THE FUTURE OF MUSCLE RELAXANTS

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In the epilogue of a lucid and comprehensive monograph, Foldes summarized his look into the future of muscle relaxants: "The goal of this search (for other drugs) will be to find a nondepolarizing muscle relaxant which will be as short acting and controllable as succinylcholine, its fate in the organism being little affected by pathological changes, its breakdown products having no neuromuscular blocking effect and which will be easily reversible by a harmless antagonist, in the rare instances, when an atypical response will make this necessary." 1

No one could quarrel, except in small detail, with this ultimate goal. Yet, the specter of imperfection is raised in the concluding phrase of Foldes' hope. Obviously, there is no way of knowing how soon it will be taken toward this any other "goal," but some guesses can be made as to the nature of the end path. One way of looking toward the future is to assess the general areas of agreement, at least among clinicians, as a guide toward the directions of search and study in the years to come.

The use of a muscle relaxant of short duration of action like succinylcholine to intubate the trachea is a practice of clear and universal acceptance. To be sure, there are variations in technique, but these are largely matters of detail. There are, for example, differences of opinion as to the proper dose of drugs and differences of opinion as to the best method or methods of inducing anesthesia under these conditions. The important point is the fact that in the majority of instances of intubating the trachea, a muscle relaxant is used and it is almost always succinylcholine.

A second point of reasonable agreement is the use of light planes of general anesthesia or analgesia, made possible by muscle relaxants, to minimize or prevent the harmful effects of deep anesthesia following large doses of anesthetic agents. This principle is emphasized very much by the concept of "balanced" anesthesia, "ether analgesia," "nonpotent gas" anesthesia, and "nitrous oxide-oxygen-relaxant" anesthesia. It has been both praised and condemned by the word polypharmacy. All these concepts of anesthetic management have in common the preservation of compensatory responses to surgical trauma, hemorrhage and other forms of injury by establishing automatic floors to the depth of anesthesia. This state of affairs during operation with general anesthesia is possible only with the use of muscle relaxants.

The practical application of this method has many variations in the basic theme. All imaginable ways of using muscle relaxants have their advocates. There are those who argue that curare in substantial dosage is the agent of choice for these purposes because it provides ideal working conditions for the surgeon and can be reversed by a specific antidote, neoestigmine. The side effects of the antidote can be prevented by atropine. 2 This group of clinicians see no useful purpose in employing agents other than nitrous oxide and oxygen once intubation of the trachea is successfully accomplished with the aid of a barbiturate and a relaxant. There are those who modify this procedure by adding narcotic drugs, more barbiturates, or more potent general anesthetics permitting a reduction in the dose of muscle relaxant.

Another generalization accepted among clinicians is the fact that muscle relaxants produce relatively few side effects of importance except for the complications resulting from neuromuscular blockade. The chief of these is depression of breathing. This position is held by many despite the imposing factual array presented by Beecher and Todd 3 and the con-
siderably modified view of this problem taken
by Dripps. This peculiar conflict of “belief”
and “fact” remains one of the curiosities of
anesthesiology.

This area of conflict brings into range one
view toward the future. Drugs even so widely
used as relaxants, cannot at the same time, be
an important cause of death during anesthesia
and a boon to safer anesthetic care. One way
of help in this quandary lies in those studies
which will provide clarity in understanding the
basic mechanisms of action of relaxants beyond
that of convenient (and argumentative) classi-
cation labels. Equally important, theoretically
and practically, would be improved under-
standing of what takes place when relaxant
“antagonists” are used. Until some of these
questions are answered more precisely it will
not be possible to proceed with vigor and cer-
tainty toward better clinical use of relaxants in
the future.

Many of the significant problems under in-
vestigation have been described in consider-
able detail in the articles in this issue. How-
ever, some points can stand emphasis at the
risk of repetition and a few points have not
been touched upon in appropriate framework
for the clinician. A clinician would like to ask
the pharmacologist whether drugs which par-
alyze by depolarization, but change the ex-
citability of adjacent muscle to a limited and
controllable degree even after prolonged usage
could be found. This question arises from the
evidence that the persistence of action of de-
polarizing agents is due to progressive depres-
sion of excitation of this area. If there can
be an affirmative answer, we might have safer
and more flexible drugs.

A second question a clinician might ask is
the possibility of development of specific
“pairs” of agonists and antagonists in the relax-
ant field. An elegant contribution to the
clinician would be a desirable relaxant with a
totally inactive antagonist so close in molecular
configuration that a “receptor” would be oc-
cupied with greater ease by the inactive mem-
ber of the pair. Should the chemist accomplish
this task with relaxants of different properties,
a group of specialist-pairs for different clinical
purposes could be made available.

Another problem of interest relates to the
fact that all relaxants in current use do not af-
fect the normal release of acetylcholine. With
competitive relaxants, nervous transmission is
normal, muscular excitability is normal, and
there is a normal release of acetylcholine. Curare
and similar drugs act by the prevention of
muscle response to normal stimulation pre-
sumably because of the occupation of receptors
on the external aspects of the muscle. The de-
polarizing agents also act in the presence of
normal elaboration of acetylcholine, but dif-
fer from the curare type of block in that elec-
trical inexcitability at the end-plate region and
its immediate surroundings develops. This lat-
ter property, according to Paton, is a most im-
portant characteristic of the action of depolar-
izing drugs.

It is possible, in view of these facts, to con-
sider the development of a drug which inter-
feres in a predictable, controllable way with
the liberation of acetylcholine or perhaps a
drug which hastens its destruction in an equally
controllable fashion. However, this type of
drug may also have undesirable actions on the
central nervous system and perhaps other sys-
tems as well. A clinician would like to see in-
terested pharmacologists explore the possibility
of finding drugs or methods which may impair
the synthesis or hasten the hydrolysis of acetyl-
choline specifically at the neuromuscular junc-
tion of skeletal muscle.

Any consideration of future events in the
field of muscle relaxants must come to terms
with the problem of interference with respira-
tion. In the first place, one must restate the
proven fact that apnea is not necessarily relax-
ant-inspired. In a given patient, there are aids
to establishing the relationship of relaxant ac-
tion to apnea. It has become plain that fur-
ther studies of the action of relaxants on the
central driving force of respiration are needed.
More information on the action of carbon di-
oxide on the center during the action of relax-
ants is required. Since positive pressure respi-
ration in one form or another is used when muscle
relaxants are employed, one must understand
more about neural reflexes under these condi-
tions and their possible role in the change of the
driving force of respiration. It may be that
one could block the neural effects generated by
positive pressure respiration and its effects on
pulmonary receptors, or that one might discover a drug or drugs that would be useful in keeping the driving force to breathing in the central nervous system normal and intact.

Extensive physiological and pharmacological study is required to develop knowledge beyond the relatively primitive stages of current uses of "antagonists" to the respiratory effects of muscle relaxants. More must be known about the importance of the ionic environment of the nerve and muscle cell on the action of anticholinesterases on a curare type block; the influence of the circulation on all types of block by muscle relaxants requires elucidation; and the effect of local or generalized tissue changes on these phenomena must be studied further.

It is now clear that the actions of some "antagonists" on both neuromuscular blockade and respiration may be quite complex. For example, pyridine-2-aldoxime methiodide (2-PAM), an "antagonist" under special conditions, has been shown to stimulate breathing and yet at the same time potentiate the action of depolarizing relaxants in a peripheral skeletal muscle in both the cat and man. This apparent conflict in action is not as yet understood. The specific antagonist to decamethonium (BW 49-204) may, and does frequently, depress respiration at the same time that it relieves a depolarizing type of block in a peripheral muscle. Are these unexpected respiratory responses central in origin? Why may respiration be increased in amplitude in the face of a clearly potentiated peripheral muscle paralysis? Does this mean that the muscles of respiration are, in some as yet poorly understood way, different from other types of skeletal muscle?

In any event, these data show that the measurement of any one function as an index of neuromuscular blockade, even if it be respiration, may be misleading. It cannot be assumed that respiratory activity and peripheral muscle blockade are changed in the same way by depolarizing relaxants in all circumstances or that respiratory depression and neuromuscular blockade can be "antagonized" by the same "antagonist." More knowledge of the central drive to breathing during the action of muscle relaxants must be obtained before one can expect to develop a relaxant which is relatively or entirely free of this most important undesirable side effect of relaxants.

Recent work suggests that thiamine, which has curare-like action in large doses, may also have the ability to antagonize muscle relaxants. In small doses thiamine and thiamine fragments appear to antagonize relaxants of both the competitive and depolarizing types. It is difficult to explain the antagonism between thiamine and thiamine derivatives against curare on the basis of classical theory. It is easier to understand the antagonism against the depolarizing agents. It could be that thiamine and thiamine derivatives act in some unexplained way, depending on dosage, to displace all muscle relaxants regardless of type from the end-plate area. This may be due to a specific effect on blood flow, on electrolyte concentration, or on the binding properties which thiamine may have to a greater degree than the muscle relaxants. The picture is further confused by the fact that thiamine apparently does not interfere with acetylcholine action under these circumstances.

The future is therefore not so simple a situation as finding a drug which hits, runs, and leaves no memory. More needs to be known about the basic function of the neuromuscular junction before one can build the right sort of drugs. The continued work of the pharmacologist in studying the subtle, important details of physiology at the neuromuscular junction and his assistance to his clinical conferees in the grosser studies of neuromuscular physiology and pharmacology in man under complex clinical conditions should help point the way to better understanding and a more rational use of relaxants, and to the development of better drugs.

REFERENCES


ANNUAL MEETING

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