Neuromuscular Effects of Beta-adrenergic Blockers and Their Interaction with Skeletal Muscle Relaxants

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Intra-arterial pronethalol and propranolol produced a short-lasting neuromuscular blockade in the soleus nerve-muscle preparation of the cat. Intravenous pronethalol and propranolol prevented repetitive potentials of the soleus nerve as well as twitch potentiation and fasciculations of the soleus muscle induced by intravenous succinylcholine, but potentiated neuromuscular blockade. MJ 1999 did not protect fully against succinylcholine stimulation. Curare, 200–350 μg./kg., intravenously produced partial-to-complete neuromuscular blockade which was potentiated by intravenous pronethalol or propranolol. No significant potentiation was induced with corresponding doses of MJ 1999. We conclude that the neuromuscular effects of beta-adrenergic blockers are independent of their interaction with catecholamines. The prevention of succinylcholine-induced potentials is ascribed to a presynaptic effect of beta blockers which depends on the "local anesthetic" activity of the drugs.

BETA-ADRENERGIC BLOCKING AGENTS have proved effective against a variety of experimentally-induced cardiac arrhythmias. Early studies [1-4] have demonstrated that these drugs have a twofold action; in small doses, they counteract arrhythmias induced by sympathomimetic amines, whereas in larger doses, arrhythmias induced by digitalis glycosides are antagonized. The former effect has been related to blockade of the beta-adrenergic receptors, whereas the latter has been linked to an unspecific "quinidine-like" or "local anesthetic-like" effect on the heart.

Because larger doses of sympathetic beta-blocking agents also affect other excitable tissue, namely the central [5,6] and peripheral nervous systems,[3] their effects on the myoneural junction have been investigated. The results have been conflicting. In 1965, Morales-Aguilera and Vaughan Williams [5] reported that repeated intravenous administration of 5 mg./kg. doses of pronethalol (isopropyl-amino-1-(2-naphthyl)- ethanol (Nethalide®) did not depress neuromuscular transmission in guinea pig and rabbit soleus–gastrocnemius preparations. In the same year, Turker and Kiran [7] found that 5 mg./kg. pronethalol intravenously blocked neuromuscular transmission in the cat sciatic nerve–gastrocnemius muscle and rat phrenic–diaphragm preparations. Interestingly, the neuromuscular-blocking dose of pronethalol used approximated the amount that protects the heart against digitalis intoxication. In 1966, Standaert *et al.*[8] confirmed the neuromuscular blocking effect of pronethalol in the cat, in vivo. In addition, depression of motor nerve terminals by pronethalol was demonstrated.

Recently, the new beta-adrenergic blocking agents propranolol (1-isopropylamino)-3-(a-naphthoxy)-2-propanol HCl (Inderal®) [9-13] and MJ 1999 (dl-4-2-isopropylamino-1-hydroxyethyl methanesulfonanilide) HCl [14-15] have been synthesized and introduced for clinical trial. Propranolol suppresses epinephrine-induced as well as digitalis-induced arrhythmias.[9] MJ 1999 is effective only against cardiac arrhythmias induced by catecholamines.[14] Since the effects of these drugs on the neuromuscular junction have not been investigated fully,† the present experiments were designed to determine the neuromuscular activity of the new beta-adrenergic blockers, to compare their potency with that of pronethalol, and to study

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Received from the Department of Pharmacology, Cornell University Medical College, New York, New York. Accepted for publication December 12, 1967. This study was supported by Research Training Grants TO-GMO-1714-01 and C56 NIH-H-5010.

† The myoneural effect of MJ 1999 recently was reported by F. G. Standaert and J. Roberts: A neural action of pronethalol, Ann. N. Y. Acad. Sci. 139: 815, 1967.

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the interaction of these agents with the skeletal neuromuscular blockers, succinylcholine and curare.

Methods

The experiments were performed in cats anesthetized with 80 mg./kg. choralose, intravenously. The methods employed are illustrated in figure 1. Basically, they included recording of the soleus muscle twitch tension and soleus nerve action potentials. The former is a fundamental pharmacologic technique for the study of neuromuscular transmission; the latter method, developed by Riker *et al.*[16] and Standaert[17] permits assessment of function of the nerve terminal. When a nerve is stimulated either electrically or by drugs, an action potential is propagated throughout the axon—orthodromically as well as antidromically—and can be recorded at any point on the axon. The experiment is performed most conveniently on a ventral spinal nerve root.

The popliteal fossa was dissected to expose the soleus muscle, with its nerve and blood supply. The isometric contraction of the soleus muscle in response to supramaximal shocks applied to the sciatic nerve (2.5 sec. interval, 0.5 msec. duration) was recorded on a Texas oscilloriter. In selected experiments, a lumbar laminectomy was performed to expose the L7 ventral root, the origin of the soleus nerve. The root was detached from the spinal cord and subdivided until a filament containing a single active axon was located. This was placed on a bipolar recording electrode. Nerve potentials from the single axon were displayed on a Textronix oscilloscope and photographed. The popliteal fossa and lumbar region, held open by sutured retention cords, were filled with paraffin oil equilibrated with 95 per cent O_2–5 per cent CO_2. Temperature was maintained at 37° C. with a regulated heat lamp. A tracheotomy was performed. When necessary, ventilation was assisted with a Harvard pump respirator. Arterial blood pressure and pulse in the carotid artery were recorded via an indwelling catheter and a Statham pressure transducer connected to the Texas oscilloriter.

Drugs: Pronethalol, propranolol, MJ 1999, succinylcholine and *d*-tubocurarine were dissolved in saline solution and the concentrations adjusted so that the dose per kilogram was 0.1 ml. intra-arterially or 1 ml. intravenously. In five experiments, increasing doses of a given beta blocker were injected into the popliteal artery at 30-minute intervals and a dose-response relationship of the soleus muscle twitch tension depression was determined. In all other cases, drugs were injected into the external jugular vein. In 20 experiments, the beta blockers were administered between two doses of succinylcholine; in 15, they were given during the recovery phase of a curare-induced paralysis. The degree of sympathetic beta blockade was tested with 0.5 μg./kg. isoproterenol administered intravenously.

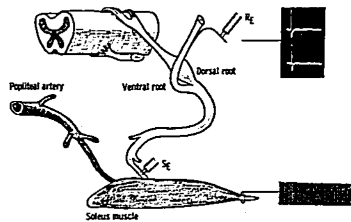

FIG. 1. Experimental method. Tendon of the soleus muscle is attached to a strain gauge for recording muscle tension (lower right). SE = stimulating electrode on soleus nerve; RE = recording electrode, which holds a single axon teased from the L_7 ventral root. Nerve action potentials are displayed on an oscilloscope (upper right) and recorded on tape.

Results

Close Intra-arterial Injection of Beta Blockers

Increasing doses of pronethalol and propranolol induced brief depression of the indirectly-stimulated twitch; pronethalol 5.5 mg./kg. and propranolo 4.7 mg./kg. effected a 50 per cent block (ED50). The difference between these doses was not significant ($P > 0.2$). Following a one-to-three minute partial paralysis, the muscle regained its initial tension. On three occasions, however, a twitch potentiation lasting from five to 16 minutes developed following recovery from

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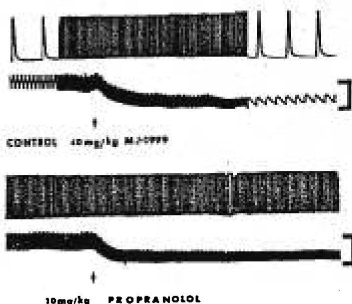

FIG. 2. Effects of intravenous MJ 1999 and propranolol on soleus muscle twitch tension and arterial blood pressure. *Top two tracings:* Marked hypotension and bradycardia but no reduction in tension of the soleus muscle contraction with 40 mg./kg. MJ 1999. Brackets (right) indicate 100 mm. Hg blood pressure. The distance between individual muscle twitches = 2.5 seconds. *Lower two tracings:* With marked fall in arterial blood pressure, 10 mg./kg. propranolol did not reduce twitch tension of soleus muscle.

neuromuscular blockade induced by propranolol. In these instances, twitch potentiation was unaccompanied by repetitive potentials in the motor nerve terminals, such as those which occurred following twitch potentiation resulting from succinylcholine administration (see below). In contra-distinction to pronethalol and propranolol, corresponding doses of MJ 1999 did not affect twitch tension of the soleus muscle. The intra-arterial injection of beta blockers caused a fall in systolic blood pressure (10–30 mm. Hg), and/or a slight decrease in heart rate (10–20 beats per minute).

Intravenous Administration of Beta Blockers

The intravenous administration of as much as 20 mg./kg. pronethalol or propranolol or 40 mg./kg. MJ 1999 was not followed by decrease in the soleus muscle twitch tension (figs. 2 and 3). All drugs, however, antagonized the positive chronotropic effect of isoproterenol on the heart (table 1). In equal mg. per kg. doses, MJ 1999 was roughly two times and propranolol ten times more potent as chronotropic beta blocking agents than pronethalol. The largest doses of the three drugs resulted in moderate arterial hypotension.

Intravenous Administration of Succinylcholine and Beta Blockers

Intravenous succinylcholine (10–50 μg./kg.) produced widespread muscle fasciculations, potentiation of the soleus muscle twitch tension and repetitive action potentials recorded from the L7 ventral root filament (fig. 4). These excitatory effects lasted 20 to 60 seconds. Larger doses of succinylcholine caused similar initial effects, and in addition, precipitated 30–100 per cent neuromuscular blockade that appeared within 30 seconds and persisted for as long as five minutes. All neuromuscular effects of succinylcholine were fairly consistent for the same animal when the injections were done at 20- to 30-minute intervals.

Intravenous pronethalol, 2.5 to 10 mg./kg., prior to administration of succinylcholine prevented repetitive firing of the soleus nerve, as well as fasciculations and twitch potentiation of the soleus muscle. The magnitude and duration of neuromuscular blockade induced by succinylcholine, however, was increased 20–40 per cent. When partial neuro-

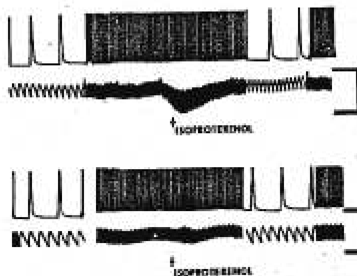

FIG. 3. Beta blocking effects of intravenous MJ 1999. Soleus muscle twitch tension and arterial blood pressure tracings. Brackets (extreme right) indicate 200 mm. Hg blood pressure. In upper tracings, 0.5 mg./kg. isoproterenol was injected at arrow. A fall in systolic and diastolic blood pressure, an increase in mean arterial pressure, and marked tachycardia developed. In lower tracings, 0.5 mg./kg. isoproterenol injections were preceded by 2 mg./kg. MJ 1999. Isoproterenol failed to induce hypotension and/or tachycardia.

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TABLE 1. Neuromuscular and Systemic Effects of Pronethelol, Propranolol and MJ 1999*

Test	Results	Pronethalol	Propranolol	MJ 1999
Depression of indirectly elicited twitch	Minimal effective dose	None up to 20 mg./kg. (6)	None up to 20 mg./kg. (8)	None up to 40 mg./kg. (6)
	50 per cent block (E D 50)†	5.5 mg./kg. (5)	4.7 mg./kg. (5)	Undetermined (5)
Potentiation of curare paralysis	minimal effective dose	2.5 mg./kg. (4)	2.5 mg./kg. (4)	40 mg./kg. (7)
Antagonism of succinyl-choline stimulation	Minimal effective dose	2.5 mg./kg. (6)	2.0 mg./kg. (8)	30 mg./kg. (6)
Antagonism of isoproterenol tachycardia	75 per cent block (E D 75)	3.1 mg./kg. (11)	0.3 mg./kg. (14)	1.5 mg./lg. (11)
Potentiation of curare/antagonism of isoproterenol	Dose ratio	0.8:1	8.3:1	26.6:1

* Figures in parenthesis = number of experiments done.
† Intra-arterial administration; in all other instances, drugs were injected intravenously.

muscular block was achieved with succinylcholine, intravenous pronethalol or propranolol caused further reduction of twitch height. The more intense the blockade, the smaller was the dose of pronethalol or propranolol required to affect neuromuscular transmission (fig. 5). In doses as large as 30 mg./kg. MJ 1999 did not have the modifying effects of the other beta blockers. Slight prolongation of the neuromuscular blockade and partial prevention of the stimulatory effects of succinylcholine were observed with doses of 30–40 mg./kg.

Intravenous Administration of Curare and Beta Blockers

Intravenous administration of 200–350 μg./kg. curare resulted in 40 to 100 per cent neuromuscular blockade, which was not preceded by stimulation. Recovery to control twitch occurred within 15 minutes. In contrast to succinylcholine, successive doses of curare had a marked cumulative effect. For this reason, beta blockers were tested only during the recovery period of curare-induced paralysis. Thus, intravenous pronethalol and propranolol increased the magnitude and duration of curare block in a dose-related fashion (fig. 6). Minimal effective doses of pronethalol or propanolol were 2.5 mg./kg. The effect of either drug in 5 mg./kg. doses was roughly equivalent to the effect of 50 μg./kg. curare. Tested in the same fashion, MJ 1999 had only a slight neuromuscular depressant effect at the 40 mg./kg. dose level.

Discussion

The present experiments have demonstrated that intravenous pronethalol, propranolol and MJ 1999 antagonize isoproterenol and differentially modify the neuromuscular effects of succinylcholine and curare. The same dose of pronethalol effectively produced both beta-adrenergic and neuromuscular blockade. On the other hand, neuromuscular blocking doses of propranolol and MJ 1999 were 8 and 25 times greater, respectively, than the beta blocking doses. The durations of action of beta blockade and neuromuscular depression also were independent: neuromuscular blockade persisted for a few minutes, whereas antagonism of isoproterenol continued for several hours. Thus, from both the dose-response and the time-action curves, it appears that myoneural effects of beta-adrenolytic drugs are unrelated to their interaction with catecholamines. This conclusion was not unexpected

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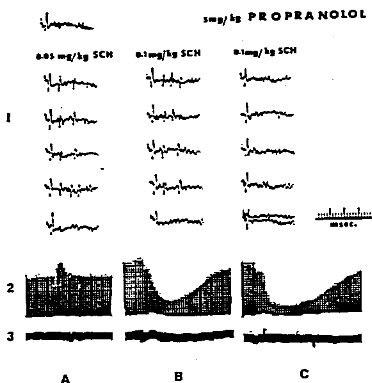

FIG. 4. Neuromuscular effects of succinylcholine before and after propranolol injection. *1.* Nerve action potentials from a single axon of the soleus nerve. Top potential control, prior to drug administration. *2.* Twitch tension of soleus muscle contraction. 3. Arterial blood pressure recordings. A, B, and C taken in the same animal at 30-minute intervals. *Column A.* Repetitive potentials in nerve (1) as well as potentiation of muscle twitch (2) were produced with 50 μg./kg. succinylcholine. *Column B.* A larger dose of succinylcholine (100 mg./kg.) was injected. Repetitive potentials were evoked in the nerve, and potentiation of twitch tension followed by neuromuscular blockade occurred. *Column C.* Five mg./kg. propranolol preceded the same dose of succinylcholine (Column B). Repetitive potentials in the nerve or twitch potentiation were not observed. Neuromuscular blockade was prolonged.

since there are no beta-adrenergic receptors at the myoneural receptor sites.

The neuromuscular actions of beta blockers could be induced by the interplay of three different effects: changes in muscle blood flow, drug interaction on plasma proteins and plasma cholinesterase, and a direct effect at the myoneural junction.

CHANGES IN MUSCLE BLOOD FLOW

Blockade of the sympathetic nervous system has a noticeable circulatory effect. The resulting hypotension and bradycardia reduce muscle blood flow while concomitantly delaying the rate of elimination of muscle relaxant from the myoneural junction. Although this mechanism might account for prolongation of muscle paralysis in a clinical situation, it cannot be held primarily responsible for the present results. Intra-arterial pronethalol and propranolol depressed neuromuscular transmission while reducing the arterial blood pressure only slightly. MJ 1999 had a minimal neuromuscular effect despite producing arterial hypotension.

INTERACTION ON PLASMA PROTEINS AND PLASMA CHOLINESTERASE

Approximately 70 per cent of *d*-tubocurarine present in the blood stream is bound loosely to protein, presumably to plasma albumins. The remaining 30 per cent circulates in free plasma water.[18] Since the unbound drug is in equilibrium with muscle relaxant at the neuromuscular junction, the unbound fraction represents the pharmacologically-active drug. A variety of agents used during surgery and anesthesia, including local anesthetics,[19] can displace muscle relaxants from plasma proteins, thus increasing their concentration at the myoneural junction. Whether beta blockers are capable of displacing curare from plasma proteins remains to be determined. The alternative possibility for drug potentiation applies to succinylcholine only. Since succinylcholine is metabolized by plasma cholinesterase, it is possible that beta blockers prolong succinylcholine paralysis by enzymatic inhibition, but this is unlikely. In other experiments,[25] we did not find significant reduction of the splitting activity of plasma cholinesterase incubated with 10^{-5} to 10^{-4} concentrations of pronethalol, propranolol or MJ 1999. It should be noted that these *in vivo* concentrations of beta blockers are somewhat higher than those expected *in vivo* following the injection of experimental doses.

INTERACTION AT THE NEUROMUSCULAR JUNCTION

Drugs can interfere with neuromuscular transmission by affecting presynaptic and/or postsynaptic structures. For example, it is agreed generally that the hemicholiniums act on nerve terminals,[21] that neuromuscular blockers act on postsynaptic membranes, and that magnesium affects both.[22] Within the past few years, however, it has been shown that several effects of skeletal muscle relaxants

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may be induced by drug action at presynaptic sites.[8, 16, 23, 24, 25] An example of such presynaptic effects is the appearance of repetitive potentials immediately following the injection of succinylcholine.[23] The neural origin of these potentials is supported mainly by two observations: they always precede corresponding potentials in the muscle, and they have a completely independent dose-relation and time course in relation to other effects of succinylcholine (for instance, to neuromuscular blockade). Recognition of this stimulatory action on the nerve terminal is important since it explains the muscle fasciculations and twitch potentiation induced by administration of succinylcholine. The arrival of succinylcholine at individual motor units is not uniform because of delay in transportation of the drug by the bloodstream. The uncoordinated stimulation of motor nerve endings causes individual muscle fibers to contract asynchronously; thus, muscle fasciculations occur. On the other hand, repetitive potentials in the nerve change the single electrical stimulus into a brief tetanus, prolonging the active state of the muscle, and thus, producing the twitch potentiation. The demonstration of a presynaptic origin of stimulatory effects of succinylcholine has another important implication. Since repetitive potentials are neural events and beta blockers depress them without depressing the transmission of single twitches, beta blockers must act by selective depression of the motor nerve terminal.

Results of the present experiment have demonstrated that neuromuscular effects of beta blockers do not depend on interaction with catecholamines; instead, they seem to depend on the nonspecific or "local anesthetic" effect of these drugs. There is evidence to support this assumption. In general, the neuromuscular effects of beta blockers strikingly resemble those of local anesthetic compounds, in that both groups can produce neuromuscular block-

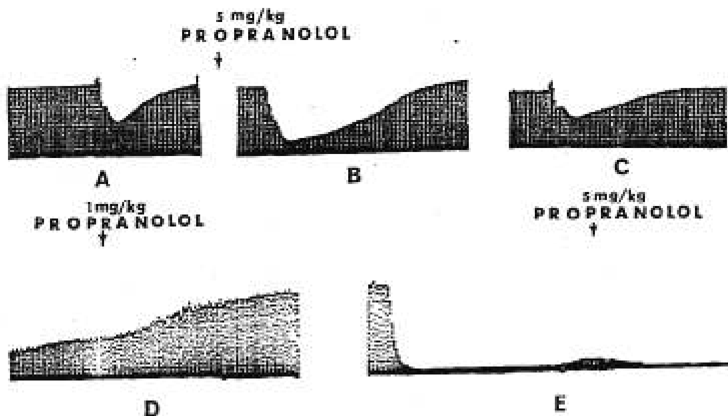

FIG. 5. Effect of intravenous propranolol on neuromuscular paralysis by succinylcholine. *A.* Intravenous injection 100 μg./kg. succinylcholine produced partial neuromuscular blockade preceded by twitch potentiation. *B.* 30 minutes later, 5 mg./kg. intravenous propranolol injected before the administration of 100 mg./kg. succinylcholine. More prolonged, longer-lasting neuromuscular blockade not preceded by potentiation resulted. *C.* Thirty minutes after B, a third dose, 100 mg./kg. succinylcholine, produced twitch potentiation and neuromuscular blockade. *D.* Intravenous propranolol, 1 mg./kg., injected during the recovery phase from succinylcholine-induced paralysis, did not curtail muscle power appreciably. *E.* Intravenous propranolol, 1 mg./kg., injected during an earlier phase of recovery from succinylcholine-induced paralysis, produced 100 per cent neuromuscular blockade.

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ade; they present the initiation of repetitive potentials, twitch potentiation and muscle fasciculations induced by succinylcholine; and they prolong muscle paralysis induced by skeletal neuromuscular blockers.[24, 25, 26] More specifically, pronethalol and propranolol are also local anesthetics with potencies approximating that of lidocaine.[3, 5] Therefore, the observation that pronethalol and propranolol are equally potent myoneural depressants is in accord with what is known about the local anesthetic potency of these drugs. Furthermore, MJ 1999, a weak myoneural depressant is almost devoid of any local anesthetic effect.[14, 15] The striking similarity between the effects of beta blockers and local anesthetics on the motor nerve terminal is not restricted to this portion of the nervous system. Given intravenously, both groups of drugs can depress spinal reflexes,[5, 27] prevent cardiac arrhythmias and vomiting due to digitalis,[2, 28] prolong barbiturate anesthesia, and produce generalized convulsions in the experimental animal.[1] Thus, the effects at motor nerve terminals are another example of the generalized neural actions of the drugs.

Unlike the suppression of repetitive potentials, which can be pinpointed as a prejunctional effect, the explanation for other neuromuscular effects of beta blockers is rather unsatisfactory. One of the phenomena difficult to explain is the twitch potentiation that occasionally followed administration of propranolol. Because there were no repetitive potentials in the nerve, this can be suspected of being due to a drug effect on the muscle fiber. In this regard, it is pertinent to recall that antiarrhythmic drugs such as quinidine can increase the peak tension of skeletal muscles by slowing the propagation of the action potential along the muscle fiber, that is, by prolonging the duration of the active state. The second debatable subject is the mechanism of neuromuscular blockade. In the two studies previously describing the effect, Turker and Kiran[7] postulated a reduction of transmitter output, whereas Standaert *et al.*[8] envisaged a further depression of nerve terminals as the cause of neuromuscular blockade. Since we have no new evidence to present and our knowledge of neuromuscular depression by beta blockers is incomplete (for instance, the endplate potential has not yet been determined), further discussion of the subject would be noncontributory.

The clinical significance of these results deserves comment. Although species differences preclude authoritative conclusions, we do not believe that small doses of beta blockers will depress the muscle strength of normal individuals or prolong the effect of curare during general anesthesia. Normally the most important and dangerous effects of beta-adrenergic blocking agents occur in relation to the circulation. However, certain patients with muscle dysfunction undergo anesthesia and operation. Some myasthenic patients manifest irregularities of cardiac rhythm[29, 30] which often are treated with local anesthetic injections, quinidine, or procainamide. The administration of antiarrhythmic drugs to these patients occasionally has resulted in aggravation of their weakness.[31, 32] For that reason, the injection of drugs such as pronethalol, in which the beta blocking and the "local anesthetic" actions occur within the same dose range, is potentially hazardous. In myasthenic patients the use of drugs exhibiting the widest divergence between the beta-adrenergic and the myoneural depressant doses, such as propranolol or MJ 1999, would appear more desirable. Finally, the prevention of the stimulatory effects of succinylcholine by some beta blockers should be considered. Because pronethalol and propranolol share these properties with local anesthetics, it is possible that beta blockers can also prevent the postoperative muscle pain induced by succinylcholine administration.[33] A careful postoperative follow-up of patients who have received beta blockers could provide this information.

Summary

The neuromuscular effects of the beta-adrenergic blocking agents pronethalol, propranolol and MJ 1999 were studied in the soleus nerve-muscle preparation of the cat. The beta blocking effects of these drugs were assessed by the intravenous injection of isoproterenol. Intra-arterial administration of pronethalol and propranolol resulted in a dose-dependent, short-lasting neuromuscular block-

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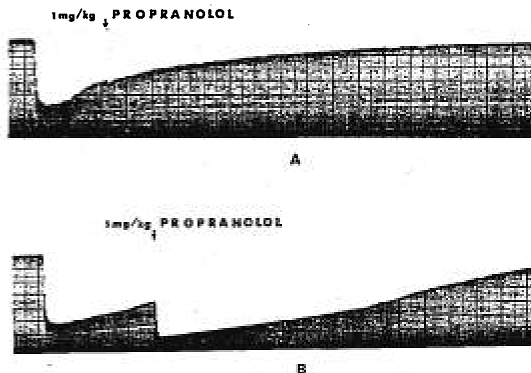

FIG. 6. Effect of intravenous propranolol on curare-induced paralysis. A. Intravenous propranolol, 1 mg./kg., had no effect on twitch tension of the soleus muscle during recovery from the effect of 200 μg./kg. dose of curare. B. Intravenous propranolol, 5 mg./kg., potentiated and prolonged the neuromuscular depression produced by 250 mg./kg. curare.

ade. The ED_{50} of pronethalol was 5.5 mg./kg. and that of propranolol 4.7 mg./kg. Corresponding doses of MJ 1999 had no appreciable effect on neuromuscular transmission. The intravenous administration of beta blockers was not followed by any reduction of the twitch tension, despite demonstration of long-lasting beta-adrenergic receptor blockade.

Succinylcholine, 10–50 μg./kg. intravenously, induced repetitive potentials of the soleus nerve, muscle fasciculations and twitch potentiation. Larger doses caused the same initial stimulatory effects followed by neuromuscular blockade. Administration of pronethalol or propranolol prior to succinylcholine prevented repetitive potentials of the nerve and the fasciculations, as well as twitch potentiation in the muscle, but potentiated the neuromuscular blockade. MJ 1999 did not protect fully against succinylcholine stimulation.

Curare, 200–350 μg./kg. intravenously, produced partial-to-complete neuromuscular blockade which was potentiated by intravenous pronethalol or propranolol. No significant potentiation was induced with corresponding doses of MJ 1999.

On the basis of the dose-effect and the time-action relationship, we conclude that neuromuscular effects of beta blockers are independent of their interaction with catecholamines; rather, neuromuscular effects depend on "local anesthetic" activity of the drugs. For this reason, the use of beta blocking agents with high local anesthetic potency is considered hazardous in patients with neuromuscular dysfunction. The prevention of succinylcholine-induced repetitive potentials, muscle fasciculations and twitch potentiation is ascribed to a presynaptic effect of beta blockers. The site of the other actions is unknown.

The author is indebted to Dr. Walter F. Riker, Jr., and Dr. Frank Standaert for their invaluable advice and to Mr. Dalton Chiscolm for his devoted and skillful technical assistance. MJ 1999 was obtained from Dr. Paul Lish, Mead Johnson Research Institute, Evansville, Indiana.

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Erratum

In the article "Metabolism of Drugs Employed in Anesthesia," which appeared in the March–April issue (Anesthesiology 29: 332, 1968), the sentence "The only important oxybarbiturate *not* excreted unchanged is barbital" (p. 332, right-hand column) should read "The only important oxybarbiturate excreted unchanged is barbital."

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