CURRENT COMMENT

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A Note on the Intravenous Use of Anesthetic Emulsions in Animals and Man with Special Reference to Methoxyflurane

JOHN C. KRANTZ, JR., PH.D., HELMUT F. CASCORBI, M.D., MARTIN HELRICH, M.D., RAYMOND M. BURGISON, PH.D., MARTIN I. GOLD, M.D., FRIEDA RUDO, M.S.

Since the introduction of ether and chloroform as inhalation anesthetics more than a century ago, there have been several attempts to administer these agents intravenously in aqueous solution (Burkhardt[1]). The procedure was fraught with many difficulties. Foremost among the problems encountered was the low degree of solubility of the anesthetics in normal salt solution, thus necessitating the injection of large volumes of fluid to maintain anesthesia. Other difficulties involved were hemolysis of red cells, pulmonary edema and thrombosis of the vein at the injection site.

Our experience with hexafluorodiethyl ether by intravenous injection in the treatment of mentally ill patients prompted us to attempt the injection of volatile anesthetic agents.[2] All of our efforts with a variety of well established anesthetic agents in different solvents were unsatisfactory. It then occurred to us to emulsify the anesthetic and proceed with animal studies. A large variety of emulsions with many types of emulsifying agents and anesthetics were prepared. The most satisfactory product was prepared with the anesthetic 1,1-difluoro-2,2-dichlorethyl methyl ether (methoxyflurane) used for inhalation anesthesia.[3] The composition of the emulsion is shown in the following formula:

Methoxyflurane	3.5 ml.
Lecithin (soy bean)	4.0 Gm.[4]
Dextrose	4.2 Gm.
Pluronic F 68 *	0.25 Gm.
Cotton seed oil	3.0 ml.
Water for injection	sufficient to make 100 ml.

* Pluronic F 68 is an oxyethylene oxypropylene polymer used in the emulsification of fat for intravenous fat feeding.[6]

Received from the Department of Pharmacology, University of Maryland School of Medicine, Baltimore 1, Maryland.

The emulsion is stable at least over several months. It permits sterilization without separation. It is devoid of pyrogens. A particle size analysis demonstrated that the anesthetic-oil particle ranged from 0.1 to 5 microns.

Extensive laboratory studies on dogs, monkeys, rabbits and rats showed that the emulsion was compatible with the elements of the blood. Induction was best achieved with thiopental sodium, followed immediately by the emulsion. The anesthetic was removed from the circulation by the lungs in the expired air.[5] The volume of emulsion required for surgical anesthesia in 45 dogs was on the average 6.2 ml./kg./hour. Dogs tolerated rates of 2 and 3 times this amount when respiration was supported. The respiratory pattern in animals anesthetized with the emulsion was similar to that which prevailed when the inhalation procedure was used. Recovery time (when the animal was able to walk unassisted) was generally one half the period of anesthesia.

Laboratory studies revealed that the lecithin was rapidly cleared from the blood. Blood pressure remained slightly below (15 to 20 mm. mean systolic fall) control levels during anesthesia. This was due to the anesthetic agent in the tissues and not the emulsion. There were no significant electrocardiographic changes. Bromosulfalein tests in dogs revealed no diminution of dye excretion after anesthesia. Histologic studies on the lungs, liver and kidneys revealed no pathologic findings attributable to the anesthetic or other constituents of the emulsion.

Having completed these studies one of us (H. F. C.) subjected himself to anesthesia by

this procedure. The anesthesia was similar to that observed in animals. The subject was lightly anesthetized for a period of about 10 minutes. Forty-two ml. of the emulsion were given, recovery was uneventful except for a slight urticaria. There was no glottis edema. With 10 mg. of Chlor-trimeton intramuscularly, the urticaria cleared in less than one hour. The reaction was presumably due to the lecithin. The subject showed a positive skin test to purified soy bean lecithin. Ten other persons so tested showed no sensitivity reaction. A second individual was anesthetized to a light plane of surgical anesthesia by the same procedure for a period of 15 minutes. Sixty-two ml. of emulsion were administered. Recovery was slow but without incident. A third subject was anesthetized to a moderate plane of surgical anesthesia in a similar manner for a period of 25 minutes. Eighty ml. of the emulsion were used. There was evidence of some thrombotic reaction in the ante-cubital vein. Relaxation was good and recovery followed the foregoing pattern. A fourth person was a patient undergoing surgery (dilatation and curettage). The anesthesia followed the foregoing pattern. Pain reflexes were abolished and recovery was uneventful.

Summary. It has been demonstrated that a volatile anesthetic agent, in an emulsion of the oil-in-water type, injected intravenously to animals and man evokes satisfactory anesthesia. Our search of the literature reveals that this is the first time this anesthetic procedure has been used in man. If further clinical experience, which is under way, confirms these observations, many relatively high boiling point anesthetic agents may be made available to the armamentarium of the anesthesiologist.

REFERENCES

1. Burkhardt, L.: Uber Intravenose Chloroformnarkose, Muenchen. Med. Wschr. **2**: 1678, 1909.
2. Krantz, J. C., Jr., Truitt, E. B., Jr., Speers, L., and Ling, A. S. C.: New pharmaco-convulsive agent, Science **126**: 353, 1957.
3. Artusio, T. F., Jr., Van Ponak, A., Hunt, R., Tiers, F., and Alexander, M.: Clinical evaluation of methoxyflurane in man (abstract), Fed. Proc. **19**: 273, 1960.
4. Geyer, R. P., Watkins, D. M., Matthews, L. W., and Stare, F. J.: Vasodepressor activity of soybean phosphatide preparations, J. Lab. Clin. Med. **34**: 688, 1949.
5. Chenoweth, M. B., Robertson, D. N. and Erley, D. J.: Blood and urine distribution of methoxyflurane, ether, chloroform in dog, The Pharmacologist **2**: No. 2, 1960.
6. Wadell, W. R., Geyer, R. P., Olsen, F. R., and Stare, F. J.: Clinical observations on use of norphosphatide (Pluronic) fat emulsions, Metabolism **6**: No. 6, 1957.

Control of Postanesthetic Emesis with Trimethobenzamide

Dr. Arnold M. Sobel, Pascack Valley Hospital, Westwood, New Jersey, evaluated trimethobenzamide (Tigan), a new antiemetic with virtually no side reactions, for its effect on postanesthetic emesis.

Patients in whom ether was the primary anesthetic agent (premedication was with pentobarbital and/or meperidine and a belladonna derivative) were selected at random. Some were given no antiemetic medication (controls) and others were given trimethobenzamide intramuscularly during the period of anesthesia, at least thirty minutes and no longer than sixty minutes before discontinuing the anesthetic. The dosage scale recommended by the manufacturer was used: under 30 pounds—50 mg., 30 to 60 pounds—100 mg., 60 to 90 pounds—150 mg., and over 90 pounds —200 mg. Patients who had not fully reacted within one-half hour after discontinuing the anesthetic were not included in this study. Only one dose was given. The patients were evaluated for a period of four hours postanesthesia. The duration of action of the drug is reputed to be approximately four hours.

It was not considered necessary to use placebos, since the patients were not aware of the administration of any antiemetic drug. Evaluation of the postanesthetic results were noted by three trained recovery room nurses who had no way of differentiating control from treated cases. No tabulation of results was done until the study was terminated. It is believed that this provided an adequate