CLINICAL PRACTICE WITH MUSCLE RELAXANTS

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When curare was first used in medical practice, its potential beneficial effect and its inherent danger to the organism into which it was introduced were recognized. One is impressed with the courage as well as the foresight of the men responsible for exploring the possibilities of curare as a therapeutic agent. Scientists, among whom were De la Condimine and Fontana, were fascinated by tales told by explorers who had visited the Indians of South America and had seen the preparation of the lethal mixture used by them in hunting. The scientists were impressed with the potency of the concoction and intrigued by it. The crude material made available to them by the explorers was investigated, a reliable mode of action was determined, and the unpredictable preparation introduced into human beings for the treatment of numerous disorders.

The men who had the imagination to make use of the information supplied from the laboratory were West, Burman, Mitchell, Tiercelin and Benedict, and Hunter. The disorders which seemed logically vulnerable to curare were those due to neurological lesions associated with trauma, tetanus, strychnine poisoning, chorea, rabies, Parkinson's disease, hemiplegia, hypertension, and epilepsy. These courageous though logical ventures into new therapeutics achieved some success. Failures were due usually to unreliable preparations. In addition, they were unprepared to compensate for the concomitant respiratory insufficiency associated with effective doses. They were either unaware of or skeptical of the useful investigations of Sibson and Waterton in which it was established, by the application of curare to horses, that life could be maintained if adequate pulmonary ventilation was performed. Brodie had determined earlier that the drug affected respiration primarily. The research of Sibson and Waterton was outstanding not only because it demonstrated that curare could be used with safety but also because it demonstrated the value of artificial respiration. Their technique of pulmonary ventilation was almost identical to that found to be most effective in the light of data available today.

All of these men had a profound respect for the potency as well as the potential of the preparation. In this same atmosphere of inquisitiveness and caution, Richard Gill, with the help of McIntyre and Bennett, managed to overcome the reluctance of scientists in the Squibb Laboratories to the extent that they prepared a stable and predictable product from the botanical specimens Gill brought back from Ecuador. It is of interest that the same fundamental explorer-scientist relationship existed in the twentieth century between Gill, McIntyre and Bennett as was apparent in the seventeenth and eighteenth centuries between De la Condimine and Fontana. To Dr. Louis Wright we are indebted for his conviction that curare was a drug with a future in anesthesia. Dr. Harold Griffith, with foresight and courage, established this new application (not even considered by West, his predecessors or contemporaries) for the intriguing drug from the jungle.

It is not surprising that Gill had difficulty in trying to promote the development of curare as a useful drug in modern clinical medicine. He, as well as all the others involved in fostering this phenomenal drug, was consistently concerned with the hazards associated with the widespread application of curare. They recognized it as a drug with lethal potential, especially if used in indiscriminate fashion or by personnel unaware or unconcerned with the disruption of normal physiologic mechanisms. Apprehension as well as enthusiasm must have plagued these men. Each of them had faith in the potential of curare and that faith has been substantiated after sixteen years of widespread application in many different aspects of clinical medicine. In addition, there has been a sig-
significant bonus, not wholly unanticipated, in the improved understanding of neuromuscular transmission made possible by the availability of a predictable and stable product. The reputation of curare as a therapeutic agent has been good.

Part of this reputation may have been the result of having the basic principles outlined and emphasized early in the clinical application of the drug. These same principles have been reiterated with the presentation of other relaxants which were not anesthetic, analgesic or sedative drugs. It was recommended * that curare and similar drugs be used only in those circumstances in which muscle relaxation was the indication. The muscle relaxants were expected to be an adjuvant to anesthesia, not a substitute for it.

The precepts were as follows: (1) Anesthesia should be established within the limits of safety of one or more anesthetic drugs. (2) The relaxants should be administered only after the anesthetic had been established at a point of maximum efficiency. (3) Surgical procedures requiring relaxation could be accomplished with anesthesia established by the less potent agents such as nitrous oxide and ethylene in combination with the relaxants provided maximal effort was made to secure optimum anesthesia with nitrous oxide or ethylene. (4) Higher and sometimes deleterious concentrations of the more potent anesthetic agents could be avoided by inducing necessary relaxation with the relaxants. (5) Restriction of ventilation was recognized as a usual accompaniment of the use of relaxants and urgent and specific recommendations for the prevention and treatment of this complication were listed. (6) Hypotension, especially in the poor risk patient to whom large doses were administered, was recognized as a possibility and suggestions for prevention and treatment of this complication were published.

It was anticipated that abuses would accompany the use of relaxants. These abuses in general are a function of an effort, either deliberately or inadvertently, to use relaxants as substitutes for anesthesia rather than as adjuvants to anesthesia. Concern was expressed, and this concern has been justified, that the relaxants would be used to cover up deficiencies in the management of anesthesia. For the anesthetist whose primary object in anesthetic management is to satisfy the acute demands of the surgeon, regardless of the impact upon the patient, curare and other relaxants are a boon. For such an anesthetist, who chooses to ignore or fails to recognize the source, the relaxants are the panacea for laryngospasm, the discommodious working conditions associated with upper respiratory obstruction of other types, and the inadequate relaxation accompanying carbon dioxide retention. Anesthetists of this caliber and attitude became less concerned about the production of a suitable anesthetic state and drifted toward the production of a paralyzed rather than an anesthetized patient. There have been situations in which patients were made inactive but not insensible; a situation not always appreciated by patients, although seemingly satisfactory for some anesthetists and surgeons. The inept or indifferent anesthetist who leans inordinately upon relaxants for the solution of his problems in anesthesia often fails to become aware of the fact that most surgeons made happy at the time of surgery are distinctly less appreciative when the patient succumbs as a consequence of mismanagement of anesthesia including the use of relaxants.

One of the most subtle abuses of relaxants is overdose. Familiarity with the relaxant drugs and their relatively inconspicuous hazards has led to a blasé attitude about dosage. Because it is easy to produce profound relaxation and because a generation of surgeons is developing which is dissatisfied with anything less than cadaveric operating conditions, most patients are overdosed with relaxant drugs. There is little attempt made to tailor the administration of either the type or the dose of relaxant to the operative procedure or any part of that procedure. Other than hypoventilation, there is a minimum of immediate deleterious effect from relaxants and anesthetists often err on the side of too much rather than too little relaxant. Now it is established that although proper attention to ventilation can obviate the hazard of overdose during the period of anesthesia, there is significant hangover effect in the post-anesthetic period. This may not be apparent unless measurement is made, and even then it may not be recognized unless extra demand is made upon the respiratory system. Residual
effect may be expected also with the short acting relaxants. In either case, long or short acting, the incidence and extent of residual effect is directly proportional to the total dose employed. It is a curious and disconcerting paradox that anesthetists, who should be most concerned with respiratory inadequacy, are often the most indifferent to it.

Misadventures in anesthesia are not alleviated by relaxants. On the other hand, they compound the difficulties and although the fatalities attributed to relaxants may have been exaggerated, there is no doubt that they contribute to mortality. It must be disappointing to those who have been instrumental in introducing these valuable adjuvants to anesthesia to have their warnings ignored and to find that relaxants are used to cover up deficiencies in anesthesia rather than to augment good anesthesia.

In the not too distant past it was easy to be dogmatic about the anesthetic state and the changes associated with its induction and maintenance. Sleep, analgesia, and relaxation were produced with varying degrees of efficiency by the same agent. Nowadays, as has been recently pointed up by Woodbridge, the definition of an "anesthetic state" is more difficult. Coincident with the introduction of curare into clinical anesthesia was the popularization of combinations of drugs known usually by the term "balanced anesthesia." It was expected that each of the drugs in the mixture contributed either analgesia, sleep, sedation, or relaxation to the total depression of the patient. In each patient in different stages of the anesthetic process it became necessary to attempt to determine whether analgesia, sleep, sedation, or relaxation was needed in order to apply the appropriate drug. "Anesthesia" is often a conglomerate of various types of depression, and relaxants are an important part of the process of producing suitable working conditions for the surgeon. As different relaxants were made available and as anesthetists became bolder, there was a shift to more liberal use of relaxants without special regard for the presence or absence of need for muscle relaxation. One cannot afford to be critical of this trend without more data. However, the evidence is certainly not overwhelming that the most satisfactory answer to most of the problems in anesthesia is to paralyze the patient rather than to anesthetize him.

Of the relaxants available today (and we may anticipate that more will become available soon) each has reasonably specific properties in addition to their ability to produce muscle relaxation. The various properties of these different relaxant drugs have been outlined in this symposium. It may seem that the situation is becoming more confused rather than clearer. Nevertheless, information of a precise enough nature is available to facilitate the selection of different drugs for specific requirements in individual patients. Relaxants can be applied on the basis of known properties rather than on the basis of pure personal preference or habit. One gets the impression that a particular relaxant is used exclusively for such quixotic reasons as (1) it was the first one ever used; (2) it produces sufficient relaxation—why bother with any other? (3) I've had good luck with it—why change? (4) this is the one my favorite drug detail man recommends; (5) I read a paper once about it, and (6) the hospital gets the best deal on this one.

A working knowledge of the fundamental properties of the various relaxants, which certainly can be gained from the available literature as well as from this symposium, should make it possible to be more logical in the clinical application of these drugs. Better results can be secured and significant improvement made in the management of the total anesthetic. The end result should be lower morbidity and lower mortality.

Our information is such in these days of modern anesthesia that we can apply the various muscle relaxants in clinical situations with some predictability as to the sort of actions and interactions which may take place in connection with various disease states in patients and with various depressant drugs employed in the anesthetic process. Although there are many properties of the relaxants which are poorly understood or totally unknown, we do know something about such things as (1) length of action, (2) mode of action, (3) changes in mode of action, (4) histamine producing effects, (5) ganglionic blocking effects, (6) absorption and excretion, and (7) interactions.

If one uses as a sole criterion the ability of the drug to produce satisfactory muscle relaxation,
any of the preparations are acceptable. However, if one applies to the use of muscle relaxants the same fundamental principle of individualization that he applies to the choice of anesthetic agent and technique, it is possible to be more precise in the selection of a relaxant and consequently more definitive in the care of patients. For example, if one desires to produce a brief period of relaxation such as for endoscopy, closure of the abdomen, or reduction of a fracture, the short acting preparations, succinylcholine and decamethonium, might be preferable to a longer acting drug such as d-tubocurarine. On the other hand, d-tubocurarine or gallamine might be more suitable for the production of relaxation for long procedures. There are proponents of the practice of administering short acting preparations continuously in low concentrations on the assumption that control is more critical and recovery more prompt. This is debatable not only on the fundamental issue of the propriety of extending the application of a drug designed for short action but also upon the evidence, now available, that the mode of action of some of these preparations alter as its administration is prolonged and/or as the total dose is increased.

Likewise, if one elects to be as precise as possible in the use of relaxants, one should be aware of the potential difficulty associated with the use of a depolarizing drug, especially succinylcholine, in patients with a low pseudocholinesterase level. Patients with debilitating diseases and perhaps with deficient liver function may be especially susceptible.

Consideration should be given also to the production of histamine by d-tubocurarine and its use limited or avoided in patients in whom elevation of the level of histamine may provoke undesirable responses such as bronchospasm or hypotension. Patients who manifest this sort of response appear infrequently, but if their susceptibility is known, a drug such as gallamine might be employed. However, if in such a patient, or in any other patient, one wishes to avoid an increase in pulse rate, it might be wise to avoid gallamine and use one of the depolarizing drugs.

Although it was reported that d-tubocurarine was useful in eliminating undesirable reflex effects, there has been no substantiation of the effectiveness of the relaxants in producing significant ganglionic blocking in ordinary therapeutic doses. It is evident that there are certain interactions, such as antagonisms, potentiations, and alterations of action that take place if various relaxants, especially depolarizers and antidepolarizers, are used in the same patient within a relatively short period of time. The sequence of administration seems to have significance. In clinical anesthesia, it is reasonably common practice to employ these preparations without much regard for interactions that may occur. Fortunately, little obvious ill-effect from this indiscriminate mixing has occurred, but with increasing evidence of prolongation of action, particularly of an occult nature in the postanesthetic period, and with the evidence presented in this symposium of the antagonistic and synergistic effects, it seems unwise to mix relaxants, at least those with different basic actions, without deliberate intent and full knowledge of the possible result.

One of the more fascinating aspects of the clinical application of muscle relaxants has been the employment of these drugs with nitrous oxide and no other depressant drugs. Theoretically, nitrous oxide provides the necessary analgesia and loss of consciousness and relaxants provide the necessary muscle paralysis. There is no doubt that a satisfactory working state can be provided for the surgeon, and there seems to be limited adverse effect upon the patient with this combination. On occasions, if nitrous oxide is not completely effective in the functions it is supposed to serve, patients may be more responsive than is desirable. In addition, the relatively large doses necessary may result in protracted relaxation. The fascinating part of this method of "anesthesia" is the possibility that the relaxant may contribute to the depression of the cerebrum as well as to muscle relaxation. This is not in accord with objective measurements of cerebral function, but experience with this method does leave one with a question in his mind about the impact of relaxants upon body functions other than muscle tone. Furthermore, it enhances the confusion surrounding the whole mechanism of the anesthetic state.

Antagonists, at the present time essentially limited to those effective against the anti-depolarizing drugs, are available. These preparations have been discussed elsewhere in this
symposium. Their place in clinical anesthesia is reasonably well established. However, as has been pointed out, these antagonists are not without depressant properties of their own and must be used cautiously. It must not be assumed, for example, that all ineffective respiration or apnea is due to relaxants. In these days of polypharmacy in anesthesia, many drugs may be used in the same patient and any of them or the combination of several of them may cause the respiratory deficiency.

Because the antagonists may produce respiratory deficiency, it is wiser to avoid applying them to patients, particularly those in apnea, until an evaluation has been made of the situation and a determination made that the respiratory deficiency is, at least in part, due to a relaxant. In the absence of any ventilatory effort by the patient, no assessment (except by history) can be made of the cause for the apnea. The indiscriminate administration of an antagonist, if the depression is due to a drug other than a relaxant, may augment the deficiency. The patient should be making ventilatory effort prior to the administration of an antagonist.

Usually respiratory deficiency due to relaxants can be distinguished from that due to other depressant drugs. It is characterized by a diminution in tidal exchange, an accentuation of diaphragmatic action, a loss of effective intercostal function and inclusion of the accessory muscles. Rate may be about normal but often is elevated. This can be distinguished from the slow rate of narcotic depression and the shallow but unlabored effort of the patient under barbiturates.

The choice of edrophonium or neostigmine is largely a matter of personal preference. Because of the more pronounced muscarinic effect of neostigmine, a prior injection of atropine is advisable. Caution should be applied in the administration of these drugs even in the presence of “pure” relaxant depression in order to avoid augmentation of the relaxation with the antagonist by overdose.

There may be newer relaxants and antagonists with more precise properties which will facilitate management of particular problems. These new agents may be of such a nature as to produce selective relaxation and antagonism based upon different types of muscle, or different susceptibilities of postjunctional membranes. (Contrary to some concepts, there is limited, if any, specificity in action or “sparking” action of any standard relaxant on particular muscle groups.) If these are made available, and this is not unreasonable to expect, the work and the obligations of the anesthetist will be even greater if he takes advantage of the increased information for the benefit of his patient. Do not look for a panacea in relaxants, but do attempt to use with precision the drugs now available and those to be introduced.

REFERENCES