tion technology have increased the life span of tableting tools.

Keeping and reviewing of tool life records can lead to considerable savings in time and money in tablet manufacture. Under optimum conditions, life records of controlled tableting tools can show the maximum life expectancy of the equipment. When tool life is below these expected standards, reasons can usually be determined from the knowledge gained rather than just intuition. Benefits derived from the program have been substantial, and as a consequence, it will be continued as a valuable control procedure.

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Keyphrases

Tableting tool life records—evaluation
Punches—variables affecting wear
Dies—variables affecting wear
Record card—punches

Notes

Effect of Paralyzation with Dimethyltubocurarine on Cortical After-Discharge Duration

By ROBERT N. STRAW

Paralyzation with dimethyltubocurarine iodide increased the duration of cortical after-discharge in a manner similar to that previously reported for gallamine triethiodide. The after-discharge duration was determined from EEG records obtained from cats fitted with electrodes.

PARALYZATION WITH gallamine triethiodide, but not with decamethionium bromide or succinylcholine chloride, increases the duration of cortical after-discharge (1–3). The purpose of this investigation was to examine the effects of paralyzation with dimethyltubocurarine iodide on after-discharge duration.

METHODS

Five adult cats of both sexes were used in these experiments. Stainless steel screw electrodes were threaded into the skull under sodium pentobarbital anesthesia as previously described (1, 3). Preliminary trials to determine the threshold for a bilateral cortical after-discharge began after a 2-week recovery period. Each cat was stimulated with a 5-sec. train of 1-msec., monophasic square wave pulses at 50 p.p.s. (delivered from a Grass S-4 stimulator *via* a Grass SIU-4B stimulus isolation unit and Grass CCU-1A constant current unit) starting from 2.5 ma. and with increments of 2.5 ma. At least 5 min. elapsed between stimuli. The threshold was redetermined 2 days later starting with a current 5 ma. below the previously determined threshold. The threshold value obtained at this second trial was then used in each experimental trial. Throughout all experimental trials the cats, restrained only by the confines of their cage, were stimulated once on every other day.

The medial ectosylvian gyrus was chosen as the cortical area to be stimulated since, according to Garner and French (4), it has a relatively low seizure threshold. In addition, a generalized clonic overt seizure always accompanies the bilateral after-discharge elicited by stimulation of this area (5).

The stereotaxic coordinates (6) of the bipolar stimulating electrodes were $A = 10; L = 16; A = 2; L = 14$. Bipolar EEG recordings were made from both the stimulated site and the contralateral homologous area. In addition, EEG recordings were made from the posterior lateral and posterior sigmoidal gyri. All EEG recordings were made on a Grass model III electroencephalograph.

In the paralyzation experiments, the animals were given dimethyltubocurarine iodide (1 mg./kg.) intravenously. This dose was selected because it produces apparent total neuromuscular blockade of sufficient duration to conduct a trial under complete paralysis. Artificial respiration (Harvard pump set at 16 strokes/min.) was immediately started, the tidal volume being based on the animals' weights.

The after-discharge duration was determined from the EEG record. Analyses were performed on the data using a randomized complete block analysis of variance or by use of a Student's t comparison (7). For all tests, $p < 0.05$ was selected as the significant probability.

Received April 24, 1968, from the Department of Pharmacology, The Upjohn Company, Kalamazoo, MI 49001
Accepted for publication June 25, 1968.
The author wishes to acknowledge the technical assistance of Mr R. E. Williams.

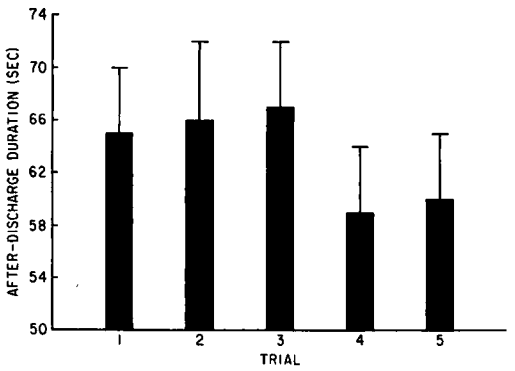

Fig. 1—Plot of mean duration versus *trial. Each value is the mean of 5 cats used throughout these experiments. The vertical line is the limit of the standard error.*

RESULTS

Figure 1 illustrates the trial-to-trial variability in the mean duration during the preparalyzation trials. An analysis of variance on these data showed no evidence for a difference among trials. The F ratio for trials was 2.41. There was, however, a significant difference among cats. The coefficient of variability for this analysis was 7.8%.

Table I documents the effect of paralyzation with dimethyltubocurarine on the duration of cortical after-discharge. As can be seen, the duration was significantly longer in the paralyzed state than in the nonparalyzed control trial.

In all trials (both control and paralyzed), all animals were in the alert state prior to stimulation. In the control (nonparalyzed) trials this was judged on the basis of overt behavior and the EEG record. During the trial under dimethyltubocurarine paralysis the state of arousal was determined from the EEG record.

DISCUSSION

The data from this investigation demonstrate that dimethyltubocurarine increases the duration of cortical after-discharge in a manner similar to that previously reported (1–3) for gallamine.

It has been previously speculated (3) that the mechanism whereby gallamine increases the duration of cortical after-discharge is *via* blockade of phasic inhibitory bursts arising in the muscle spindles during a motor seizure. As decamethonium and succinylcholine stimulate, rather than block, afferents arising in the muscle spindles (8), no increase would be expected following paralysis with these agents.

In contrast, Halpern and Black (2) have attributed the increase in cortical after-discharge duration following gallamine to a central action of this agent. However, as no increase in duration occurs following gallamine in an *encéphalé isolé* preparation (3) the effect of this agent would appear to be mediated from a more peripheral site(s).

As dimethyltubocurarine also blocks muscle spindles (8) one would expect an increase in duration following paralysis with this agent if the above "peripheral" hypothesis is correct. Such an increase was demonstrated in this report.

However, central effects of tubocurarine have been reported by several investigators (*cf.* 9–15). While there seems to be little doubt that tubocurarine exerts a central effect when applied directly to the brain (*cf.* 9, 10), conflicting reports as to central effects following intravenous injection have been presented. Some investigators (*cf.* 11–13) have found no changes in the CNS following administration of the drug while others (*cf.* 9, 14, 15) have reported various effects, primarily of a stimulant nature.

Thus, the effect of dimethyltubocurarine on cortical after-discharge duration cannot, at this time, be stated with certainty to be of either peripheral or central origin. It is obvious that further definitive work is necessary to fully describe the mechanisms whereby the neuromuscular blocking agents affect cortical after-discharge duration.

TABLE I—EFFECT OF PARALYZATION WITH DIMETHYLTUBOCURARINE IODIDE ON CORTICAL AFTER-DISCHARGE DURATION[a]

	Control[b]	Paralyzed
Mean	60	72[c]
SE	4.5	8.0

[a] Values are duration, in sec. [b] Trial immediately preceding that in which animal was paralyzed. [c] Significantly different from control; Student's t, paired comparison, $p < 0.05$.

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Keyphrases

Dimethyltubocurarine iodide
Paralyzation—dimethyltubocurarine
Cortical after-discharge duration—induced paralysis
EEG monitoring—after-discharge duration