A NEW RELAXING AGENT: WIN 2747®: A CLINICAL EVALUATION

JOHN GORDON, M.A., M.R.C.S., D.A.*

Surrey, England

Received for publication July 30, 1952

IN 1950 Cavallito, Soria and Hoppe (1) described a new relaxing agent 2, 5,-*bis*-(3-diethylamino-propylamino) benzo quinone-*bis* (benzyl chloride), and this drug (hereafter referred to as WIN 2747) has been favorably reported on by Arrowood (2), in America.

PHARMACOLOGY

WIN 2747® is a red crystalline solid, soluble in water to the extent of 2.5 per cent, and is supplied in a 0.3 per cent solution, so that 1 cc. contains 3 mg. of the drug.

The formula of the drug conforms to the hypothesis of Barlow and Ing (3) regarding curariform activity in that there are about 14 Angström units separating the two quaternary nitrogen atoms.

WIN 2747 is active when administered either by the oral, subcutaneous or intravenous routes, and its curariform activity and toxicity vary considerably in different experimental animals. The potency of the drug exceeds that of curare, but with equipotent doses the toxicity of the drug is less.

Arrowood stated that curarising doses do not cause any significant changes in the pulse rate or blood pressure. Although 1,500 times the curarising dose can be administered to dogs receiving artificial respiration without cardiac arrest, WIN 2747 is a profound vagal depressor, and in clinical practice marked bradycardia is noticed. Arrowood also stated that the drug exerts no effect on the autonomic ganglia or vagus, but this statement is open to criticism as the bradycardia can be partially abolished when the vagus is protected with an adequate dose of atropine. The bradycardia can be so profound that the blood pressure may fall rapidly and, as in one case in the series here described, circulatory failure may ensue.

WIN 2747 causes a marked increase in mucous secretion from the upper respiratory tract, increase in tear and salivary output, and increased peristalsis. The drug does not cause the liberation of histamine.

* Consultant Anaesthetist to the Rowley Bristow Orthopaedic Hospital and to the Kingston-on-Thames and St. Helier Groups of Hospitals, Great Britain.

WIN 2747 is inactivated by copper and brass, so that syringes must not contain these metals, but it is not affected by stainless steel or nickel (4).

There does not appear to be any effective antidote and although prostigmin® has been used in this instance, it also exerts a depressing effect on the vagus and, therefore, is not suitable.

DOSAGE

Arrowood suggested an initial dose of 4.5 to 9 mg., using 3 to 6 mg. as a maintenance dose, but she appears to have used either ether or cyclopropane as her main anaesthetic agent. In this present series using thiopentone (thiopental sodium), pethidine (demerol), nitrous oxide and oxygen I found that an initial dose of 12 to 15 mg. was required in an average case, usually the larger dose, and this would give adequate muscular relaxation for twenty to thirty minutes. Ether potentiates the action of WIN 2747 and, thus, less of the relaxant is required when this anaesthetic is used.

For intubation, the full dose of 15 mg. is required with thiopentone to obtain adequate relaxation. Although smaller doses have been used and the jaw is adequately relaxed, the cords may go into spasm when touched.

The largest dose used in the series was 42 mg. during a period of two and a half hours for a partial gastrectomy, using 1.0 Gm. of thiopentone and 200 mg. of pethidine as the anaesthetic agents, and 21 mg. for a boy of 15 years undergoing appendicectomy.

MUSCULAR RELAXATION

Muscular relaxation is adequate for all abdominal operations, and the cases in the series included gastrectomy, cholecystectomy, hysterectomy and ureterectomy. The relaxation obtained is comparable more to the complete flaccidity of curarisation than to the type of relaxation obtained with decamethonium iodide.

The speed of onset of relaxation is comparable to that of curare, and is not so rapid as that of decamethonium iodide or succinylcholine chloride. Although Arrowood reported that the maximal degree of relaxation is not apparent for twelve to fifteen minutes, in this series relaxation seemed to be complete within three minutes.

RESPIRATORY SYSTEM

WIN 2747 does not depress respiration to the same extent as any other relaxant drug. Curare in sufficient amount to obtain a given degree of relaxation would cause marked respiratory depression whereas with WIN 2747 only a minimal depression is caused. The depression is brought about by a decrease in amplitude and there is no change in rate or rhythm. In no case did respiration cease from the

effect of the WIN 2747, and in only one case was it necessary to assist respiration. Arrowood stated that when thiopentone was used as the anaesthetic agent she sometimes found that the patient was apnoeic but not relaxed, although she never noticed that phenomenon with ether. This did not occur in the present series but, by using smaller doses of the drug and ether as the anaesthetic, relaxation by the potentiating action of the two drugs is more easily obtained.

Circulatory System

WIN 2747 does not appear to have any direct effect on the myocardium or blood pressure, but the strong parasympathetic action it exerts on the vagus nerve causes marked slowing of the heart, thus reducing the cardiac output and lowering the blood pressure. Alteration in cardiac rhythm has not been observed.

Early in the series, an obese man was being anaesthetised for a difficult interval appendicectomy. WIN 2747, 15 mg., had been administered but the relaxation was not adequate; the pulse rate was 72 beats per minute. An additional 9 mg. was then given and as the relaxation improved there was a sudden slowing of the pulse to 45 beats per minute, with marked pallor of the face which became cold and sweaty. The respirations became very shallow so respiration was assisted, and it was apparent that the heart was beginning to fail. Six minutes later, atropine, 1/100 grain, was administered intravenously. Within three minutes the pulse rate had increased to 70 beats per minute and his condition was much improved. The appendix was removed, relaxation being adequate throughout the procedure, and it was noticed that peristalsis was much increased, borborygmi being audible throughout the operating theatre. The patient collapsed again when he was returned to the ward. He was given 4 cc. of coramine, and thereafter he made an uneventful recovery.

Following this case I made it my practice to give an intravenous injection of 1/100 grain of atropine just before the first dose of WIN 2747 was administered and, although this prevented any further cases of collapse and controlled the excessive salivation and eye watering, all patients showed a bradycardia of about 10 beats per minute.

Patients recovered consciousness rapidly after the use of the drug, and there were no postoperative complications referable to it.

Excretion

WIN 2747 is excreted in the urine and, following large doses, the urine is colored red.

Comment

WIN 2747 is a good relaxant of skeletal muscle but it is not a drug that will find a place in day-to-day anaesthetic practice.

Its main advantages lie in the fact that it does not cause the release of histamine, and relaxation is achieved with minimal respiratory depression.

Its disadvantages are: the injection fluid is red, and aspiration of blood is not easily visible in the syringe. The syringe itself must not contain certain metals. A relatively large amount, 5 cc., of fluid must be injected as an initial dose and this necessitates the inclusion of a 5 cc. syringe in the anaesthetist's armamentarium, whereas all other relaxant drugs can be administered by the more usual and convenient 2 cc. syringe.

WIN 2747 is a strong parasympathetic stimulant and causes considerable bradycardia which may lead to circulatory collapse. Although this can, in most cases, be prevented by the administration of atropine, all the patients in the series who received atropine prior to the injection of the WIN 2747 showed some bradycardia. This combination of drugs can prove to be dangerous as a fairly large total dose of atropine must be given during a long abdominal operation. The relaxation for major abdominal surgical procedures is more safely achieved by other means.

For shorter operations WIN 2747 is a useful drug, but it is easier and quicker to use one of the other relaxant drugs and thus eliminate the extra injection of atropine, which can be irksome during a long and busy operating list.

In its present form, WIN 2747 is not a satisfactory or safe relaxant and its general use is not recommended. The fact that there is minimal respiratory depression suggests that the investigation of drugs with similar chemical formulae might be undertaken, as this is a most useful property for a relaxing drug to possess.

SUMMARY

The pharmacology, dosage and action on the body of a new relaxant drug, WIN 2747, have been described.

The advantages and disadvantages have been discussed.

WIN 2747 would not appear to be a suitable drug for use in general anaesthetic practice.

ACKNOWLEDGMENT

My thanks are due to Messrs. Bayer Products, Ltd. for the supply of the WIN 2747, and also to Dr. Ripley Oddie, of that firm, for helpful advice and criticism.

REFERENCES

1. Cavallito, C. J.; Soria, A. E., and Hoppe, J. O.: Amino and Ammonium-Alkyl Aminobenzoquinones as Curarimetric Agents, J. Am. Chem. Soc. **72**: 2661 (1950).
2. Arrowood, J. G.: Mytolon Chloride: A New Agent for Producing Muscular Relaxation, Anesthesiology **12**: 753–761 (Nov.) 1951.
3. Barlow, R. B., and Ing, H. R.: Curare-like Action of Polymethylene *bis*-Quaternary Ammonium Salts, Brit. J. Pharmacol. **3**: 298, 1948.
4. Oddie, R. Personal Communication (1951).