# Effects of CI 744 on Skeletal Muscle Activity in Monkeys *(Macaca mulatta)*

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## SUMMARY

CI 744, an experimental dissociative anesthetic, was administered intramuscularly to 8 rhesus macaques *(Macaca mulatta)* and orofacial muscle activity was monitored electromyographically (EMG) for 60 to 150 minutes. Complete skeletal muscle relaxation of selected muscle groups was demonstrated. Only slight muscle hyperactivity was evident, occurring during the later stages of the recovery period. The swallowing reflex was retained during the period of anesthesia. Six of the 8 monkeys were behaviorally subdued after the drug-related EMG effects had disappeared.

Phencyclidine[5] and its analogue ketamine[8] presently are the most frequently used dissociative anesthetics in primates. Both agents, given by intramuscular injection, produce profound analgesia and cataleptoid anesthesia.[1,2,8] Tiletamine (CI 634),[3,6] an arylcycloalkylamine and an analogue both of phencyclidine and ketamine, also produces anesthesia in primates, having a duration of action intermediate between the long-acting phencyclidine and the short-acting ketamine. A potential disadvantage in the clinical use of these agents, however, sia, as evidenced in part by the occurrence of athetoid sia, as evidenced in part by the occurence of athetoid movements of limbs and head.[3,8] This could adversely affect certain surgical procedures or limit the usefulness of the agents in studies involving muscle function.

Primates generally must be anesthetized before EMG studies can be started. A key question is the extent to which the anesthetic agent induces drug-related muscular effects. Obviously, the agent which induces the fewest effects is the drug of choice. Recently, ketamine and phencyclidine, each alone and in combination with pentobarbital sodium, were investigated with respect to their effect(s) on skeletal muscle activity in the orofacial region.[7] Duration of drug-related muscular effects was shorter and normal functional patterns returned more quickly after ketamine was given than after the other agents (phencyclidine alone, phencyclidine with pentobarbital, ketamine with pentobarbital) were used.

The purpose in the present experiment was to evaluate the effects(s) of CI 744, an experimental dissociative anesthetic agent, on orofacial muscle activity in rhesus macaques. The agent has been shown to produce surgical anesthesia both in dogs and monkeys.[4] The anesthetic consists of tiletamine in combination with zolazepan (CI 716), a diazopenone having minor tranquilizer properties. When used in dogs and monkeys, quality of the anesthesia was judged to be excellent and skeletal muscle relaxation was greater than with tiletamine, ketamine, and phencyclidine.[3,4,8]

## Materials and Methods

*Animals, Anesthetic Agent, Dosage Schedule*—Eight juvenile and young adult rhesus macaques, weighing 4.2 to 7.9 kg each and in good health, were used (Table 1).

TABLE 1—Duration of CI 744-Related Effects in *Macaca mulatta*

| Monkey No. | Body weight (kg) | Dose (mg/kg) | Duration of anesthetic-related effects (min) |
|---|---|---|---|
| 1 | 7.7 | 3.1 | 90 |
| 2 | 7.5 | 3.4 | 75 |
| 3 | 7.9 | 3.0 | 61 |
| 4 | 6.2 | 3.2 | 150 |
| 5 | 5.9 | 3.0 | 60 |
| 6 | 4.2 | 2.9 | 60 |
| 7 | 5.3 | 2.7 | 65 |
| 8 | 6.7 | 2.9 | 93 |

The agents comprising CI 744 were combined in an arbitrarily selected ratio of equal parts of tiletamine and flupyrazapon, 30 mg of each in a milliliter, to produce anesthesia and muscular relaxation. The dose used was 3 mg of the combined agents per kilogram of body weight, this being based on a report of tiletamine used alone.[3] This dose was administered in the outer quadrant of the posterior thigh muscles. For technical reasons it was deemed not feasible to weigh the monkeys until after they were anesthetized. Thus, the amount of CI 744 actually administered was based on the estimated body weight. However, the estimates proved sufficiently accurate that the actual dose was close to 3.0 mg/kg (Table 1). The monkeys lost the righting reflex within 2 minutes and EMG recordings were then initiated.

*Recording Methods*—Each monkey had 1 EMG recording session which began 8 to 12 minutes after injection of CI 744. Immediately after loss of the righting reflex, each monkey was placed in a specially designed restraint chair specially equipped with a head holder which permitted the

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TABLE 2—Effects of Anesthetic Agents on EMG Recordings

| Drug-related effects | CI 744 (N=8) | Other anesthetics[7] | | | |
|---|---|---|---|---|---|
| | | Phencyclidine HCl (N=8) | Phencyclidine HCl-pentobarbital sodium (N=6) | Ketamine HCl (N=10) | Ketamine HCl-pentobarbital sodium (N=8) |
| Reduced activity in all muscle groups | 0 | 0 | ++ | 0 | ++ |
| Reduced activity in selected muscle groups | ++ | ++ | ++ | + | ++ |
| Loss of antagonistic muscle function | ++ | +++ | +++ | + | ++ |
| Selective muscle group hypertonicity | + | +++++ | +++ | ++ | ++ |
| Burst discharges from muscle tremors | 0 | ++ | ++++ | + | ++++ |

Summary of frequency and duration of drug-related effects in neuromuscular recordings. This representation of effects does not relate to any given monkey, but is based upon evaluation of electromyographic (EMG) recordings of all monkeys.

0 = Effect not observed; + = minimal frequency and duration of effect; +++++ = effect most frequently observed, longest in duration. An unanesthetized monkey would have a rating of 0 in each column.

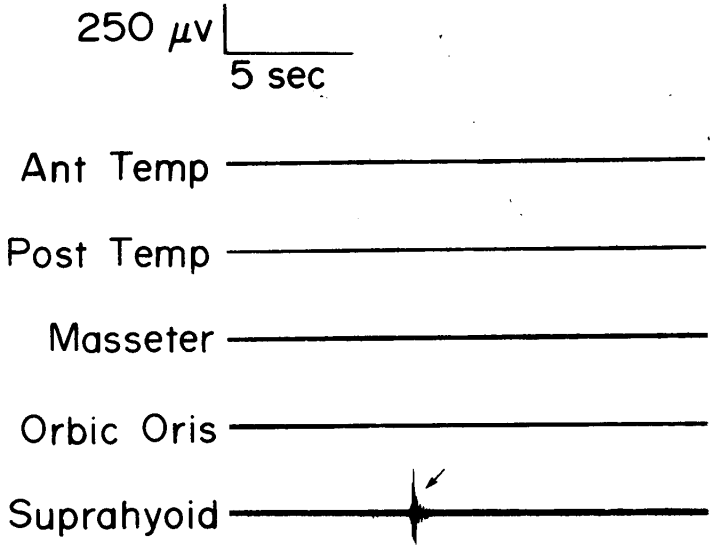


Fig 1—Initial relaxation of selected muscle groups usually occurring during the first 15 to 25 minutes of the recording period (monkey 3). Postural activity is not seen in the masticatory musculature. However, the swallowing reflex is maintained, as indicated by the burst of activity in the suprahyoid muscle group (arrow).

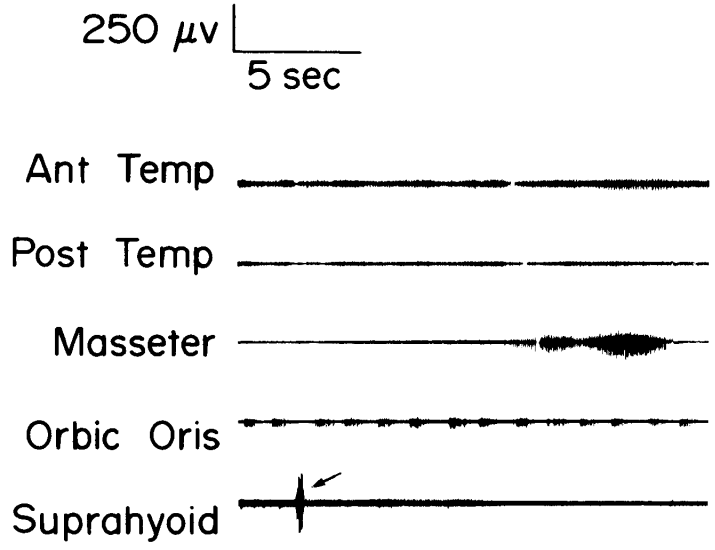


Fig 2—Gradual return to postural activity usually was observed during the middle of the recording period (monkey 5). Notice the tonic firings in the anterior and posterior temporal, orbicularis oris, and the suprahyoid musculature. Increased activity in the masseter muscle is also evident. A teeth-apart swallow, with no synchronized elevator muscle participation, is identified (arrow).

monkey to have complete freedom of movement of the mandible.[9]

Bipolar platinum needle electrodes were inserted aseptically into the anterior temporal, posterior temporal, anterior border of the superficial head of the masseter, orbicularis oris, and the suprahyoid musculature on the left side. Tracings[a,b,c] were recorded continuously until the monkey emerged fully from the anesthesia or to a maximum of 150 minutes. All recordings were made in a semidark, soundproof room to prevent exposure to external stimuli that would interfere with the recording sessions. Monkeys were judged to have emerged from anesthesia when drug-related artifacts were no longer being recorded. In addition, coordinated random jaw movements were observed and synchronized elevator activity was evident during deglutition. At the conclusion of the recording session, each monkey was tested for grasping function and biting capability to confirm the EMG interpretation of wakefulness.

## Results

The effects of the anesthetic CI 744 were observed during every recording session (Table 2) and these effects tended to mask the normal functional patterns of the monkeys.[10,11] The manifestation of these effects depended upon the elapsed time after onset of anesthesia. The initial EMG recordings, taken during verification of electrode placement 8 to 12 minutes after the time of injection, indicated no postural activity from the masticatory muscles in 7 of the 8 monkeys. Slight tonic activity from the masseter muscle was observed in 1 monkey. In all monkeys, reflexive activity from the elevator muscles was seen when the lower jaw was manually depressed by the investigator.

Throughout the recording period, the swallowing reflex was evident in all monkeys (Fig 1). The suprahyoid musculature showed distinct bursts of activity which corresponded with the typical swallow pattern in the rhesus macaque.[11] During the first 30 to 45 minutes after CI 744 was given, these swallows could be classified as "teeth-apart" in that there was usually no elevator activity associated with the suprahyoid burst.

After 15 to 25 minutes, there was a gradual return of tonic activity in the masseter, anterior temporal, orbicularis oris, and occasionally in the suprahyoid musculature (Fig 2). Antagonistic muscle function was not

[a] Dynagraph Type R amplifier, Beckman, Southfield, MI.

[b] Visicorder, Model 1108, Honeywell Inc, Detroit, MI.

[c] Linagraph direct print paper, Eastman Kodak, Rochester, NY.

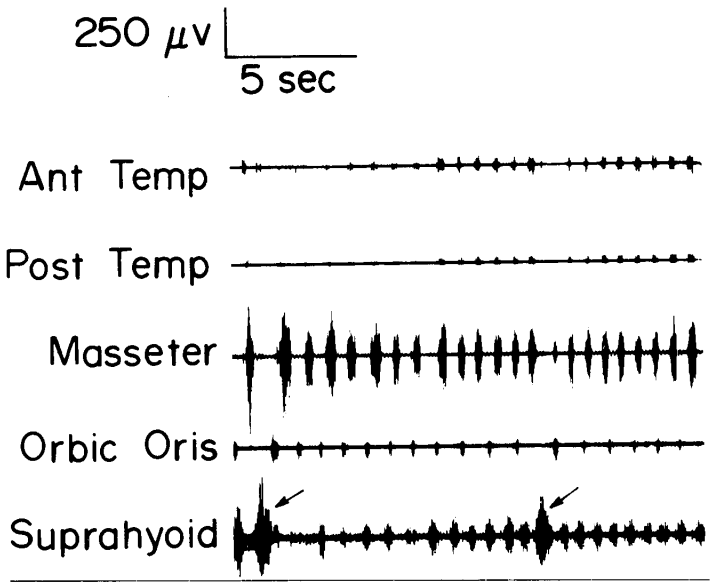


Fig 3—Establishment of coordinated functional patterns at the end of the recording period (monkey 7). Notice the sequential activity of the elevator (masseter and temporal) musculature and the depressor (suprahyoid) musculature. The participation of both elevator and suprahyoid muscles in 2 teeth-together swallows is identified (arrows).

observed during this time. The monkeys appeared to be free of drug-related EMG effects at 80 minutes (av; minimal-maximal time, 60 to 150 minutes) after the anesthetic was injected (Table 1). At this time, there was a return to coordinated random jaw movements (Fig 3). A variable number of "teeth-together" swallows with synchronized anterior temporal, masseter, and sometimes posterior temporal activity were also recorded. At no point in any of the sessions were discharges associated with muscle tremoring observed.

At the end of the recording period, each monkey demonstrated grasping and biting capability. However, only 2 appeared as active as a typical unanesthetized monkey or as a monkey which had emerged from ketamine anesthesia. The 6 other monkeys appeared subdued or tranquilized.

## Discussion

This study indicates that CI 744 has specific effects on skeletal muscle activity. Relaxation of selected muscle groups, loss of antagonistic muscle function, and selective muscle group hypertonicity were observed. The reduction in activity of selected muscle groups was similar to that observed for ketamine. The loss of antagonistic muscle function with CI 744 was greater than that produced with ketamine and less than that with phencyclidine (Table 2). The CI 744 caused only a slight increase in the hypertonicity of selective muscle groups. This hypertonicity was much less than that observed with phencyclidine or with phencyclidine combined with pentobarbital. In addition, burst discharges associated with muscle tremors were not recorded with CI 744, whereas such discharges were often observed with phencyclidine and occasionally with ketamine when those agents were used alone or in combination with pentobarbital sodium.[7]

Six of the 8 monkeys were behaviorally subdued at the end of the EMG recording periods. These were not as alert and active as nonanesthetized monkeys or monkeys that had emerged from anesthesia after administration of ketamine or of ketamine and pentobarbital sodium. The presence of this effect of CI 744 could affect its use in studies of neuromuscular function in which normal behavioral activity is desired soon after the end of the anesthetic period. However, in other respects CI 744 appears to have positive advantages. As with ketamine, all EMG drug-related effects disappeared promptly, and during anesthesia, CI 744 affected EMG recordings to a lesser extent than did ketamine or phencyclidine.

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