Cardiovascular effects of muscle relaxants

LEAH E. KATZ, CRNA, MA
Los Angeles, California

The author discusses the cardiovascular effects noted with the commonly utilized muscle relaxants and relates these effects to principles of physiology, pharmacology and cardiovascular patho-physiology. Emphasis is placed on the role of cardiovascular changes caused by relaxants which may influence the anesthetic management.

Knowledge of the cardiovascular effects of muscle relaxants is important as a contribution to planning the total anesthetic management of a patient. These effects must, however, be considered in light of the total physiology and pharmacology involved. The cardiovascular effects noted may be utilized to the anesthetist’s advantage in selecting appropriate drug combinations for patient care or in maintaining cardiovascular stability of the compromised patient.

This article will focus on a basic review of the pharmacology and physiology of the cardiovascular effects of relaxants, followed by the specific clinical effects which the anesthetist may note in administering the commonly used depolarizing and non-depolarizing muscle relaxants.

Pharmacology

The effect of any drug administered is influenced by many factors. These may include the pharmacologic structure, ionization, and solubility of the drug which will determine the site of drug action and influence the effect. The clinically useful neuromuscular blockers are quaternary ammonium compounds. These are almost completely ionized within the biologic pH range. The relaxants are highly water soluble and very slightly lipid soluble. They, therefore, do not pass the blood brain barrier easily nor is placental transfer clinically significant.

Relaxants may have both pre- and post-synaptic blocking effects at the neuromuscular junction; presynaptically blocking the release of acetylcholine from the synaptic vesicles, and postsynaptically blocking the cholinergic receptor site at the neuromuscular junction. The latter effect inhibits acetylcholine which is released from binding with the receptors and allows its degradation into acetate and choline.

The muscle relaxants affect not only the neuromuscular junction, but also may affect all cholinergic receptors. Receptors activated are classified as nicotinic or muscarinic. Nicotinic receptors are located at the neuromuscular junction where non-depolarizing muscle relaxants compete with acetylcholine or where the receptor is activated by succinylcholine, and at the autonomic ganglia. The receptors at the autonomic ganglia may be blocked by some nondepolarizing muscle relaxants such as d-tubocurarine.

Muscarinic receptors are found in the bowel.
bladder, bronchi, sinus node of the heart and pupillary sphincter. The major muscarinic effects observed with relaxants occur at the sinus node of the heart. The inhibitory action of these receptors is noted with the administration of gallamine and pancuronium, and is similar to the inhibitory action caused by atropine. Many of the cardiovascular effects of muscle relaxants occur through effect on the muscarinic and nicotinic receptors at sites other than the neuromuscular junction.

Other factors in the pattern of uptake and distribution of relaxants may also influence the clinical effects noted. The size of the bolus given may modify cardiovascular changes, a large bolus causing the most profound and immediate reaction. The protein binding ability of the relaxant is important in that relaxants such as d-tubocurarine may be significantly bound by protein, therefore showing exaggerated effect in patients with low serum protein. Pancuronium is not significantly protein bound, and shows little modification in patients with reduced protein levels.

The total blood volume, which acts as a diluent, may influence the effects of relaxants as may the cardiac output which affects the delivery of the drug to target organs. The amount of drug entry into red blood cells decreases the amount available for immediate clinical activity and the ability of the drug to be absorbed at action site, the number of receptors available for drug action, and the amount of drug loss to inactive tissue sites. The route and speed of biodegradation and elimination of the drug also modify the clinical effect.

The route of drug administration, the rate of administration and the concentration of drug administered may influence drug effect. In addition, alteration may be seen from enzyme induction and inhibition, drug interaction, and genetic factors. An example of the latter is the patient with atypical pseudocholinesterase. This condition may delay hydrolysis of succinylcholine and other esters.

The muscle relaxants may be eliminated by hepatic degradation followed by biliary elimination, or by urinary excretion. Gallamine, decamethonium and metocurine are drugs which are significantly eliminated by the kidneys; therefore, their effect may be prolonged if urinary excretion is inhibited. Consideration should be given to the use of these agents in patients with limited renal function.

The uptake and distribution pattern of muscle relaxants is diagramed in Figure 1.

The cardiovascular effects observed with muscle relaxants may be caused by anaphylactic or allergic reactions, histamine release, release of vasoactive peptides such as bradykinin, immunologic effects, overdose, modification of the synaptic transmitter or receptor, or modified sensitivity of the end organ. It is important to note that the cardiovascular response noted after the administration of muscle relaxants is largely influenced by the state of autonomic balance of the patient at the time of administration. The effects seen will vary from patient to patient depending on the sympathetic and parasympathetic effects predominating prior to relaxant administration.

**Physiology**

In a consideration of cardiovascular physiology, one must view clinical effects in terms of preload (the amount of volume available for the heart to pump), afterload (the resistance against which the heart must pump), contractility (the ability of the heart to generate a strong pumping

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Figure 1
Muscle relaxant uptake and distribution

- Blood volume → Cardiac output
- Entry into RBC's
- Urinary excretion
- Hepatic degradation
- Biliary elimination
- Intravascular reabsorption
- Target organ cell volume → Adsorption at action site

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force) and heart rate. All of these factors combine to influence cardiac output and cardiac workload which, in turn, may alter myocardial oxygen consumption and delivery. In essence, if the heart must pump against an increased resistance, it must work harder and it subsequently utilizes more oxygen. If the heart rate is high, as after gallamine administration, oxygen delivery to the heart may be decreased due to the decreased diastolic filling time, while oxygen demand is increased.

Adequate preload may be decreased after relaxant administration because of the pooling of blood in venous capacitance vessels from lack of muscle contraction which normally assists in returning blood to the heart. Positive pressure ventilation may also decrease venous return by modification of intrathoracic pressures.

**Autonomic effects of relaxants**

The autonomic margin of safety of nondepolarizing muscle relaxants was outlined by Saverese. He found that in man the ED 95, the dose necessary to achieve 95% twitch depression or effective relaxation for most types of abdominal surgery, produced varying autonomic effects with different relaxants. He measured neuromuscular block at the ED 95 for a given relaxant and compared this with the dose producing ganglionic block and histamine release.

Both of these effects may cause vasodilation leading to the clinical effect of hypotension followed by the reflex effect of tachycardia. The dose of relaxant needed to produce vagal block leading to tachycardia was also measured. On testing the nondepolarizing relaxants it was found that d-tubocurarine showed more profound autonomic effects than did either pancuronium or metocurine. (These effects will be further described for each drug in the following section.)

**D-tubocurarine**

The cardiovascular effects noted after administration of d-tubocurarine are largely due to neuromuscular block, vagolysis, and sympathetic ganglionic block—all of which occur in a similar dose relationship. Hypotension may be noted due to the ganglionic block which causes a delay of sympathetic impulses with a subsequent vasodilation, or histamine released by relaxants causing direct vasodilation.

It has been found that an antihistamine given prior to injection of d-tubocurarine will result in a 50% reduction in occurrence of hypotension. This indicates that histamine is not the only cause of the decreased blood pressure, but that the ganglionic block also contributes to this clinical effect.

The degree of hypotension noted after the administration of d-tubocurarine is related to the dose administered, the rapidity of the administration, and the combination of anesthetic agents utilized. Hypotension is augmented by large doses of drug rapidly administered and by the administration of nitrous oxide and narcotics.

Hypotension has also been shown to be directly related to the concentration of halothane given. Munger and Miller found no change in blood pressure with the administration of 0.5% or less halothane. However, they found a twofold increase in the magnitude of hypotension when halothane concentration was increased to 1.5% as compared with 0.7%. They also noted that when the dosage of d-tubocurarine was increased from 12mg per meter square to 18mg per meter square, during the administration of 0.5% halothane and 60% nitrous oxide, a twofold increase in the magnitude of hypotension occurred.

A slight tachycardia may be seen reflexly after the administration of the d-tubocurarine.

The clinical consequences of increased heart rate and decreased systemic vascular resistance depend upon the ventricular function and vascular volume of the patient. Hypotension will be more profound in the patient who is hypovolemic or in the patient who is not able to increase his cardiac output due to pathophysiology or the pharmacologic effect of other drugs. The patient who is able to maintain good ventricular function and who has an adequate volume will often be able to compensate for the pharmacologic effects and avoid prolonged hypotension.

Although the cardiovascular effects of d-tubocurarine have limited its use in the past few years, the anesthetist’s understanding of these effects can enable one to use this drug as an adjunct in neuromuscular block and cardiovascular control. It also permits the anesthetist to minimize undesired effects by using this drug in combination with others which do not potentiate hypotensive effects or by administering the drug slowly, in small increments, so that profound effects are decreased.

**Metocurine Iodide**

Metocurine (Metubine®) which has been available for more than 25 years, is currently being utilized more frequently as a nondepolarizing neuromuscular blocker. Although chemically related to d-tubocurarine, this drug exhibits fewer cardiovascular side effects. The entire dose response curve for neuromuscular block is produced with
no sympathetic ganglion block, therefore decreasing the occurrence of hypotension. There is no vagolytic effect leading to tachycardia.

Histamine release has been noted by Savarese, in approximately \( \frac{1}{3} \) of the patients and in less than 10% of the patients by Fogdall. Venodilation does occur; however, there is no effect on the arterial vasculature and the systemic vascular resistance remains unchanged. The occasional occurrence of decreased blood pressure after administration of this drug may be attributed to the effects of histamine or the effects of decreased preload.

In the normal patient, arrhythmias have not been noted after the administration of metocurine. In patients with coronary artery disease, there has been an increase in cardiac output combined with a decrease in systemic vascular resistance. The combination of these two effects could indicate an ability for the heart to work more effectively in patients with compromised cardiovascular status.

It appears that metocurine has a minimal effect upon the circulatory system of man. Metocurine may be used when it is desirable to avoid tachycardia or the systemic vascular effects noted with other agents.

Since this drug is excreted by the kidneys, it is questionable that it should be the agent of choice in patients with renal compromise. In the absence of kidney metabolism, however, it may be metabolized by the liver.

As metocurine is an iodide compound, it may be advisable to avoid its utilization in patients with iodide sensitivity. Further research may clarify the above questions and perhaps extend the common clinical use of this relaxant.

**Gallamine**

It is commonly known that tachycardia and hypertension may follow the administration of gallamine (Flaxedil). These clinical effects are caused by the vagolytic action of this drug which is initiated at a lower dose than is the neuromuscular block. Therefore, cardiovascular effects will be apparent in patients who have been given an adequate neuromuscular block.

A decrease in peripheral resistance has been noted to occur with gallamine: this may in part be due to histamine release. However, the incidence of histamine release with gallamine is less than with \( d \)-tubocurarine. The decreased peripheral resistance noted may also be secondary to the increase in cardiac output which reflexly decreases the resistance.

Tachycardia noted with gallamine decreases the diastolic filling time of the coronary arteries. The amount of time available for effective oxygen delivery to the heart is therefore reduced. Because of the increased heart rate, cardiac oxygen consumption is increased. In patients with compromised coronary circulation, consideration should be given to the advisability of utilizing gallamine for neuromuscular block. If one is concerned with possible compromise by increased heart rate, another blocking agent should be administered.

Although gallamine provides a significant vagal block, atropine given following gallamine will further increase the heart rate. Conversely, if atropine is given prior to gallamine, gallamine does not cause further tachycardia. This indicates that atropine does have a more profound vagal blocking effect than does gallamine.

It is interesting to note that in a study of blood loss, an increase in blood loss was observed with gallamine, as compared to curare, in patients undergoing hysterectomy by the same surgeon. The mean blood loss noted with curare was 132 cc (range 62-300 cc), and with gallamine it was 292 cc (range 55-880 cc). This was after the administration of 120 mg of gallamine compared with 30 mg of \( d \)-tubocurarine. Although there were several unequal variables to be considered in this study, it appears that the tachycardia and increase in cardiac output created by the administration of gallamine may contribute to the increased blood loss.

One should consider both the positive and negative factors in the administration of gallamine, utilizing this drug if the vagal effects are desired, while perhaps selecting another agent when these effects would be detrimental.

**Pancuronium**

Pancuronium has achieved popularity in recent years primarily because of the lack of histamine release noted with this drug. Though cardiovascular effects may be noted, those most frequently seen include increases in heart rate, cardiac output and mean arterial pressure. There is no change noted in systemic vascular resistance or afterload. Hughes observed that the vagal dose response curve is to the right of the neuromuscular response curve. This indicates that muscle relaxation occurs prior to the vagolytic effects.

Vagal block, however, is noted in doses necessary to achieve intubation, and some tachycardia is almost always clinically noted in doses adequate for surgical muscle relaxation. If atropine is given intravenously prior to induction, there is no further increase in heart rate following the injection of pancuronium.
Arrhythmias may be seen after pancuronium administration; those most commonly noted are atrial tachycardia, dissociation at the atrial-ventricular node, and ventricular extra-systole. These may be due to the vagolytic effects of the drug, an effect on calcium available to the heart, or a modification of intracellular potassium and its effect on action potential. Arrhythmias are more common during halothane anesthesia.

Although vagolytic effects are found with pancuronium, the heart rate increase is much less significant than that found with gallamine in doses producing comparable neuromuscular relaxation. Slow administration of pancuronium may allow neuromuscular block to be achieved without causing significant effects on heart rate or other cardiovascular functions. Miller found that the increase in heart rate noted with pancuronium was inversely proportional to the control heart rate. (The higher the heart rate of the patient prior to the administration of pancuronium, the lesser the rate increase noted.)

The cardiovascular stimulating effects of pancuronium may be used as an adjunct in anesthesia to counteract the depressant effects of many of the anesthetic agents. Thus, effects of the various drugs used in producing anesthesia may be balanced for the cardiovascular stability of the patient.

Succinylcholine

Succinylcholine, a depolarizing muscle relaxant, mimics acetylcholine at both the muscarinic and nicotinic receptors. Effects noted will occur not only at the neuromuscular junction but also at the autonomic ganglia and other muscarinic receptors of the bowel, bladder, bronchi, sinus node of the heart, and pupillary sphincter.

It is commonly known that succinylcholine may produce bradycardia. However, tachycardia may also be seen. This tachycardia may be due to the muscarinic effect on the sinus node, and clinically, it may not be observed since the anesthetist may be causing a concurrent increase in sympathetic response due to intubation or light anesthesia. Both of these effects may mask the succinylcholine effect of tachycardia. Such tachycardia is not often clinically of concern.

Bradycardia from increased vagal tone may also be observed following administration of succinylcholine. This occurs frequently in children after the first dose of the relaxant has been given. The incidence of bradycardia is increased in adults following the second dose of succinylcholine. Mathias and Evans-Prosser and Lupprian and Churchill-Davidson found that after the administration of the second dose of succinylcholine, 80% of patients were noted to have bradycardia.

The effect on heart rate noted after succinylcholine administration depends upon the balance of the sympathetic and parasympathetic tone at the A-V node. This may be related both to the dose and rate of administration of succinylcholine as well as to pre-existing factors. High infusion rates for succinylcholine drip can produce a progressive bradycardia; however, upon discontinuation of the drip, the bradycardia gradually lessens and the effect is most commonly transient.

The mechanism of action of succinylcholine-induced bradycardia may be that it mimics acetylcholine and acts on the cardiac cholinergic receptors at the vagal terminal in the S-A node. Or, as proposed by Churchill-Davidson, the bradycardia may be caused by reflex activity. In any case, it is the agonist effect of succinylcholine which is thought to cause the bradycardia.

Bradycardia is most often noted when the second injection of succinylcholine is given five minutes following the first injection. This may be due to sensitization of the receptor by the breakdown products of the first dose of succinylcholine. The vagal effect may be eliminated by pretreatment with a vagolytic drug such as atropine or by pretreatment with a vagolytic nondepolarizing relaxant such as gallamine.

It is best to avoid large repeat doses (1 mg/kg) of succinylcholine if possible since this may precipitate an alarming bradycardia or sinus arrest, even in adults. Potassium efflux may also be a cause of cardiac arrhythmias. Potassium effect is augmented in the patient with demyelinating nerve injuries, massive burns, central nervous system disease, or immobilization. It is possible that potassium release may not be blocked by pretreatment with a non-depolarizer. Consequently, it is advisable not to administer succinylcholine, if at all possible, in patients who have the potential to increase serum potassium to levels which may have significant cardiac effect.

The anesthetist may use several mechanisms to protect against the bradycardia and arrhythmias following succinylcholine injection. Intravenous atropine is probably the most common method used. It should be noted that the intramuscular utilization of atropine in premedication is usually ineffective in protecting against the cardiovascular effects of succinylcholine and should be supplemented with intravenous atropine prior to injection if the vagolytic effect is desired. The anesthetist should also try to time the interval of
the first and second dose of succinylcholine so that the second dose is administered in less than 3 minutes or after 30 minutes following the first dose, thus avoiding the 5 minute period where arrhythmias are consistently seen.24

Thiopental has been shown to have a protective effect against succinylcholine arrhythmias as has hexofluorium, which prolongs the breakdown of succinylcholine. Mathias and Evans-Prosser showed that pretreatment with d-tubocurarine, 5 mg, has provided a protective effect. Halothane was not noted to be protective following injection of the second dose of succinylcholine and bradycardia was noted with this combination.25

Changing the phase of the succinylcholine neuromuscular block from depolarizing to phase II block does not directly affect the cardiovascular system; therefore, similar effects may be noted with both types of block.26

Although cardiovascular side effects may be noted with succinylcholine administration, it still continues to be the most widely used neuromuscular blocker. This is primarily due to its rapid onset and short duration of action. Most of the side effects may be avoided, prevented, treated or tolerated; but often these remedies are only partially effective and fatal complications may still occur. Researchers currently are investigating non-depolarizing drugs with a shorter onset of action, and if found, these will undoubtedly be a great asset to the anesthetist.

**Relaxant interactions**

Savarese has delineated the following drug interactions found with commonly used relaxants. These interactions should be of special concern to the anesthetist.

1. After endogenous release or exogenous administration of catecholamines, ventricular arrhythmias may be seen with the administration of succinylcholine, gallamine and pancuronium. This is from beta adrenergic stimulation, vagal block, ganglionic stimulation, and facilitated A-V conduction caused by the combined effects of the catecholamines.

2. In combination with halothane or cyclopropane, ventricular arrhythmias may be seen after succinylcholine, gallamine and pancuronium due to a lowered myocardial threshold for depolarization and myocardial sensitization to catecholamines.

3. During halothane administration, the hypotensive action of d-tubocurarine may be potentiated because of the depression of synaptic trans-

mission and the decreased catecholamine release noted with the use of these drugs.

4. When d-tubocurarine is utilized in conjunction with other ganglionic blocking drugs or histamine releasing drugs, the hypotensive action may be potentiated.

5. If beta-blocking drugs are used, tachycardia and hypertension after the administration of pancuronium, gallamine or succinylcholine may be inhibited.

6. After pretreatment with non-depolarizing relaxants, succinylcholine-induced bradycardia may be inhibited due to inhibition of myocardial depolarization.

7. When a patient has been on diuretics preoperatively, succinylcholine-induced ventricular arrhythmias may be potentiated by lowered serum potassium. Potassium levels should be obtained prior to anesthesia on all patients on diuretics.

8. Patients on guanethidine, methyldopa, reserpine or bretylium may have decreased adrenergic transmitter release and, therefore, will have increased hypotensive effects after the administration of d-tubocurarine.

9. Patients on digitalis may have a lowered serum potassium level, thus lowering the myocardial threshold for depolarization and increasing the potential for ventricular arrhythmias after administration of succinylcholine.

10. Administration of anticholinergic drugs such as atropine prior to the administration of gallamine and succinylcholine may produce an additive tachycardia and inhibit the succinylcholine-induced bradycardia. The mechanism for this action is the vagal block produced by the anticholinergic drug.27

**Summary**

The cardiovascular effects which may occur concurrently with muscle relaxation may pose difficulty in caring for the patient with cardiovascular pathology. The anesthetist should be familiar with the effects of these drugs and determine the effects which will be most harmful for the patient. Some patients may benefit by the slight hypotension caused by decreased systemic vascular resistance of agents such as d-tubocurarine, while other patients may be compromised by the tachycardia and hypotension caused by gallamine.

The patient's preanesthetic condition should be noted in terms of cardiovascular problems, and other pathology including dehydration, fluid load, anemia or bleeding. Agents should be selected to assist in managing the appropriate condition. In cardiac conditions such as aortic insufficiency or
mitral insufficiency, hypertension may aggravate regurgitation. Therefore, drugs such as gallamine should probably be avoided.

In conditions such as aortic stenosis, subaortic stenosis, and mitral stenosis, hypotension is poorly tolerated because a decrease in systemic vascular resistance does little to increase flow. Thus, concern is generated over lack of adequate perfusion pressure to vital organs.

Patients with coronary artery disease and mitral stenosis tolerate tachycardia poorly. With tachycardia, the diastolic filling time and coronary artery perfusion is decreased. It also reduces the time for ventricular filling, subsequently reducing preload. In patients with a fixed stroke volume, bradycardia should be avoided since it is poorly tolerated. These patients are not able to increase their cardiac output by increasing contractility. In patients susceptible to premature ventricular contraction, bradycardia should also be avoided as this may increase the potential for activation of the re-entry mechanism.

In coronary artery disease the anesthetist should attempt to keep the arterial blood pressure approximately at the awake resting level. Both hypotension and hypertension can lead to coronary ischemia. With congestive heart failure and coronary artery disease, the patient might benefit from vasodilation, but agents which might further depress cardiac contractility and conduction should be avoided.

The anesthetist should select the neuromuscular blocking agent which best benefits the physical state of the patient and avoids the undesirable effects which are particularly detrimental to patients with specific conditions.

Muscle relaxants may also be utilized to supplement anesthetic techniques of choice, such as planned hypotensive anesthesia. If one desires to use this technique, the hypotensive agent may be used to supplement a drug such as d-tubocurarine.

If one finds it desirable to use muscle relaxants which release histamine, one can counteract this side effect by using H-1 and H-2 blockers prior to relaxant administration. Adequate volume replacement may counteract the hypotensive effects of drugs. The establishment of an adequate maintenance level of anesthesia prior to relaxant administration may reduce cardiovascular effects.

In the healthy patient, the cardiovascular effects of relaxants may not be significant to the anesthetist. However, in the patient with severe coronary artery disease or other related pathology, no matter what type of surgery is involved, the anesthetist should be aware of these effects of relaxants and utilize the relaxant most appropriate for the desired effect.

One should remember that, in addition to the pharmacology of each drug, the "milieu" into which the drug is administered is probably the most important condition. Therefore, the anesthetist should know the history and the present condition of the patient and should select all agents—including muscle relaxants—to benefit the individual.

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AUTHOR

Leah E. Katz, CRNA, MA, is a graduate of the Ohio State University School of Nursing and the Ohio University School of Nurse Anesthesia. She earned her Master’s degree from Lindenwood College in St. Charles, Missouri and is currently a Doctoral student at Pepperdine University in Los Angeles. After several years of experience as a staff nurse anesthetist specializing in cardiovascular anesthesia at both the Cleveland Clinic in Cleveland, Ohio, and Baylor College of Medicine in Houston, Texas, Mrs. Katz is presently employed as Director of the Master of Science Program in Nurse Anesthesia at the University of California in Los Angeles. The original presentation related to this article was for the Michigan Association of Nurse Anesthetists in May, 1980.