CLINICAL NOTES

TRIPELENNAMINE HYDROCHLORIDE FOR TOPICAL URETHRAL ANESTHESIA

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Clinical interest in the anesthetic activity of the antihistamines has been greatly stimulated by the need to provide safe and effective anesthesia for patients who have shown atopic responses to commonly used topical anesthetic preparations. About two years ago we presented a preliminary report on the use of tripelennamine (Pyribenzamine) hydrochloride for the production of topical urethral anesthesia [1]; this report reviewed the pertinent literature. In the preliminary report the results obtained with tripelennamine hydrochloride solution in our first 100 patients were presented. A 4% solution had been used in the first 50 on a purely empirical basis, and, because of the fairly high incidence of initial burning on instillation into the anterior urethra (18 of the 50 complained of a degree of burning rated 2 to 4+), a 2% solution of the drug was used in the next 50 patients, with a gratifying reduction in that complaint. In all cases, regardless of initial burning (which was usually transitory), excellent anesthesia was obtained. Eighty-two per cent of the patients stated that tripelennamine was far more satisfactory than 4% piperocaine (Metycaine) hydrochloride, with which they were familiar from previous treatments. Several patients in the series had received dilations without the benefit of anesthesia because of previous allergic response to other topical anesthetic preparations and were convincing witnesses of the effective anesthesia produced with the antihistaminic solution.

Once the anesthetic potency of the preparation was ascertained, a 2% solution was accepted as standard and the patients were no longer informed that a new preparation was being used or asked if the medicament burned on instillation. The fact that only an occasional patient will volunteer the information that a transitory burning discomfort occurred attests to the fact that when it does occur it is seldom worthy of comment. Production of such burning in some patients appears to be an inherent quality of tripelennamine even in 0.5% solution and is not significantly altered even with the buffered nasal solution. The cessation of the burning was considered an end-point of the production of anesthesia in the original series and hence may actually be of some practical value. Regarding the question of absorption and toxicity, it was pointed out that the urethral mucous membrane is a very effective absorbing surface, as demonstrated by the fact that emesis occurs in three to five minutes after the injection of 1% apomorphine into the urethra of the male dog. Since the oral median lethal dose (L. $D._{50}$) of tripelennamine ranges from 210 mg. per kilogram of body weight in mice to 570 mg. per kilogram in male rats, it was shown that even assuming complete absorption of the amount injected into the urethra it still does not approach a dangerous dose. The results of the preliminary report therefore suggested tripelennamine as an effective and safe topical anesthetic agent for urologic use.

Immediately after the submission of the preliminary report further statistical tables were for a time compiled; however, as extensive further use failed to disclose any side-reactions or complaints, routine use of tripelennamine in place of other anesthetic solutions was adopted and statistical tabulations were discarded. In this study, with two years' additional routine use in over 2,000 patients, no untoward reactions were noted and there were practically no failures of anesthetic action. In relation to effectiveness of this or any topical anesthetic agent, three obvious but often neglected points must be kept in mind: adequate time must be allowed for production of anesthesia (disappearance of initial burning upon instillation provides a convenient end-point); topical anesthesia, however effective, is not block anesthesia and has inherent limitations in control of pain; and the most effective anesthesia does not give us license to forget the basic precept of gentleness in handling living tissues.

On the basis of our clinical experience in over 2,000 urologic cases during a two-and-one-half year period, in conjunction with the knowledge of similarly good results in other specialty practices,[2] 2% solution and 2% jelly of tripelennamine are recommended for use as preparations of a safe, potent, topical anesthetic agent in dosage not exceeding 300 mg. in adults.

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1. Fitzpatrick, R. J.; Orr, L. M., and Stubbart, F. J.: Antihistamines as Local Anesthetic Agents for Urethral Manipulation, J. A. M. A. **150**: 1092-1094 (Nov. 15) 1952.

2. Sheddan, F. G., Jr., and Bellanger, P. M.: Topical Use of Tripelennamine in Urologic Procedures, New England J. Med. **252**: 141-143 (Jan. 27) 1955.

USE OF DIOCTYL SODIUM SULFOSUCCINATE (AEROSOL O. T.) FOR SEVERE CONSTIPATION

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The purpose of this communication is to direct attention to the usefulness of dioctyl sodium sulfosuccinate (Aerosol O. T.), developed some 15 years ago, in the treatment of severe fecal impaction and lesser degrees of constipation. As one of the very first of the synthetic wetting agents it was originally popularly described in *Life* magazine without implication of medical usefulness, and readers may recall that its remarkable properties were illustrated by the cover picture of a duck sinking in water to which a small concentration of this material had been added. The effectiveness of this material for treating constipation is consequent to its ability to allow a hard fecal mass to be penetrated by water or by mineral oils so that it becomes effectively softened. Its action thus seems to be the simple physical effect one would expect

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from a detergent that allows water and fatty material to be better mixed. Wide experience has confirmed the fact that this material, even with prolonged use, causes no intestinal irritation, does not interfere with normal bowel function, and brings about no other evident ill-effects. This substance has been in use now by us and our associates with a great deal of success for over 12 years. In this communication we do not attempt to offer quantitative or controlled observations regarding its effect on constipation, since no alternate series of cases of quite similar nature or degree of severity could be treated by this and other methods of therapy. Each case, in a way, has to act as its own control with comparison of results with antecedent treatment in the same patient. In severe cases of impacted feces, preceding treatment and experience quite confirms our confidence in the effectiveness of this material. In cases of milder degrees of constipation one cannot conclude with surety that other remedies would not have been as effective.

TOXICITY

Animal experiments and extensive clinical observations have failed to reveal any evidence of toxicity.[1] Fifty rats given up to 0.87 gm. per kilogram of body weight per day remained healthy for six months. Three dogs given 0.1 gm. per kilogram of body weight remained in good health for six months. Rabbits and monkeys also tolerated like doses, and white blood cell count, red blood cell count, and differential count, plus postmortem examination, revealed no abnormalities. Repeated physical examinations on men handling the drug for years have been normal. We have given individual doses of 50 mg. per kilogram of body weight to many infants without any evidence of distress. The dosage used generally for the treatment of constipation has varied considerably, depending upon the severity of the condition to be treated, but maximum dosage has been less than 2 mg. per kilogram of body weight or much less than the above doses. Many hundreds of patients under our care have taken this material over the past decade without anything that would suggest ill-effects.

ABSORPTION STUDIES

It seemed logical to expect that if this agent had any effect on absorption of food stuffs from the intestine, it would increase absorption, particularly of fats. It was our hope originally that the drug might be of therapeutic value in certain types of nutritional disorders with associated poor intestinal absorption, such as cystic fibrosis of the pancreas and celiac disease. With this possible use in mind, certain preliminary food absorption studies were made. Since it was impractical for us to do complete balance studies, simultaneous amino acid absorption curves and vitamin A absorption curves were carried out on a considerable series of infants, including four with proven cystic fibrosis of the pancreas and four with celiac disease. The details of the study will not be reported here as our results were quite equivocal. Of 10 amino-nitrogen absorption tests, 3 showed better absorption of protein with the use of dioctyl sodium sulfosuccinate, 3 showed better absorption of protein without dioctyl sodium sulfosuccinate, and 4 were essentially unchanged. Three of the vitamin A absorption curves revealed better absorption of fat with the addition of dioctyl sodium sulfosuccinate to the test mixture, and four showed better absorption of fat without it.

The results were equally inconsistent in the patients with celiac disease, those with cystic fibrosis of the pancreas, and the others. We have concluded that the variations in absorption revealed in this small series of studies resulted from day to day changes in the disease state and that the synthetic wetting agent, as we used it, had no dependable effect in either improving or inhibiting the absorption of foodstuffs from the intestine. Subsequent clinical use of the drug over long periods of time in many hundreds of cases has strengthened this impression, although it is obvious that only good balance studies can give a certain answer.

CLINICAL USE

Dioctyl sodium sulfosuccinate is marketed both in solid pellets and in 10% aqueous solution. We have used it routinely in 1% aqueous solution, diluting the commercial preparation with distilled water. In the concentrated form, this material has an exceedingly bitter taste, but in the concentrations used, the taste can easily be disguised in most vehicles. In bottle-fed infants the material can be satisfactorily added to the formula or milk. Any of the fruit juices are quite satisfactory for older children and adults. The material has been used by itself and in combination with mineral oil.

We have used dioctyl sodium sulfosuccinate in four types of patients. Its most dramatically successful and important use has been in patients with impacted feces. These have occurred most commonly in children with various types of megacolon. In several instances we have encountered such severe impaction that obstructive symptoms began to appear, and the possibility of laparotomy was entertained, since cathartics and repeated enemas of traditional types were unsuccessful. Dioctyl sodium sulfosuccinate given by mouth and by enemas, with mineral oil, has successfully softened up fecal matter too hard and too extensive to be digitally removed, so that spontaneous evacuation eventually occurred. The use of dioctyl sodium sulfosuccinate by itself should not be considered a satisfactory method of management of megacolon secondary to congenital absence or dysfunction of part of Auerbach's plexus; however, it has been exceedingly valuable as an adjunct treatment. In the care of patients with megacolon, both before and after operative interference, we have used the following medication: dioctyl sodium sulfosuccinate, 1% aqueous solution, 2 cc. three times daily, by mouth, in milk or fruit juice; and enemas of 1 or 2 oz. (30 to 60 cc.) of mineral oil; or sometimes sodium chloride, combined with 5 cc. of 1% dioctyl sodium sulfosuccinate. As an example, one patient, 19 months of age, with severe megacolon diagnosed at 3 months, had attacks of severe fecal impaction leading to obstructive vomiting in spite of energetic use of ordinary cathartics at 3 months and at 5 months of age; but the following year, with the use of dioctyl sodium

1. Benaglia, A. E.; Robinson, E. J.; Utley, E., and Cleverdon, M. A.: The Chronic Toxicity of Aerosol-O T, J. Indust. Hyg. & Toxicol. 25:175 (May) 1943.

sulfosuccinate, 15 drops twice a day by mouth and in mineral oil enemas once or twice weekly, no great difficulty with fecal retention occurred. At 16 months of age this child was subjected to the Swenson procedure (resection of the aganglionic area of the rectum or sigmoid colon) and since that time has got along very well without any treatment.

Much more common are the problems of young babies with hard lumpy feces, often after anal fissures have occurred. Although this is not an important medical problem, it is one that is very annoying to parents. Dioctyl sodium sulfosuccinate has been exceedingly useful with this problem, as the material could be used safely for relatively long periods without the disadvantage of frequent formula changes and without enemas. In this situation, 15 drops twice in a 1% solution in the formula has been satisfactory, with no additional mineral oil usually necessary. As a typical example, a 6-week-old baby, brought to the well baby clinic by its worried mother, was eating well and gaining weight but was nevertheless much disturbed, with bowel movements only every four days. The fecal mass consisted of hard lumps accompanied by three or four hours of apparent great distress on the part of the infant. Blood-streaked feces had been passed. There were palpable fecal masses in the abdomen. With the simple addition of dioctyl sodium sulfosuccinate (in the dosage prescribed above) to the formula, bowel movements became regular, without apparent discomfort. Mineral oil was used as an adjunct for a few days, but then therapy with drug alone was continued for two months without subsequent difficulty. There have been a great many such patients so treated.

Infants with postoperative anal atresia often have great difficulty in having normal defecation. It is important that the stools remain soft and pliable to protect the operative site until complete healing can occur. In these patients dioctyl sodium sulfosuccinate given by mouth (sometimes with the addition of mineral oil) has very successfully controlled the tendency toward constipation.

Poliomyelitis patients and others incapacitated by muscle weakness, who are immobilized in bed, almost without exception pass through a period of more or less severe constipation, particularly during the early periods of their illness. In patients with severe paralysis, such as those requiring the use of a respirator, constipation as a rule is very severe and presents an annoying therapeutic problem. These patients almost routinely require medication for constipation, and in such cases the disadvantage of irritant cathartics is obvious. Mineral oil alone has certain well-known disadvantages. We have for years very successfully treated such patients with dioctyl sodium sulfosuccinate and occasionally with the addition of magnesium hydroxide (Milk of Magnesia). The adults are given 2 cc. of 1% solution of dioctyl sodium sulfosuccinate and the children approximately half that dose. In severe cases, occasionally enemas with dioctyl sodium sulfosuccinate in sodium chloride solution have been necessary, and, in new patients with fecal retention, oil retention enemas with 5 cc. 1% dioctyl sodium sulfosuccinate in 3 oz. (90 cc.) of mineral oil have been used. Other cathartics are rarely necessary.

SUMMARY AND CONCLUSIONS

A synthetic wetting agent, dioctyl sodium sulfosuccinate (Aerosol O. T.), has been used extensively on the University Hospital clinical services for the past 12 years in the treatment of constipation in many different types of patients, including those severely distressed with fecal impaction associated with megacolon, anal fissure, postoperative anal atresia, and in bedridden patients of many types, including patients convalescing from poliomyelitis and some elderly invalids. In mild and moderate forms of chronic constipation this material has been found to be effective by itself. We have also found it exceedingly useful combined with mineral oil in the early treatment of the most severe constipation. Experience with many hundreds of cases failed to reveal any evidence of toxicity of any sort. A limited number of absorption studies have indicated that dioctyl sodium sulfosuccinate has no dependable and probably no significant effect upon fat or protein absorption from the intestine. In our opinion, dioctyl sodium sulfosuccinate has wide usefulness in the treatment of constipation because a good therapeutic effect can be obtained without the danger of toxicity or decreasing effectiveness even when used regularly for indefinite periods of time.

Automobile Accidents.—Since a study of the type of injuries encountered indicates that many of them could have been prevented by alterations in design of the automobile itself, . . . certain basic safety measures should be incorporated in all cars and required of all manufacturers. Among these measures which should be required are: (1) Control of speed by the development of a governor limiting the top speed to 55 miles per hour but in no way interfering with acceleration at lower speeds. The manufacturers oppose this because they stated that reserve speed is necessary in passing other cars. But if everyone knew his top speed was 55 miles per hour, he would be governed accordingly and many serious accidents and deaths would be avoided. (2) Since the majority of head injuries are due to impact against the windshield or dashboard, the windshield should be ejectable on impact, and the dashboard should be padded. Of course, all projecting knobs and buttons should be eliminated. (3) The front bumpers should be mounted on "oleo shock absorbers" in a manner similar to the landing gear in airplanes. One would not expect them to absorb all the shock of a collision, but the absorption of even a small percentage would give added safety to the passengers. (4) Since the majority of injuries suffered by the driver are chest injuries, a hydraulic steering column which will move forward under a force of approximately 100 foot pounds should be provided. (5) The backs of both front and rear seats should be rigidly locked in position; then, if waist and shoulder belts are worn by all passengers, the car itself would act as protective armor in collision and they could withstand a crash of 40G or more as has been done in airplanes. The only alternative to the use of belts is to have all guest seats face the rear of the car. (6) A flashing red light or auditory signal should be provided to indicate when a speed of 55 miles per hour has been reached, if a governor has not been installed. (7) The use of a polarized windshield would minimize glare in daytime driving and when coupled with oppositely polarized lenses on headlights, would minimize night blinding. The present day tinted windshields are dangerous when driving at night and particularly so if dark glasses are worn at the same time.—F. D. Woodward, M.D., and C. N. Moon Jr., M.D., The Physician's Responsibility in the Prevention of Automobile Accidents and Deaths, *Virginia Medical Monthly*, April, 1955.