A STUDY OF EFOCAINE *

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INTRODUCTION

MANY patients dread and postpone surgical procedures because they dread the severe discomfort following operation. This has been of great concern to all surgeons and anesthesiologists. A long-lasting local anesthetic is needed: (a) to allow the patient to rest more comfortably; (b) to allow appetite, fluid intake, and elimination quickly to return to a normal level (1); (c) to allow early ambulation; (d) to reduce the need for narcotic drugs (2); (e) to allow the patient to cough effectively following abdominal and thoracic surgery, thereby helping to prevent hypoventilation and atelectasis (3); (f) to require less nursing care(4).

Efocaine † has been offered to the profession as an injectable, long-lasting local anesthetic solution, to counteract postoperative pain.

COMPOSITION

The composition of efocaine is as follows (1, 2, 4–6):

Procaine base	1%	
Procaine hydrochloride	0.25%	Anesthetic base
Butyl-*p*-aminobenzoate	5%	
Polyethylene glycol	2%	Aqueous miscible solvents
Propylene glycol	78%	
Sodium metabisulfite	0.1%	Preservatives
Phenylmercuric borate	0.004%	
Water	20%	

The safety and the efficacy of procaine have been established by numerous pharmacological and clinical investigations. Butyl-*p*-aminobenzoate (butesin, U.S.P.) has been used as a topical anesthetic and for relief of pain in burns (7). Propylene glycol has many uses in industry (8–10), and has been used as a solvent or a vehicle for dietary and medicinal products (11–15). The United States Food and Drug Administration classifies polyethylene glycol as toxic (8).

MECHANISM OF ACTION

The mechanism of action is as follows (4, 16–20). Procaine and butyl-*p*-aminobenzoate are present in their saturation limits in the

* Accepted for publication August 31, 1954.

† Efocaine, a product of E. Fougera and Co., Inc., 75 Varick St., New York, N. Y.

specially balanced solvents, propylene glycol, polyethylene glycol 300 and water. The addition of even minimal quantities of body fluids causes precipitation of the active ingredients, which are absorbed slowly, thereby producing a prolonged anesthesia. The manufacturer states that it will produce anesthesia safely for twelve to fourteen days.

BASIC PRINCIPLES IN USE

The following basic principles have been recommended in using efocaine (2, 19, 21). As with other local anesthetics, surgical asepsis of the injection site is important. Traumatized or inflamed tissues should be avoided. The agent must be placed accurately around nerve trunks or fibers to produce the desired effect. Aspiration should be carried out before any solution is injected and should be repeated frequently during the procedure. Deposition of excessive amounts of the drug should be avoided. Efocaine should not be used for spinal, caudal, or epidural anesthesia, since prolonged block of motor nerves is undesirable. Intravenous injection is contraindicated.

RECOMMENDATIONS FOR USE

Efocaine has been recommended for the control of postoperative pain in the fields of thoracic and abdominal surgery, proctology, gynecology, and dermatology. Its use has been advocated in excision of lipomas, sebaceous cysts, and tonsils. Anorectal infiltration (4, 5, 17, 19, 22, 23), lateral or peri-incisional blocks (2, 17, 20, 23), intercostal blocks (2, 16, 21), and paravertebral somatic blocks (2, 6, 11, 18, 24, 25) are the recommended techniques to use.

CLINICAL REPORTS

Many articles have been published on the clinical use of efocaine (2, 5, 6, 16–18, 20, 22, 23, 26, 27). The majority of the reports did not mention any undue tissue reactions. When used, the analgesic and the sedative drugs were not required postoperatively, or were used at a minimum. Other authors have reported pain at the site of injection and occasionally in the nerve distribution (29), transverse myelitis, anhidrosis, and pain, swelling, and weakness in an extremity (28).

PURPOSE OF THE STUDY

The purpose of this study was to observe the effects resulting from the injection of efocaine and its constituents into laboratory animals. The animals used were 50 hamsters, 6 rabbits, and 4 dogs. Gross and histological studies were made.

ANIMAL STUDIES

Hamsters

Intraperitoneal injections, varying from 0.5 to 4.0 cc., of efocaine were made into 18 different male and female hamsters weighing from

85 to 150 Gm. each. Immediately after the injections, the animals had an opisthotonic reaction for approximately 1 minute. Their lips and their digits were cyanotic. All died, the time of death varying from thirty minutes to eleven days, depending upon the dosage of the drug used. Histological studies revealed an inflammatory exudate in the abdominal cavity. Pathological changes in the kidney varied from reversible cloudy swelling and hydropic degeneration of the kidney tubules to irreversible karyolysis, karyorrhexis, pyknosis, and necrosis. The majority of the kidneys showed blood or casts in the tubules. The

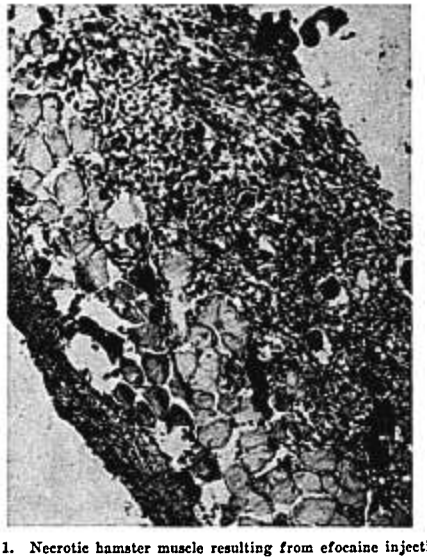

FIG. 1. Necrotic hamster muscle resulting from efocaine injection.

liver changes were not outstanding, a few having some fatty degeneration. The lungs varied from being normal to showing evidences of congestion and an interseptal inflammation. The intestinal changes varied from normal to gross distension, with microscopical evidence of atrophied mucosa. Changes in the spleen were negligible.

Injections of 0.1 cc. of efocaine were made in the submucosa of the hard palates of 4 hamsters. All had evidence of necrosis of the injected area on gross and microscopical study.

Intramuscular injections of 0.5 cc. of efocaine were made in all four extremities of another hamster and studies made at seventy-two

hours, forty-eight hours, twenty-four hours, and forty-five minutes. After the forty-five minute period, a typical, diffuse inflammation was present. The other specimens showed a diffuse, severe inflammatory reaction with extensive necrosis (fig. 1).

Subcutaneous injections of 0.5 cc. of efocaine in the abdominal walls of 2 female adult hamsters resulted in ulceration and necrosis. Saline controls were negative.

Similar studies were made with propylene glycol, propylene glycol with aminobenzoate (5 per cent), and polyethylene glycol 300.

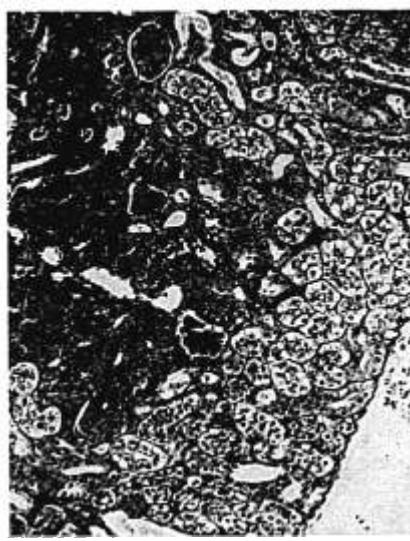

FIG. 2. Hydropic degeneration of hamster kidney resulting from intraperitoneal injection of propylene glycol and aminobenzoate (5%).

When propylene glycol was injected intraperitoneally, a typical opisthotonic reaction did not occur. The histological studies were similar to those described with efocaine, however. Intramuscular, submucosal, and subcutaneous injections with propylene glycol were similar to those with efocaine, but less intensified.

Propylene glycol with aminobenzoate (5 per cent) and polyethylene glycol 300 were injected in a similar manner with results almost identical with those previously described (fig. 2).

Similar studies with isotonic saline and 2-isobutylaminoethyl-*p*-aminobenzoate (monocaine®), 2 per cent, were negative.

Rabbits

Intravenous, intracardiac, intramuscular, and subcutaneous injections were made on 6 rabbits. The marginal ear veins were used to inject 0.5 to 1.0 cc. of efocaine intravenously. The reactions varied from loss of equilibrium, to opisthotonus, to death. Thrombi developed in the veins and the ears became drooping, edematous, and necrotic. Histopathological sections of the spleen, the heart, the lung, the intestine, and the liver were not outstanding. One of the kidneys

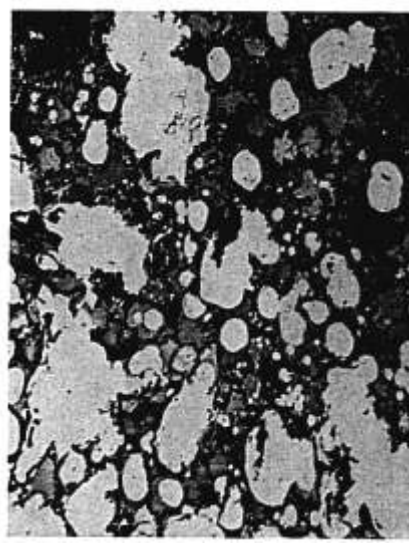

FIG. 3. Rabbit lung following an intracardiac injection of efocaine, showing edema, hemorrhage, thrombosis, and intraseptal inflammation.

showed cloudy swelling, pyknosis, karyolysis, and karyorrhexis of the tubule cells.

Subcutaneous and intramuscular injections of efocaine (0.5 cc.) again showed necrosis of the involved area on histopathological study.

An intracardiac injection of 1.5 cc. of efocaine in a 2.3 Kg. rabbit resulted in an immediate convulsive seizure and death within thirty seconds. Figure 3 depicts the lung from this animal.

Propylene glycol, propylene glycol and aminobenzoate (5 per cent) and polyethylene glycol 300 again resulted in necrosis when injected subcutaneously or intramuscularly. An intravenous injection of 1.75

cc. of propylene glycol and aminobenzoate (5 per cent) resulted in almost immediate death of a 2.3 Kg. rabbit.

Dogs

Intravenous doses of 1.5 cc. of efocaine were injected into 2 dogs weighing 6.8 and 9 Kg. The smaller dog had an opisthotonic reaction of approximately 1 minute. The larger dog had difficulty maintaining equilibrium, but became normal at the end of 1 minute.

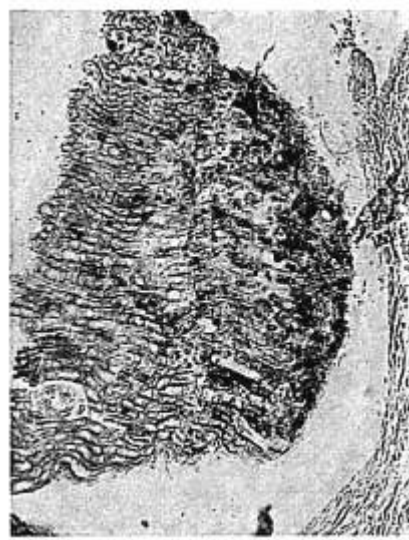

FIG. 4. Section of cauda equina of dog following an intraspinal injection with efocaine (Marchi's staining method).

Intraspinal injections with 1.0 cc. of efocaine in each of 2 dogs resulted in fatty degeneration of the cauda equina fibers (fig. 4). The spinal anesthesia lasted about ten hours.

An injection of 2.0 cc. of efocaine in the mucobuccal fold of a dog resulted in swelling of the area at least three times its normal size within 4 hours. A histopathological section of the area showed edematous tissue with scattered polymorphonuclear leukocytes.

Four intercostal injections were made on another dog, 1.0 cc. of efocaine being injected in each block. A histopathological study 1 week later showed necrosis of fat and muscle in the involved areas.

When 1.0 cc. of efocaine was injected in a peri-incisional manner, one superficial and one deep, around wounds in the abdominal wall of a dog, there was a delay in healing, ulceration, necrosis, and severe inflammation, as compared with a control wound on the same dog.

SUMMARY

Efocaine, a solution composed of procaine base, procaine hydrochloride, butyl-*p*-aminobenzoate, propylene glycol, polyethylene glycol 300, and water was studied by injection into laboratory animals, to determine the effects upon various tissues. The liquid constituents were studied in a similar manner.

Widespread, severe necrosis of tissue was noted following intraperitoneal, intramuscular, subcutaneous, and intravenous injections of efocaine, propylene glycol, and polyethylene glycol 300. Efocaine was also injected intraspinally, with resulting fat necrosis of the cauda equina. A more severe reaction resulted with efocaine than any of its separate constituents.

When given in sufficiently large doses, efocaine, propylene glycol, and polyethylene glycol 300 brought about opisthotonus, cyanosis, pain, and inactivity in hamsters. In rabbits and dogs, opisthotonus, inactivity, and loss of equilibrium resulted.

COMMENT

The results of these animal studies cannot be transferred quantitatively to man for a number of reasons, and such was not the purpose of this research. However, the occurrence of severe tissue injury in virtually all phases of these experiments indicates that the substance is manifestly unsuitable for use in human subjects.

CONCLUSION

From the results in this study, it would seem that efocaine, in its present form, is contraindicated for clinical use because of the severe tissue necrosis it causes.

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