

## The Effect of Ketamine and Phencyclidine on Muscle Activity in Nonhuman Primates

TAKAYUKI KURODA, D.D.S., Ph.D.\*

JAMES A. McNAMARA, JR., D.D.S., Ph.D.†

**S**OME nonhuman primates, such as monkeys, need to be anesthetized before neuromuscular studies. The administration of anesthetic agents introduces an experimental variable not present, for example, in human electromyography or for such laboratory species as the dog, in which anesthesia is not necessary.

The present study was undertaken to determine whether muscular activity, as reflected in electromyographic (EMG) recordings of the muscles of mastication, is influenced by anesthetic agents, to describe the nature of such influences, and to record the onset and disappearance of drug-related effects relative to the time of drug administration. The duration of such effects is of critical importance, because neuromuscular

studies must be free from all extraneous influences that may mask normal physiologic functional patterns.

### MATERIALS AND METHODS

Eighteen juvenile and adolescent rhesus monkeys (*Macaca mulatta*) were used. They weighed 2.5 to 5.6 kg. and, according to current tables of tooth eruption,<sup>1,2</sup> were approximately 20 to 48 months of age. Tests involved the dissociative anesthetic agents, phencyclidine hydrochloride<sup>3,4</sup> and ketamine hydrochloride,<sup>5-9</sup> which are used commonly in primate anesthesia, altering the central nervous system by interrupting associative pathways of the brain,<sup>6</sup> and pentobarbital sodium, which is combined with either of these drugs for further muscle relaxation.<sup>10</sup>

\*Department of Orthodontics, School of Dentistry, Tokyo Medical and Dental University, Tokyo, Japan.

†Center for Human Growth and Development and Department of Anatomy, The University of Michigan, Ann Arbor, Michigan 48104 (Please send reprint requests to Dr. McNamara).

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TABLE  
Effect of Anesthetic Agents on EMG Recordings

Drug-related effects	Phencyclidine HCl (N = 8)	Phencyclidine HCl-pentobarbital sodium (N = 6)	Ketamine HCl (N = 10)	Ketamine HCl- pentobarbital sodium (N = 8)
1. Reduced activity in all muscle groups	0	++	0	++
2. Reduced activity in selected muscle groups	++	++	+	++
3. Loss of antagonistic muscle function	+++	+++	+	++
4. Selective muscle group hypertonicity	++++	+++	++	++
5. Burst discharges from muscle tremors	++	++++	+	++++

Summary of frequency and duration of drug-related effects in neuromuscular recordings. This tabular representation of effects does not relate to any particular animal but is based upon evaluation of EMG recordings of all animals. 0 = effect not observed. + = frequency and duration of effect. ++++ = effect most frequently observed, longest in duration.

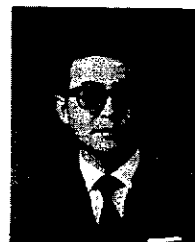
Drug dosage was a key consideration in interpreting the function of the musculature related to the stage of anesthesia. Dosage, prepared according to levels recommended by other investigators,<sup>4,5,7,10,11</sup> was as follows: phencyclidine HCl, 1.5 mg./kg. of body weight (intramuscular); ketamine HCl, 25 mg./kg. of body weight (intramuscular); and pentobarbital sodium, 5 mg./kg. of body weight (intravenous). Pentobarbital was administered intravenously only after injection of either of the other two drugs. The elapsed time between the first injection and the administration of pentobarbital was 4 to 10 minutes. "Onset of anesthesia" was marked as the time of final injection.

Eight of the experimental animals had one recording session with one drug or drug combination tested, and another eight had two sessions, using a different drug or combination on each occasion. Two monkeys received all four types of anesthesia. A minimum of 7 days was allowed between any two EMG procedures on the same animal. The distribution of the effects during the recording sessions in which each agent was tested can be seen in the table.

The anesthetized monkeys were placed in a specially-designed primate-restraining device in which the animal's head was held in a fixed position by a plexiglass holder, to allow for normal jaw function when unanesthetized. Pairs of monopolar platinum electrodes were inserted aseptically into the anterior temporal, posterior temporal, superficial masseter, deep masseter, and suprahyoid musculature on the left side. EMG tracings were taken with a Beckman Dynograph amplifier and recorded by a Honeywell Visicorder on Kodak Linagraph direct-print paper. No EMG recordings were made until the animal was properly positioned and electrode placement verified.

Elapsed time from final injection to initial recordings was usually 15 to 20 minutes with ketamine or phencyclidine and 10 minutes after the injection of pentobarbital when drugs were combined. Recordings were then taken at 10-minute intervals for 150 minutes or until such time as the animal had emerged fully from the anesthesia. Since the recordings were made with the animal isolated in a sound-proof room and no electric or mechanical stimulation was

★ DR. TAKAYUKI KURODA received his D.D.S. and Ph.D. degrees from Tokyo Medical and Dental University, Tokyo, Japan, where he currently holds the position as Lecturer in the Department of Orthodontics.



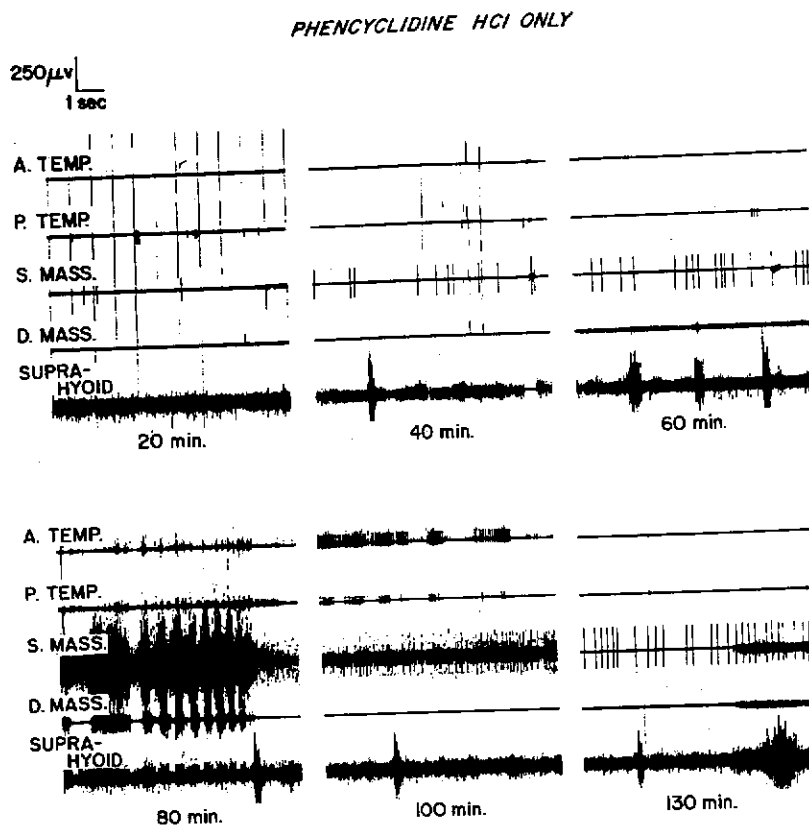


FIG. 1. EMG recordings of one animal after injection of 1.5 mg./kg. of phencyclidine HCl only. This animal did not recover normal neuromuscular function during recovery period. Note particularly hyper-tonicity in suprahyoid muscle group and burst discharges in masseter musculature at 80 minutes.

given during the experimental period, the criteria for "emergence from anesthesia" were an absence of observable drug-related artifacts and a return to coordinated oral functions consisting of teeth-together and teeth-apart swallows and coordinated random jaw movement. Visual inspection of the animal and tests for grasping and biting ability were made only at the conclusion of the recording period.

### RESULTS

The effects of the anesthetic agent, observed during every recording session, depended both upon the particular agent or agents used and upon the elapsed time after onset of anesthesia. Most drug effects seemed time related. The relative occurrence and duration of the particular artifacts observed for each drug tended to mask the normal functional recording pattern of the animal (table).

*Phencyclidine.*—This drug acted to increase tonus in selective muscle groups. Hyperactivity in the suprahyoid musculature persisted throughout the recording period, even until the arbitrary end of 150 minutes (fig. 1). Scattered action potentials were also recorded in the antigravity muscles (masseter and temporal musculature). This activity corresponded to the mild excitation usually seen with the use of this drug. However, coordinated elevator-muscle activity was almost totally reduced in the early recording stages. The reciprocal inhibitory mechanism between antagonistic muscles was not usually observed until 1 hour after the onset of anesthesia. Occasionally, a rhythmic burst discharge occurred, primarily in the masseter musculature. This was observed during the 2nd hour.

*Phencyclidine with Pentobarbital.*—The effect of this combination could be characterized by an initial reduction of muscle

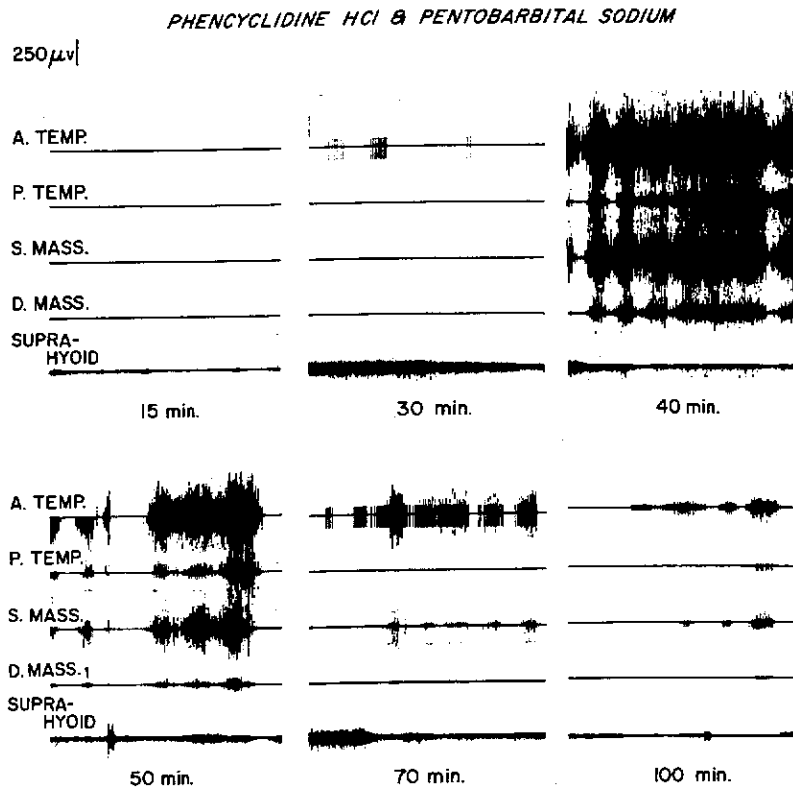


FIG. 2. EMG recordings of another animal after administration of 1.5 mg./kg. of phencyclidine HCl and 5 mg./kg. of pentobarbital sodium. Burst discharges were observed intermittently from 40 to 70 minutes after onset of anesthesia. Recordings from this animal were free from anesthetic effect by 100 minutes. Normal postural discharges of elevator musculature were then evident.

activity and by later appearance of hyperactivity and muscle tremor (table). Initially, all muscle activity was reduced (fig. 2). After 15 to 20 minutes, hypertonicity was observed in the suprahyoid musculature, while function in the antigravity muscles was minimal. Forty minutes after anesthesia, burst discharges caused by muscle tremor were observed. These discharges, which continued intermittently for the next 20 to 50 minutes, depending on the individual animal, involved all the elevator musculature and were more frequent and longer in duration than those observed when phencyclidine alone was used (fig. 1). The pattern of muscle activity was normal after 90 to 110 minutes, at which time the intermittent postural firings of the antigravity muscles were apparent.

*Ketamine.*—Fewer drug artifacts were associated with the use of this drug than

with any other agent tested. Muscle function was not reduced, as occurred with the ketamine-pentobarbital combination (table). Selective firings of antagonistic musculature were seen in early stages of the recordings. Coordinated function and inhibition mechanisms for certain spontaneous jaw movements were often apparent within 40 minutes after anesthesia. However, intermittent hypertonicity could be observed in the suprahyoid musculature and occasionally in the masseter and temporal muscles (fig. 3). In one instance, burst discharges from muscle tremors were observed when ketamine was administered, but no evidence of similar occurrences were observed in the other animals. The recorded musculature usually recovered by 60 to 75 minutes.

*Ketamine with Pentobarbital.*—Reduction of muscle activity and burst discharges

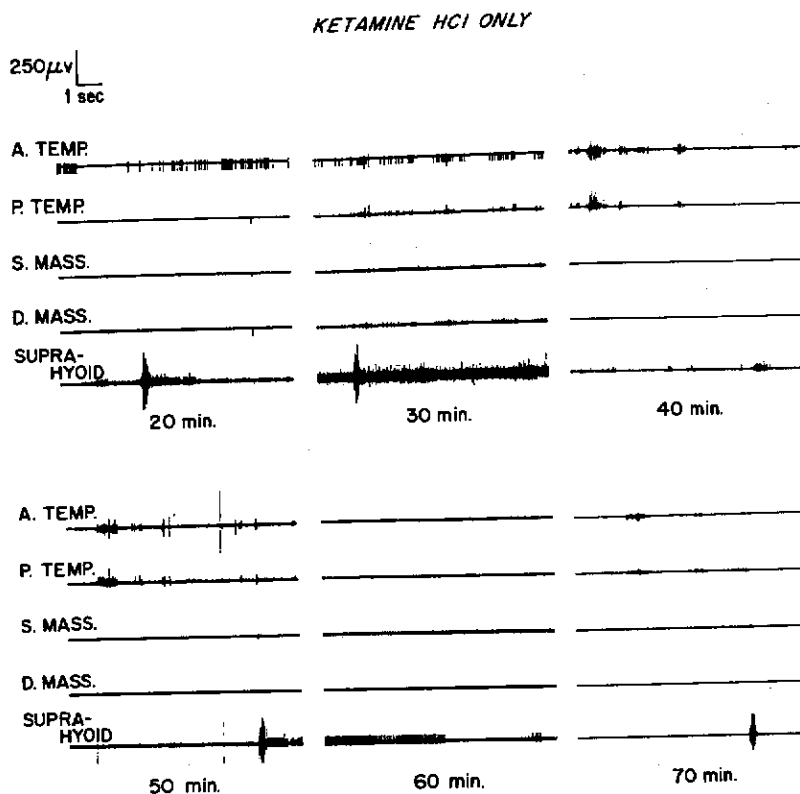


FIG. 3. EMG recordings of same animal as in figure 1 after injection of 25 mg./kg. of ketamine HCl only. Postural activity was not substantially reduced. Reflex swallows can be observed in 20, 30, 50, and 70-minute recordings. Normal neuromuscular activity was apparent in 70-minute record.

were observed with the use of pentobarbital plus ketamine, as with pentobarbital and phencyclidine (fig. 4). However, the degree of suprahyoid hypertonicity seen with ketamine-pentobarbital was lower than with the phencyclidine-pentobarbital combination. Normal muscle function was fully recovered at 80 to 100 minutes after anesthesia.

The number of experiments in which an animal was used did not seem to influence its response to a particular drug or drug combination. This may be due in part to the minimum time interval of 1 week between recording sessions.

#### DISCUSSION

This study indicates that phencyclidine HCl and ketamine HCl, administered alone or in combination with pentobarbital sodium, reduce activity of all muscles or of selective muscle groups, increase tonus in selective muscle groups, and cause burst discharges from muscle tremors. The onset

and disappearance of these anesthetic effects were related to the elapsed time after anesthesia; for example, when pentobarbital combinations were tested, a reduction in muscle function preceded muscle tremor. However, the hypertonicity of the suprahyoid musculature observed when phencyclidine was administered alone persisted throughout the duration of the recording session. Hinko and associates<sup>12</sup> noted that electroencephalographic changes were present several hours after phencyclidine administration. Chen's group<sup>3</sup> observed convulsive potentialities of phencyclidine when used in nonhuman primates.

Normal or slightly enhanced skeletal muscle tone after administration of ketamine has been noted in other studies.<sup>6,8,13</sup> Corssen and Domino<sup>6</sup> reported that the tonus of the masseter muscles and of the musculature of the extremities was usually increased, although generally a muscle relaxant was unnecessary. Occasional hypertonicity was observed in the masseter and

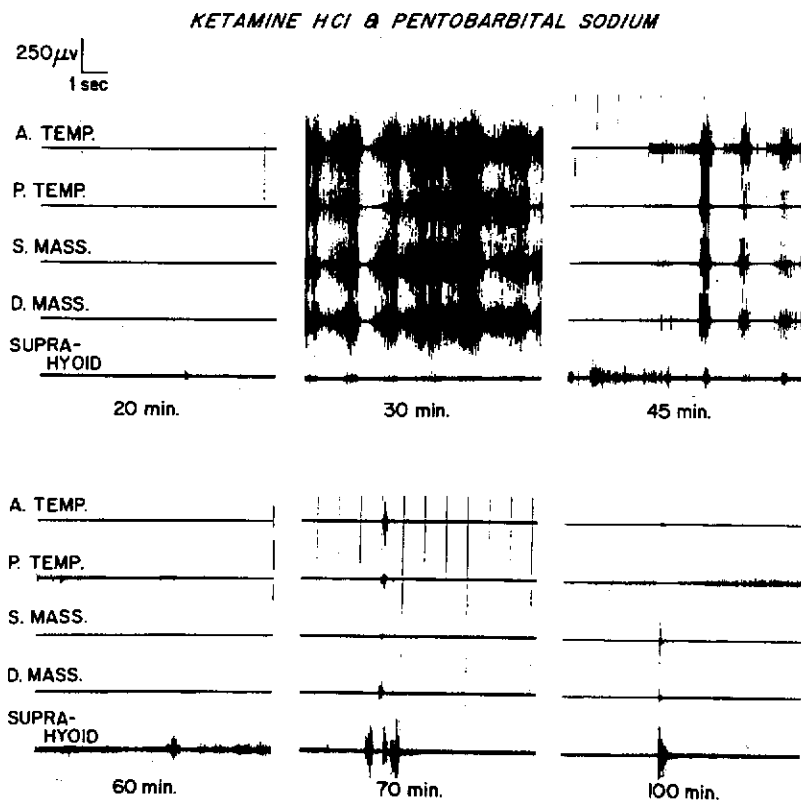


FIG. 4. EMG recordings of same animal as in figure 2 after administration of 25 mg./kg. of ketamine HCl and 5 mg./kg. of pentobarbital sodium. Intermittent muscle tremor was observed 30 to 45 minutes after onset of anesthesia. Normal postural and functional activity was evident by 100 minutes.

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temporal musculature in this study, but increased tonus was more apparent in the suprahyoid region. Other investigators<sup>7,11</sup> have noted a relaxation of the muscles of facial expression. While the facial musculature was not specifically monitored, similar findings were observed.

Neuromuscular recordings should be free from masking artifacts, to more meaningfully and accurately interpret the nature of experimental results. Since each of the agents and drug combinations tested had specific influences on muscle activity, recordings should be made with the subject unanesthetized whenever possible.

A single dose of ketamine produced the fewest drug-related effects, and more importantly, the duration of these drug effects was shorter than that observed for phencyclidine or for the phencyclidine-pentobarbital combination. It is possible to reduce the dosage of ketamine to allow for han-

dling of the animal, yet allow for a shorter time of recovery to normal neuromuscular function.

#### SUMMARY

Ketamine HCl and phencyclidine HCl, when used alone or in combination with pentobarbital sodium, have specific influences on muscle activity. The manifestation of the effects depends upon the particular agents used and the elapsed time after onset of anesthesia. Because duration of effects that alter normal functional patterns is shortest with ketamine, this agent is a drug of choice in preparing nonhuman primates for neuromuscular studies.

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Generic and Trade Names of Drugs  
 Ketamine—Ketalar, Ketaject  
 Phencyclidine—Sernylan  
 Pentobarbital—Nembutal

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Applause abates diligence.

—Samuel Johnson

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Youth is the opportunity to do something and to become somebody.

—Theodore T. Munger

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Those who make the most of their time make the most money.

—Arnold Glasow