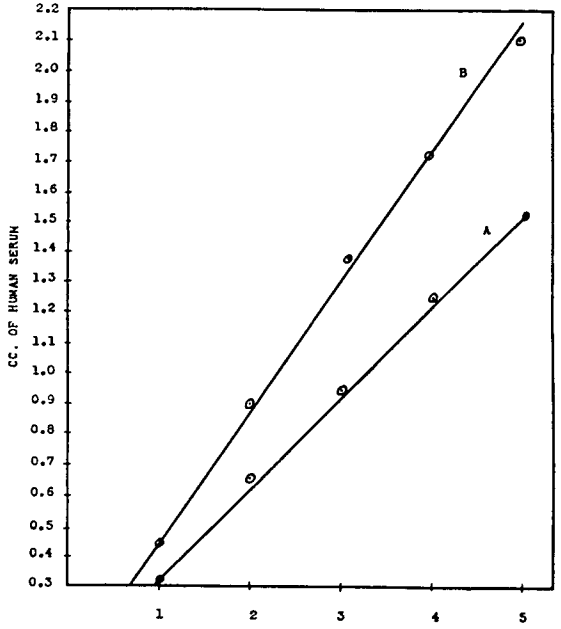

FIG. 1. Cc. of efocaine. Deposition curve of efocaine: Line A—Amount of human serum necessary to initiate deposition; Line B—Amount of human serum necessary to complete deposition.

months) have not produced local injury or systemic effects. Its use with a prolonged-acting local anesthetic agent would further reduce any untoward effect since, by definition, (that is, prolonged anesthesia), fewer numbers of injections would be required.

CHEMICAL STUDY

It was found that all of the available anesthetic bases were soluble in propylene glycol and saturated solutions could be prepared by the addition of water. However, stability testing revealed that decom-

TABLE 2

PRECIPITATION LIMITS FOR THE ANESTHETIC SOLUTIONS (CC.)* PER CUBIC CENTIMETER

No.	Anesthetic Agent	Dist. Water	Physiologic Saline Solution	Human		Spinal Fluid	Rabbit Serum	Horse Serum	Dog Serum	Cat Serum
				Serum	Plasma					
1	Procaine	0.30	0.30	0.33	0.32	0.30	0.31	0.28	0.30	0.30
		0.40	0.40	0.44	0.43	0.40	0.40	0.36	0.39	0.40
2	Butethecaine	0.25	0.26	0.28	0.28	0.28	0.26	0.27	0.27	0.28
		0.45	0.43	0.42	0.42	0.42	0.38	0.40	0.40	0.36
3	Dibucaine	0.28	0.28	0.30	0.31	0.28	0.26	0.30	0.30	0.27
		0.43	0.40	0.38	0.37	0.39	0.35	0.40	0.40	0.39
4	Piperocaine	0.36	0.34	0.38	0.38	0.36	0.39	0.37	0.38	0.40
		0.51	0.50	0.46	0.46	0.45	0.44	0.44	0.45	0.46
5	Tetracaine	0.43	0.42	0.44	0.44	0.42	0.43	0.42	0.43	0.43
		0.63	0.60	0.53	0.53	0.50	0.58	0.60	0.61	0.60
6	Benzocaine	0.21	0.21	0.26	0.26	0.24	0.21	0.26	0.21	0.24
		0.31	0.30	0.38	0.38	0.34	0.30	0.34	0.31	0.36
7	Bu-*p*-NH_2 benzoate	0.18	0.18	0.20	0.21	0.19	0.23	0.21	0.20	0.20
		0.27	0.27	0.26	0.26	0.24	0.30	0.29	0.26	0.21

* Arrived at from a titration of 3 samples of 1 cc. each with the indicated solution, using a microburette. The values recorded are the range observed; the first value is the amount necessary to initiate precipitation in 1 cc. of solution and the second value is the amount necessary to cause complete precipitation.

position took place within a relatively short period of time (table 1). This was corrected by the addition of small amounts of polyethylene glycol which acted as a protective polymer. This agent has been reported to be pharmacologically of the same order as propylene glycol and in both animal and human testing was shown to be safe for intramuscular use (44). Solutions of the local anesthetics prepared in this way were found to be stable at both room temperature and 60 C. for more than three months.

In order to determine the completeness of the deposition of the active ingredients by aqueous fluids, precipitation curves of the di-

ferent preparations were obtained. From these data, test solutions which required from 0.25 to 0.40 cc. of aqueous fluid to precipitate 1 cc. of solution were prepared (fig. 1, table 2).

SCREENING TESTS FOR DURATION OF ANESTHESIA

One cubic centimeter of the anesthetic solution to be tested was injected subcutaneously into the volar surface of the forearm at three different sites. Both arms were used, affording six determinations in each of 5 subjects. Qualitative testing for duration of anesthesia was conducted periodically and the average duration of anesthesia was determined from the total of 30 tests. These results are reported in table 3.

The injections were not painful and a slight swelling was noted in some instances which disappeared within one-half hour. In 3 instances the solution was inadvertently injected intradermally. This caused a transient burning sensation which disappeared in from one to two

TABLE 3

SCREENING TEST FOR ANESTHETIC DURATION

No.	Anesthetic Agent	Concentration, per cent	Duration of Anesthesia, days*		
			Mean	Minimal	Maximal
1	Procaine	1.00	10.1	8	14
2	Butethecaine	1.00	7.6	5	13
3	Dibucaine	0.05	9.3	7	12
4	Piperocaine	1.00	10.3	6	12
5	Tetracaine	0.10	8.1	5	11
6	Benzocaine	5.00	8.4	7	13
7	Bu-*p*-NH_2 benzoate	5.00	9.2	8	14

* To the nearest whole day.

minutes. There was no apparent evidence of tissue slough or necrosis. The anesthetized area decreased in time, indicating a continued and sustained drug-release.

From the data obtained in table 3, it was decided to develop the scope of these agents. A series of solutions was prepared with a range in concentration. Doses of 1 cc. were injected subcutaneously into the forearm and the duration of anesthesia was determined. The mean value of 10 injections was taken as the index (table 4). The duration of anesthesia apparently is not dependent upon concentration although the intensity is. Thus in most instances, a threefold or fivefold increase in concentration did not produce a corresponding equivalent increase in the duration. This is in agreement with the observed behavior of the analogous soluble salts of the anesthetic agents.

The pharmacologic activity of local anesthetic agents is known to be additive (45) but this was derived from a study of the acid salts

of the active agents. Since a determining factor in the duration of action of the insoluble bases would be their relative solubility, it was of interest to investigate a mixture of these agents. A pilot series of solutions was prepared and tested in the manner already described. The duration of anesthesia derived from the mean value of 10 injections is reported in table 5.

It is of particular interest to note that a potentiation is observed between procaine and the alkyl esters of *p*-aminobenzoic acid. The

TABLE 4

EFFECT OF CONCENTRATION ON DURATION OF ANESTHESIA

No.	Anesthetic Agent	Concentration, per cent	Duration of Anesthesia, days*		
			Mean	Minimal	Maximal
1	Procaine	0.5	8.1	5	12
		1.0	10.1	8	14
		1.5	10.9	7	15
		2.0	11.4	5	15
2	Butethecaine	0.5	6.4	4	10
		1.0	7.6	5	13
		1.5	8.5	5	12
		2.0	9.1	6	15
3	Dibucaine	0.05	9.3	6	15
		0.1	11.1	7	16
4	Piperocaine	0.5	9.0	5	11
		1.0	10.3	6	12
		1.5	10.9	6	14
5	Tetracaine	0.05	6.4	4	18
		0.10	8.1	5	11
6	Benzocaine	2.5	7.1	4	10
		5.0	8.4	7	13
		10.0	11.0	6	15
7	Butyl-*p*-aminobenzoate	2.5	8.1	4	12
		5.0	9.2	8	14
		10.0	11.1	7	15

* To the nearest whole day.

latter compounds are generally useful for their ability to penetrate tissue, whereas procaine has been described (46) as being limited in this respect. Little, if any, potentiation was noted among the other compounds. It is difficult to ascribe a basis for this activity in view of the fact that these compounds (procaine and *p*-aminobenzoic acid esters) are chemically related. They vary greatly in aqueous solubility, however, and thus might mutually influence their relative absorptions.

The preparation of choice of the latter series, FCO-211 # (see table 5) was subjected to a more critical testing. Two cubic centimeters was injected into the inner aspect of the forearm and the anesthetized area measured. The mean value of six determinations was plotted as a function of time (fig. 2). The anesthetized area decreased in a fairly uniform manner, with the greatest change in area occurring after five days, although anesthesia was observed for more than thirteen days. A confirmatory test of the anesthetic depot was conducted by establishing the presence of *p*-aminobenzoic acid in the urine. Both agents are converted to this compound through esterase activity and could be conveniently determined in the urine by the

TABLE 5

EFFECTS OF MIXTURE OF ANESTHETICS ON DURATION

No.	Anesthetic Agent	Concentration, per cent	Duration of Anesthesia, days*		
			Mean	Minimal	Maximal
FCO-101	Procaine Butethecaine	1 1	10.8	6	13
FCO-121	Procaine Dibucaine	1 0.05	10.4	7	12
FCO-210	Procaine Benzocaine	1 5	12.6	7	16
FCO-211	Procaine Butyl-aminobenzoate	1 5	14.6	6	18
FCO-301	Tetracaine Butyl-aminobenzoate	0.1 5	12.4	6	14

* To the nearest whole day.

conventional colorimetric, Bratton-Marshall method (47). *p*-Aminobenzoic acid was found to be present in the urine throughout the entire period of anesthesia.

The histopathologic ** effects of efocaine on skin, subcutaneous, submucosal, intramuscular and nerve tissue were studied in both acute and chronic experiments.

Eleven rabbits, 12 guinea pigs and 12 rats were used. Efocaine, 0.5 cc., was injected into one or more of the following sites: the lower lip, the skin of the sternal region, the triceps muscle of the left foreleg and the brachial plexus of the same leg. The muscle and brachial

FCO-211 is available as Efocaine, the trade mark of the E. Fougera Co., Inc., New York, and consists of procaine base 1 per cent, procaine hydrochloride 0.25 per cent, butyl-*p*-aminobenzoate 5 per cent, polyethylene glycol-300, 2 per cent, propylene glycol 78 per cent, sodium metabisulfite 0.1 per cent, phenylmercuric borate (1:25,000) and water 20 per cent.

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plexus were injected under direct vision by surgical exposure of the region. Injections of the brachial plexus were confined to the rabbits. All of the guinea pigs and rats and 5 of the rabbits were killed during height of the experiment. The remaining 6 rabbits were observed for varying periods up to ninety-eight days.

All of the rabbits showed a striking immediate and complete paralysis of the left forelimb which remained, with gradually diminishing severity, for at least fifteen days and with some impairment of motion lasting as long as twenty-five days. There were no apparent systemic manifestations in any of the rabbits, guinea pigs or rats.

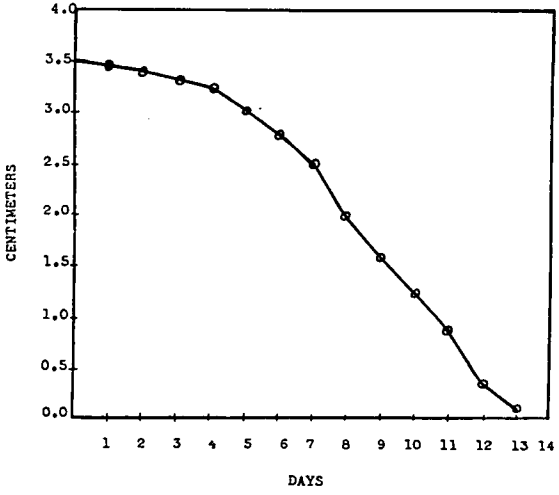

FIG. 2. Anesthetized area *vs.* time following injection of 2 cc. of efocaine. (Mean result of 6 injections.)

In all animals in which necropsy was performed at varying intervals up to thirteen days following injection with efocaine, the gross examination revealed the following: There appeared to be some degree of fibrous reaction about the brachial plexus. The muscles showed evidence of necrosis in the line of injection. Except for one section of lip which was secondarily infected, the sections of lip and skin were not remarkable.

In those animals in which necropsy was performed at varying intervals between eighty-nine and ninety-eight days after injection with efocaine the gross examination demonstrated the following: The muscle revealed no obvious abnormalities upon multiple sectioning of

the muscle. The brachial plexus was found to be lying in loose areolar tissue with no evidence of perineural fibrosis and with no other gross abnormalities being evident. The sections through the lips and sternal skin showed no gross abnormalities.

In those animals in which necropsy was performed within thirteen days following injection with efocaine the microscopic examination revealed the following: The nerve fiber bundles showed no definite histologic alterations. The surrounding fat tissue showed what could be interpreted as a healing or healed fat necrosis with a loose cellular fibrous reaction. There was no acute inflammatory exudate. Sections of the muscle showed necrosis and partial disappearance of muscle fibers, with replacement by a moderately cellular, loose connective tissue. There was little or no inflammatory reaction. Sections of the skin showed very little alteration, with some sections showing focal loose cellular fibrous reaction and occasional degenerated fat cells. Sections through the lip showed a proliferation of loose cellular connective tissue, areas of hemorrhagic extravasation and bland thrombi in dilated blood vessels with some of the thrombi showing early organization. In none of the above microscopic examinations was there any evidence of foreign body giant cell reaction or of deposition of foreign material.

In those animals in which necropsy was performed at varying intervals between eighty-nine and ninety-eight days after injection with efocaine the microscopic examination revealed the following: A small focal area of fibrous replacement of muscle fibers was found in only one muscle section. There was no accompanying inflammatory reaction. Sections of muscle from all the other animals showed no histopathologic change. The sections of the nerves of the brachial plexus revealed no evident inflammatory reaction and no perineural fibrosis. The nerve fibers showed focal loss of myelin in their sheaths as evidenced by the presence of scattered vacuoles. This was not a diffuse process; it was present in some areas and not in others. Sections through the lip and the skin of the sternal region showed no histopathologic change.

In order to make a spot check of the immediate effects of the intravenous administration of efocaine, 0.6 cc. of efocaine was injected into the ear vein of one rabbit. There was no immediate reaction. The animal was killed one hour later and sections were taken of lung, heart and kidney. No histologic alterations could be found in any of these organs.

It is evident from the observations described above that efocaine does not provoke a foreign body reaction and does not remain in a demonstrable form in the tissues. The striking apparent resolution occurring in the injected muscles, without a focal fibrous reaction remaining subsequent to the immediate necrosis, is further evidence of the lack of any permanent injurious action of the drug. The fibro-

blastic proliferation seen about the nerves during the early stages after injection was found to disappear completely, confirming the impression that the process is benign and apparently reversible or, at least, loses its characteristics and is absorbed into the surrounding tissues. With full realization that injection of 0.5 cc. of efocaine into a nerve bundle as small as the brachial plexus in the rabbit is an enormous dose, it is not surprising to find the presence of focal degeneration of the myelin sheath. The mechanical effects of injecting 0.5 cc. of any substance into such a small, confined space are to be considered of paramount importance in interpreting the histologic features. Apparently the fibroblastic proliferation and bland thrombus formation found in the sections of the lip are of the same benign character as those found in the other tissues since no histopathologic change was evident in the sections of those animals whose course was followed for a long period of time.

In view of the well known pharmacology of the ingredients of this preparation and the negative histopathology, efocaine was evaluated clinically as a means of controlling postoperative pain. Seventy-nine patients, consisting of 54 major surgical and 25 minor surgical cases, were given injections of efocaine at the conclusion of the operation while the patient was still under the control of the surgical anesthesia. The cases were unselected and were, for the most part, consecutive. The injections were made with a 22 or 24 gauge needle into the deeper subcutaneous tissue, utilizing a fan-wise injectional technic where applicable. Varying technics were utilized and were principally the following:

a) Local infiltration (minor operations),
b) Peri-incisional infiltration (upper and lower abdominal, and gynecologic surgical procedures),
c) Intercostal nerve block (upper abdominal operations),
d) Paravertebral nerve block (lower abdominal operations),
e) Anorectal infiltration (proctologic operations).

The patients were carefully questioned as to the presence of pain or discomfort and tested daily for skin anesthesia. The patients' nursing or attending staffs were not informed of the investigation and no special attention was given to the treated patients. As a confirmatory objective check of the degree of pain relief obtained, the postoperative analgesic requirements of the patients were carefully noted. The drug needs of the test series were compared with the requirements of untreated patients undergoing analogous surgical procedures concurrently and also with the amount of postoperative narcotics administered to a group of control patients undergoing identical operations by the same surgeons. Every effort was made to keep the conditions between the experimental and the control groups identical. The same drug orders were written—to be administered when necessary. All postoperative analgesic needs were included except those

administered for headache or insomnia. Drugs given for restlessness, discomfort and general malaise were included as a part of the postoperative requirements.

The results were graded in the following manner:

Excellent—when no local pain in the surgical area was experienced by the patient and no postoperative analgesic medication was administered.

Good —when there was no local pain in the surgical site and one or two doses of postoperative analgesic medication were given for a nonrelated cause such as restlessness, etc.

Fair —when no "real" pain occurred in the surgical area, but the patient experienced discomfort requiring analgesic medication.

Poor —when pain was experienced, but the drug requirements were lessened as compared to the controls.

Failure —when there was no difference in the treated patients as compared to the controls.

A summary of the surgical procedures and the results obtained is presented in tables 6 and 7.

Efocaine was used in a similar manner in the 25 minor surgical procedures for which local anesthesia was required. The patient was observed at regular intervals in order to establish the degree and duration of anesthesia. A summary of these results is presented in table 8.

TABLE 6

THE EVALUATION OF EFOCAINE IN MAJOR SURGERY

Operative Procedure	No. of Cases	Quantity of Drug Injected, cc.	Duration of Anesthesia, days*			Results				
			Mean	Minimal	Maximal	Exc.	Good	Fair	Poor	Failure
Thyroidectomy	4	5–10	6	3	10	3	1	—	—	—
Cholecystectomy	10	5–15	8	5	12	6	2	2	—	—
Hysterectomy	6	5–15	8	6	13	4	1	1	—	—
Herniorrhaphy	20	5–15	9	5	12	10	7	1	1	1
Appendectomy	4	5–10	8	6	10	3	—	—	1	—
Laparotomy	1	10	10	10	10	—	1	—	—	—
Hemorrhoidectomy	7	5–15	10	8	17	6	1	—	—	—
Fistula-in-ano	2	5–10	9	9	9	2	—	—	—	—
	54		8.3	6	11.8	34	13	4	2	1

* To the nearest whole day.

In all of these procedures there was no evidence of systemic toxicity or of local tissue reaction. No tissue slough or abscesses resulted from the use of this preparation, and no interference with wound healing

TABLE 7

COMPARISON OF POSTOPERATIVE NARCOTIC DRUG REQUIREMENTS OF CONTROL‡ AND TREATED GROUP‡

Surgical Procedure	No. of Cases	Control Group*: Morphine Sulfate, grains	Control Group*: Demerol, mg.	Control Group*: Codeine Sulfate, grains	Test Group†: Morphine Sulfate, grains	Test Group†: Demerol, mg.	Test Group†: Codeine Sulfate, grains
Thyroidectomy	4	1 1/6	975	2 1/2	—	50	—
Cholecystectomy	10	3 1/6	4,500	9 1/2	—	300	1 1/2
Hysterectomy	6	2 4/6	2,600	4 1/2	1/4	100	1/2
Herniorrhaphy	20	4 1/4	3,625	11	1/4	650	2 1/2
Appendectomy	4	1/3	500	1	—	150	—
Laparotomy	1	1/6	300	—	—	50	—
Hemorrhoidectomy	7	3	800	2 1/2	—	—	1/4
Fistulectomy	2	3/8	375	— 1/2	—	—	—
Total	54	14 3/4	13,675	31 1/2	1/2	1,300	4 3/4

* The total drug requirements of consecutive cases of analogous surgery obtained from hospital records.

† The total drug requirements for the indicated patients of the test series using efocaine.

‡ All patients had the same—p.r.n.—drug orders.

could be observed when compared with the controls. The only complaint of the patients was the sensation of a slight burning pain when this material was introduced into the superficial tissue, which occurred in 6 instances in the series having minor surgical procedures. This burning pain was transient and lasted approximately one to two minutes. It is of no clinical consequence and there were no untoward local reactions in the patients who experienced this sensation. It was found that by creating a skin wheal with procaine hydrochloride before the introduction of the needle containing the efocaine, this burning

TABLE 8

THE USE OF EFOCAINE IN MINOR AND OFFICE SURGERY

Procedure	No. of Cases	Amount of Drug Injected, cc.	Duration of Anesthesia, days: Mean	Duration of Anesthesia, days: Minimal	Duration of Anesthesia, days: Maximal	Results: Exc.	Results: Good	Results: Fair	Results: Poor	Results: Failure
Excision of sebaceous cyst	5	5–10	7	3	10	3	2	—	—	—
Excision of lipoma	5	5–10	9	6	14	5	—	—	—	—
Infiltration, pre-aural neuroma	1	2	10	—	—	1	—	—	—	—
Excision of toe nail, parenchyma, etc.	4	2–4	6	5	8	3	1	—	—	—
Infiltration for trauma, sprains, etc.	10	5–10	10	6	15	7	3	—	—	—
	25		8.4	5	11.7	19 (76%)	6 (24%)	0	0	0

sensation could be eliminated. This procedure should be utilized when the patient is not under the control of surgical anesthesia.

The anesthetic agents (procaine and butyl aminobenzoate) block both motor and sensory nerves. Prolonged motor nerve block usually is not desirable and therefore efocaine should be used chiefly for postoperative control of pain and the usual short acting anesthetic solutions used for surgical anesthesia. In some instances, however, motor nerve block may be desired (for example, relaxing the anal sphincter). In the anorectal infiltrations, sphincter control returned to normal after the third postoperative day. There were no instances of sphincteric paralysis or of prolonged spasm. As a general rule, areas of high motor innervation should be avoided when efocaine is used for control of pain.

Efocaine should be administered in a manner to block completely the operative area. Pooling of the drug in any one spot should be meticulously avoided and only the deeper subcutaneous tissues utilized. An aid to the avoidance of pooling is to introduce the needle to the desired depth and then slowly inject the solution as the needle is withdrawn or reverse the procedure and inject the solution ahead of the advancing needle.

This preparation (efocaine) appears to be admirably suited to the needs of the physician for the control of pain, and in those instances in which prolonged anesthesia is indicated. Further work is now in progress in order to develop its full scope in the practice of medicine.

SUMMARY AND CONCLUSIONS

The experimental background leading to the development of an aqueous-miscible prolonged local anesthetic is presented. By utilizing a new concept of parenteral administration, local anesthesia of approximately two weeks' duration is produced by a single administration.

Clinical study of this drug in more than 75 patients revealed that this agent was highly effective in the control of postoperative pain. There were no local or systemic toxic reactions; tissue sloughs or gross necrosis were not encountered.

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SECOND SCANDINAVIAN CONGRESS

Dr. Henning Poulsen, Secretary of the Nordisk Anaestesiologisk Forening (Scandinavian Society of Anesthesiologists), has announced that the Second Congress of that Society will be held in Stockholm, Sweden on August 8–9, 1952. The two main themes for the meeting are:

Toxic Reactions and Bi-effects in the Employment of Anesthetics.

Curarizing Drugs (Chemistry, Pharmacology, Experimental Physiology).