

THE ROLE OF MUSCLE RELAXANTS IN ANESTHESIA DEATHS

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"WHEN the muscle relaxants enter the situation, the anesthesia death rate increases nearly six-fold. . . ." This statement made by Beecher and Todd in 1955¹ was greeted with violent objections by anesthesiologists in this and other countries. Some contrary beliefs were published.² The majority of individuals contended themselves with opinions expressed heatedly in private or public. As one views this controversy from a vantage point of four years, two questions come to mind: Do anesthesiologists deny that muscle relaxants cause anesthetic deaths, or do they object to the quantitative aspects of the Beecher-Todd report, *i.e.*, that too much onus was placed on the relaxants? I suspect that the potentialities for harm of the relaxants are recognized by the majority of users. It must be the death rate of 1 : 370 to which objection is primarily raised.

If then the figures given by Beecher and Todd are incorrect and exaggerate the role of the relaxants, what is the true picture? There has been no answer to this, to my knowledge. The debate thus continues with emotional overtones clouding the issue and facts singularly lacking.

The Beecher-Todd report analyzed 599,548 anesthetics. It is unlikely that so careful a study of such large numbers of cases will ever again be undertaken. There is therefore some sense in re-examining the data. One hundred eighteen of the 384 anesthetic deaths were attributed to "curare." They were grouped as follows: error in technique . . . 37; error in choice . . . 20; error in anesthetic management . . . 36; no error apparent . . . 25.

It was stated that in the last two categories, deaths were either "not directly related to 'curare'" or occurred in patients receiving a relaxant despite the fact that "no error was apparent." Let us assume that some anesthesiologists would have excluded these cases. This

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leaves 57 deaths attributed to relaxants in the 44,100 patients to whom the drugs were given—a death rate of 1 : 772. The point is that the relaxants did cause fatalities, and in the ten hospitals concerned their use was associated with a mortality rate of sufficient proportion to suggest inquiry.

It is unfortunate that complete protocols of all of the deaths labelled anesthetic in this study could not have been presented. In the absence of the opportunity to judge, it is impossible to know how many of the deaths might have been regarded as preventable. Stated in other words, is there a toxicity inherent in the relaxants such that their use will always be associated with a mortality which cannot be reduced below a minimal figure, or, with skill, experience and intelligence can these drugs be used with as much or more safety as any of the anesthetics or anesthetic adjuvants?

One approach to this is to compare the inherent potentials for harm from the relaxants with those which could be recognized in advance and might therefore be prevented.

INHERENT TOXICITY

(1) *Idiosyncrasy*, or hypersensitivity, can probably occur with any drug. Unusual reactivity in the form of prolonged respiratory depression has been reported after 3–5 mg. doses of *d*-tubocurarine in a few conscious, non-myasthenic subjects. The incidence of this is unknown but is presumed to be low. On the basis of present knowledge idiosyncrasy to the relaxants appears to be no greater than to other drugs used in anesthesia.

(2) *Interference With the Signs of General Anesthesia*. It is difficult enough to be certain of the depth of anesthesia if only one anesthetic is being given. It is much less easy when the patient is paralyzed by a muscle relaxant. Over-dosage of general anesthetics has occurred under these circumstances. Until more reliable and practical means for determin-

ing the level of anesthesia become available, this objection to the relaxants must remain.

(3) *Respiratory Depression*. There are not, nor will there probably ever be muscle relaxants which do not depress respiration. Respiratory depression or apnea persisting into the postoperative period has been reported after the administration of all of the relaxants. The cause-effect relationship is clear. The theoretic aspects of this are discussed in this symposium by Churchill-Davidson. I wish to emphasize two points. First, this sort of persistent post-anesthetic respiratory abnormality has never been seen by us after drugs other than the relaxants, *i.e.*, we have not seen this complication follow thiopental, cyclopropane, or the opiates, all of whose respiratory depressant action is well documented. Second, it would seem reasonable to predict that postoperative respiratory tract obstruction would be less effectively overcome by the patient who is still partially under the influence of a relaxant. This is being investigated by Bendixen and co-workers.³ The respiratory depressant actions of the relaxants, whether exerted at the nerve-muscle junction or elsewhere, pose a potential hazard in the postoperative period which is specific for this group of drugs.

(4) *Circulatory Depression*. Certain pharmacologic data point to a direct effect of the relaxants upon the circulation. Liberation of histamine,⁴ production of ganglionic blockade^{5,6} and certain, as yet unassessed, actions on the central nervous system may individually or in combination alter circulatory homeostasis. Peiss and co-workers have shown in cats that *d*-tubocurarine injected into the carotid artery, intravenously or directly into the vasomotor center, depresses the excitability of the vasomotor area to electrical stimulation.⁷ Depression of the vagal nucleus was also demonstrated. The production of intestinal bleeding⁸ and of cardiac depression⁹ in the dog by tubocurarine are pertinent to the present discussion. The application of positive pressure to the airway for maintenance of ventilation may reduce blood pressure markedly.

The protocols of curarized patients who die during periods of postoperative apnea contain many references to the development of intractable hypotension. The causes for this may include the factors listed above. There are prob-

ably other disruptions of cell function remaining to be explained. The fact remains that irreversible collapse of the circulation appears under some circumstances to be associated with use of the muscle relaxants.

This is not to say that all patients who manifest an idiosyncrasy, whose depth of anesthesia is difficult to assess, or who have respiratory or circulatory depression as the result of relaxants will die. It is only to emphasize that there are certain threats to a patient which are potential each time a muscle relaxant is injected.

UNDESIRABLE REACTIONS WHICH MIGHT BE ANTICIPATED AND THEREFORE MINIMIZED OR PREVENTED

(1) *Synergism* between certain of the relaxants and streptomycin, neomycin, histamine, trimetaphan (Arfonad), homatropinium (Tropenium), hexamethonium, opiates, large doses of neostigmine, ether, halothane and thiopental have been demonstrated experimentally or clinically. Failure to recognize this synergy has resulted in the death of anesthetized patients.

(2) *Increased Action of the Muscle Relaxants Secondary to Disease or Altered Function*. In the presence of electrolyte imbalance, change in skeletal muscle temperature, reduced muscle blood flow, carcinoma (particularly of the lung), myasthenia gravis, decreased serum cholinesterase (congenital or acquired), renal and hepatic disease, the action of certain of the muscle relaxants may be prolonged and intensified. The literature contains reports of deaths explainable on the basis of some of these relationships.

These lists are unquestionably incomplete. For details the reader is referred to the paper by Foldes in this symposium. Much of the information cited has become available only recently, and was not known to the early users of muscle relaxants. The impressive thing is the long list of circumstances under which for the unwary, unexpected and marked reactions to the relaxants may occur.

There remains an additional category which might be called Gross Misuse or Abuse of the Relaxants. The following is a list of gross errors which have been described in the literature, or have been reported to me: failure to provide adequate pulmonary ventilation during anesthesia and in the immediate postoperative

period; failure to recognize a patient's intolerance to positive airway pressure as manifest by hypotension; administering intravenously a fluid containing succinylcholine when only glucose in water was thought to be in the container; failure to stop an intravenous drip of succinylcholine at the end of operation; use of relaxants during open drop ether; and, confusing the dosage of one relaxant with that of another. This list also must be regarded as only partial, and yet once again one has to point out that fatalities have resulted from such errors. The relaxants are powerful drugs. Their use by the untutored and unskilled can be disastrous.

APPRAISAL

Anesthesiologists can be divided into three groups so far as their thoughts on the dangers of the muscle relaxants are concerned.

(1) There are those who maintain that the relaxants are among the safest of the adjuvants used in anesthesia. Their reasoning is somewhat as follows: The relaxants permit a desirable reduction in the depth of general anesthesia. The only side action is the production of diminished pulmonary ventilation or apnea. The anesthesiologist, however, is accustomed to "supporting respiration" and has confidence in his ability to do so until the nerve-muscle blockade has worn off. One need merely maintain alveolar ventilation artificially until adequate spontaneous respiration returns.

(2) In a second group are those who regard relaxants with such respect that they select doses which fall short of producing apnea. To these individuals safety is relative and is increased by having some degree of spontaneous respiration present at all times. Respirations are "assisted" but not "controlled."

(3) An entirely different viewpoint is that relaxants are inherently toxic agents, use of which is associated with "an appreciable increase in the anesthesia death rate."¹ Proponents of this concept draw an analogy with the administration of arsenic, pointing out that no matter how skillfully arsenic is administered, beyond a certain dose it kills. Emphasis here does not rest entirely on the respiratory depressant action of the relaxants, but stresses additional potentially harmful consequences.

Without controlled series of patients from which firm conclusions might be drawn, it seems reasonable to adopt a middle of the road viewpoint along the following lines. The muscle relaxants have unquestionably caused some fatalities. But so have local anesthetics, ether, nitrous oxide, cyclopropane, thiopental and halothane, for example. I believe that from the quantitative standpoint the Beecher-Todd report paints too black a picture, but I cannot prove this with available information.

When prolonged postoperative apnea is followed by intractable hypotension and death, the relaxants must be implicated until proven innocent. When the relaxants are used in error, they must be blamed, however, unfairly. The great area of uncertainty is the contribution of the relaxants when they are part of a plan of management, apparently carried out faultlessly, yet the patient—usually seriously ill before operation—dies during operation, or in the postoperative period and no obvious reason for death is found other than the patient's disease. Would death have been prevented had the relaxants not been used? Here is a challenge worthy of the best clinician and investigator.

Much has been learned about the relaxants as this symposium attests. Their future in anesthesia seems assured. It is reasonable to hope that the price for this use will soon be determined. My opinion is that it will almost certainly be sufficiently low to warrant their present widespread use.

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