AMITRIPTYLINE (ELAVIL): A SEDATING ANTIDEPRESSANT WITH PRESSOR ACTIVITY FOR PREOPERATIVE MEDICATION*

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AMITRIPTYLINE HYDROCHLORIDE (Elavil), a dibenzo-cyclo-heptadiene derivative is an antidepressant with a tranquillizing influence upon the central nervous system. The drug has antihistaminic, anticonvulsive, and mild anticholinergic properties,[10] and it has no apparent influence upon the brain serotonin content.[1–8, 10, 14–17]

In view of these effects, amitriptyline was evaluated as a premedicant for surgical patients prior to anaesthesia, to allay apprehension without causing undesirable side-effects.

METHOD

A total of 40 surgical patients, from 21 to 72 years of age, without apparent cardiovascular, respiratory, or neurological disease, was divided into three groups.

Group I. Eighteen patients were monitored with the Free-Operant Behaviour Technique before, during, and after the administration of amitriptyline (0.33 mg./kg.) intravenously.

Group II. Eighteen patients were monitored with the Free-Operant Behaviour Technique before, during, and after the administration of halothane anaesthesia; nine of these patients were not premedicated, nine received amitriptyline (0.33 mg./kg.) intravenously before anaesthesia.

Group III. Eleven patients had the arterial blood pressure and heart rate continuously monitored before and after the administration of amitriptyline (0.33 mg./kg. intravenously.

Free-Operant Behaviour—Definition: The term "operant" indicates that a subject operates a lever, switch, or similar device and is promptly "rewarded" or "reinforced" by the presentation of a rewarding or the withdrawal of an aversive event. The rate of occurrence of the response is the primary datum (Fig. 1).

By means of an audiometer, a high-pitched, loud, and intermittent tone (aversive event) is produced and transmitted to the patient via earphones. The patient can decrease or eliminate the sound (reward, reinforcement) by repeatedly closing thumb and finger electrical contacts on a rubber glove. These contacts are wired to the sound apparatus and by means of a servo-system, the

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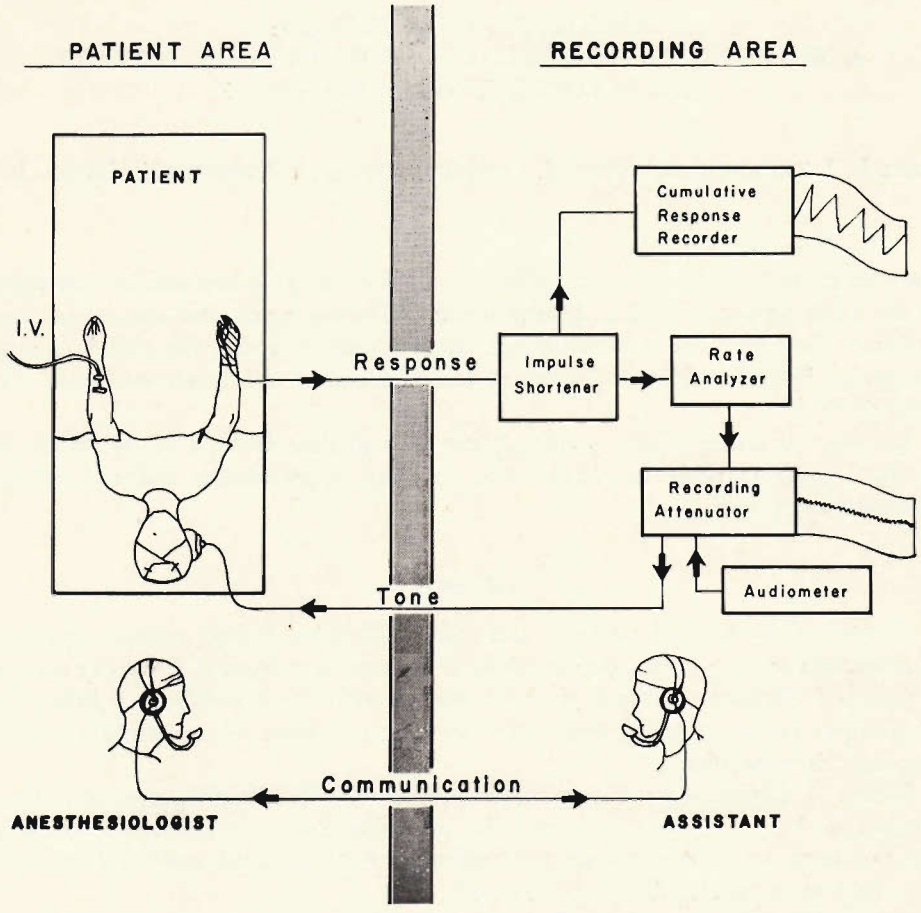

FIGURE 1. Schematic diagram of Free-Operant Behaviour Apparatus used for the study of amitriptyline.

intensity of sound varies with the frequency of thumb and finger contact. The rate of touching the thumb to the finger is recorded on paper and provides the primary response datum from the patient (Fig. 2). It was found to be objective and sensitive for any degree of sedation.[11–13]

Each subject was brought to the anaesthesia area without medication one and one-half hours before the operation. The control tracings of cumulative responses by means of the Free-Operant Behaviour Technique were run for 40 minutes. Following the initial observations, amitriptyline (0.33 mg./kg.) was administered intravenously through a three-way stopcock connected to a venotube previously inserted in an antecubital vein. In group I, the Free-Operant Behaviour was recorded for a period of two hours after the administration of the drug and before induction of anaesthesia. In group II the observations were carried out to three hours after cessation of anaesthesia. In group III the blood pressure was continuously recorded on a Sanborn recorder, using an intra-arterial polyethylene

catheter connected to a Statham transducer (P23Db). The Riva Rocci method was also employed and was read by the same experimenter on all patients.

The heart rate was determined by means of either a Telecor pulse monitor or lead II of the electrocardiogram. Mean arterial pressure was calculated by using the conventional formula.

Control readings were taken for 30 minutes after the blood pressure and heart rate were allowed to stabilize. Then amitriptyline (0.33 mg./kg.) was administered intravenously, and the two parameters were monitored for 45 minutes.

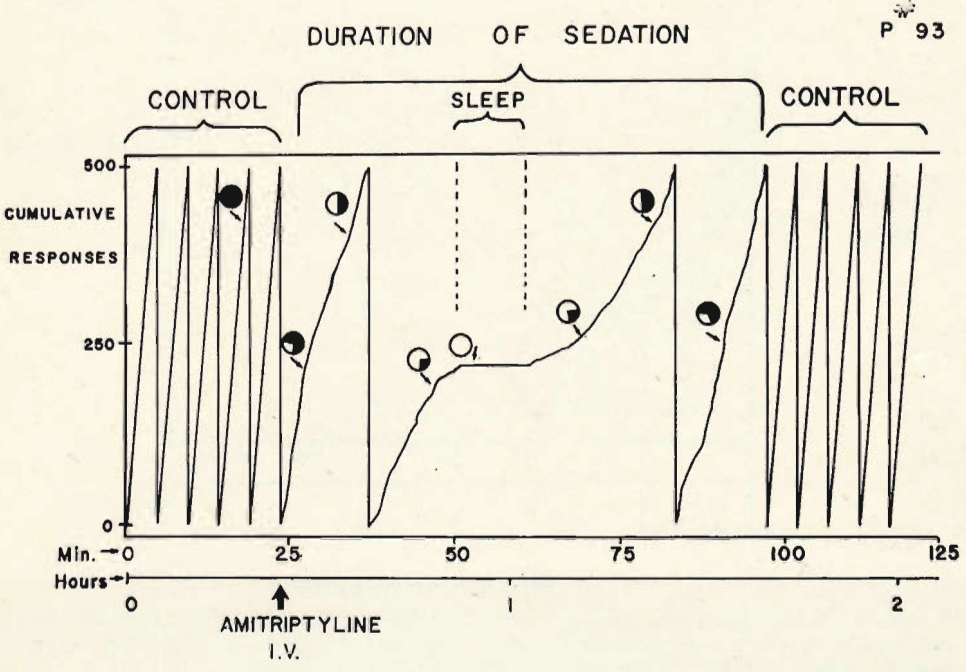

FIGURE 2. A cumulative response record (case 93) with a control rate of 110 responses per minute (indicated by filled circle). Three minutes after injection of amitriptyline the response rate is reduced to three-quarters of the control rate as shown by the three-quarters filled circle, etc. Twenty-five minutes after the injection of the drug, the rate is completely suppressed (sleep), as shown by the open circle. Sedation is shown to last for 60 minutes and recovery takes place in a reverse pattern.

RESULTS

Group I. Nine of the eleven patients showed a decrease in rate of response of the Free-Operant Behaviour after intravenous administration of amitriptyline. The mean latency time was 3.5 minutes (range, 1 to 25 minutes), and the pattern of onset and recovery from sedation for each patient is shown in Figure 3. Eight patients reached the stage of complete suppression (sleep) in an average time of 28 minutes (range, 11 to 50 minutes). This period of complete suppression lasted for a mean time of 10 minutes (range, 4 to 25 minutes). Five patients were permitted to recover fully (as seen by the return to control response rate) with

mean time of 68 minutes (range, 38 to 99 minutes). Four patients recovered partially. Two of the eleven patients showed no change in rate of response.

Group II. The mean Anaesthesia Administration Time (AAT) was 199 minutes (65 to 500 minutes) for the non-premedicated patients and 138 minutes (55 to 275 minutes) for those premedicated with amitriptyline. The duration of complete recovery (Anaesthesia Recovery Time Full—ARTF) was 65 minutes (5 to 156 minutes) for the non-premedicated patients and 55 minutes (16 to 96 minutes) for those premedicated with amitriptyline.

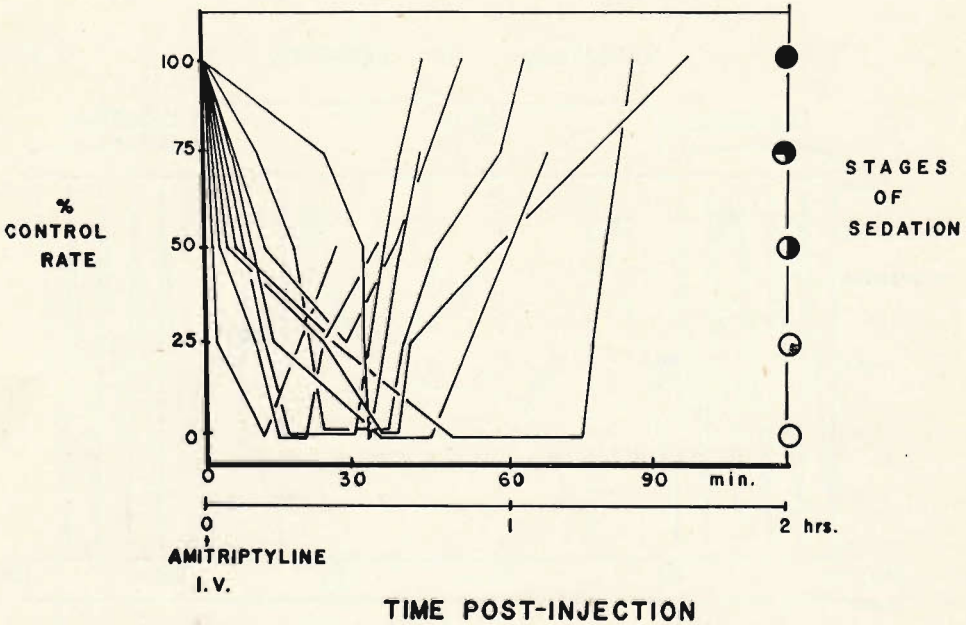

FIGURE 3. The degree of behaviour sedation following injection of amitriptyline (0.33 mg./kg.) is shown by the percentage change of the control rate and identified by the open, partially closed, or closed circles and is plotted against time of change.

TABLE I*

	Halothane without premedicant (9 patients)		Halothane with amitriptyline as a premedicant (9 patients)	
	Mean	Range	Mean	Range
AAT	199	65–500	138	55–275
ARTI	19	1–68	17	1–48
ARTQ	27	2–75	29	11–71
ARTH	43	2–96	40	12–72
ARTF	65	5–156	55	16–96
TAT	264	95–564	179	71–332

*AAT = Anaesthesia administration time.
ARTI = Anaesthesia recovery time, initial.
ARTQ = Anaesthesia recovery time, quarter.
ARTH = Anaesthesia recovery time, half.
ARTF = Anaesthesia recovery time, full.
TAT = Total anaesthesia time.

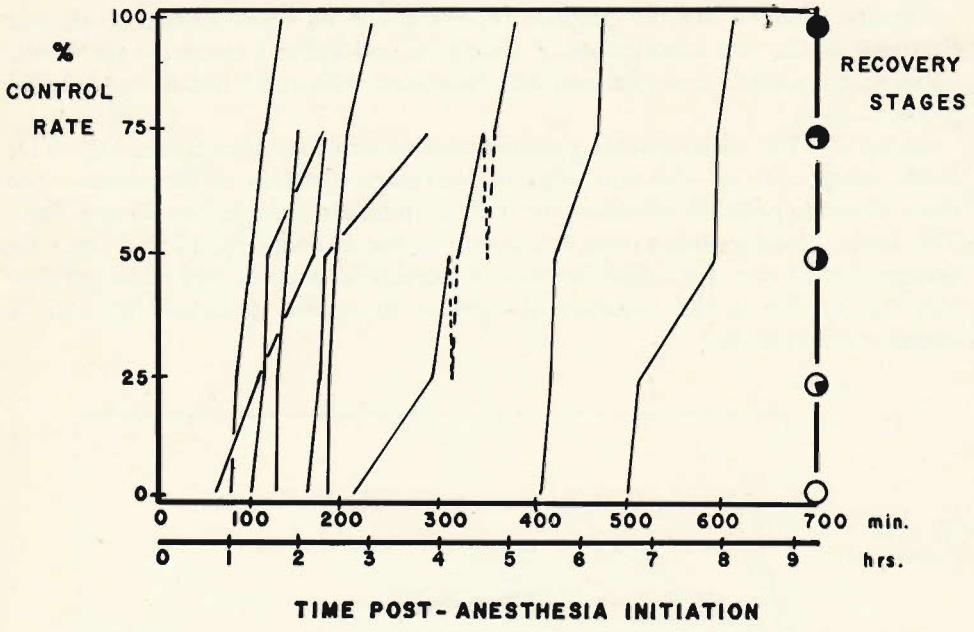

FIGURE 4. Post-anaesthesia recovery time and duration of recovery period following the administration of halothane anaesthesia without premedication plotted against percentage of control rate and stages of recovery (circles). One patient showed an episode of reanaesthetization (dotted line).

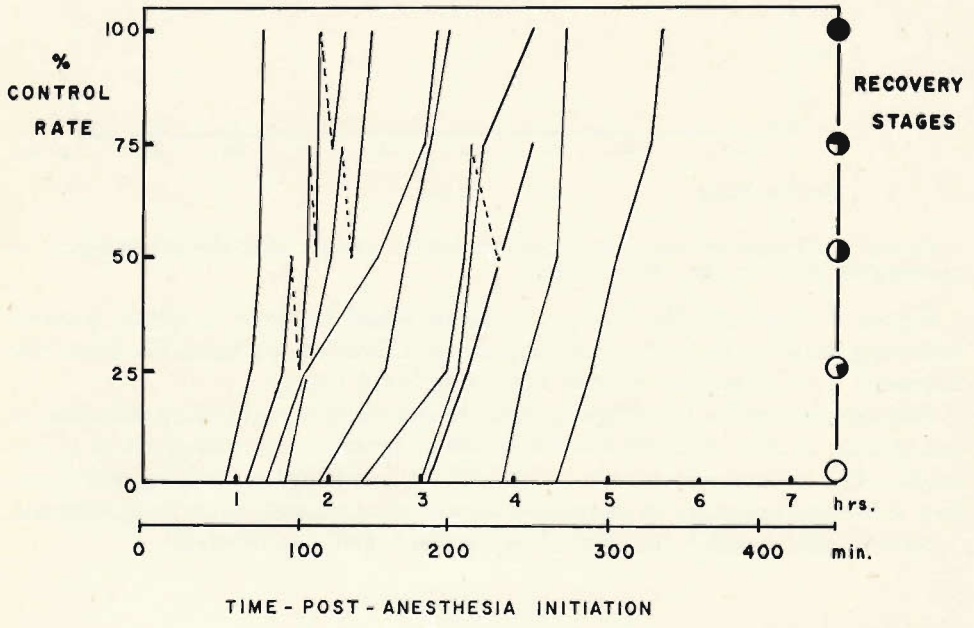

FIGURE 5. Post-anaesthesia recovery time and the duration of recovery period following amitriptyline and halothane anaesthesia plotted against the percentage of control rate and stages of recovery.

Figures 4 and 5 are the graphic representation of Free-Operant Behaviour Recovery of the two subdivisions of Group II, and Table I compares the results obtained on patients anaesthetized with halothane with and without amitriptyline premedication.

Group III. The mean systolic pressure was increased by 18 ± 2 mm. Hg (S.D., ±6.6; range, +5 to +30 mm. Hg) with average duration of 25 minutes. The mean diastolic pressure increased by 10 ± 2.7 mm. Hg (range, 0 to 25 mm. Hg). The mean blood pressure was increased on the average by 13 ± 2 mm. Hg (range, 2 to 27 mm. Hg). The duration of increase in diastolic and mean pressure was comparable to the duration of increase in systolic pressure (23 and 25 minutes, respectively).

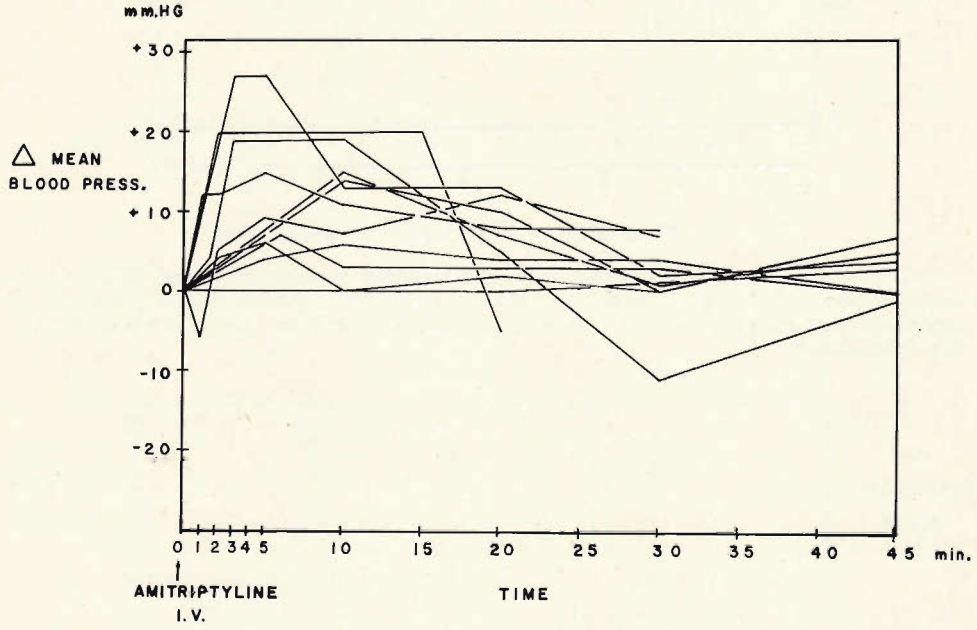

FIGURE 6. Changes in mean blood pressure for 11 patients after the administration of amitriptyline (0.33 mg./kg.) intravenously.

Figure 6 represents the changes in mean blood pressure in eleven patients following intravenous amitriptyline injections without anaesthesia. The heart rate increased 6 ± 2 beats per minute, not a significant change.

Side-effects. Profuse pharyngolaryngeal secretions occurred during induction of anaesthesia or after tracheal intubation when amitriptyline was given as a premedicant. It became obvious that it exerted no antisialagogue activity and therefore it became necessary to administer atropine immediately prior to anaesthesia.

Nausea and vomiting occurred in one patient of the entire series.

DISCUSSION

One of the main purposes of pre-anaesthetic medication is to protect the patient against the so-called psychological trauma of undergoing surgery. Other goals

may vary from the production of sedation or analgesia, the relief of apprehension or anxiety, and the facilitation of induction of anaesthesia.

Signs of apprehension may occur in patients who have received large doses of barbiturates, narcotics, or tranquillizers. Sedation resulting in deep sleep before anaesthesia is usually associated with undesirable side-effects, i.e., hypotension, respiratory depression, and nausea or emesis.[9,16]

The Free-Operant Behaviour Technique (FOBT) described in this report has been shown to be extremely sensitive to explore the scale of sleep-arousal state in man.[11–13] After a control rate of response has been obtained, any decrement of that rate is interpreted as sedation and any increment is interpreted as arousal.

If a comparison is made between clinical intermittent probing (painful stimulation, talking to patient, etc.) and the FOBT applied in this investigation the following facts emerge immediately. The stimulation used to probe the state of a patient by the common clinical means is not calibrated in intensity and is intermittent in nature, whereas the FOBT uses a continuous stimulation of *constant and calibrated intensity*. The intermittent clinical probing, because of its intermittent nature, cannot be applied without disturbing the sleep-arousal state of the patient. The Free-Operant Behaviour Technique uses a constant and continuous stimulus and reflects the level of the sleep-arousal state as related to the control level. It provides the opportunity of quantitating responses to analeptics. An above-normal response rate is interpreted as an excitement state or above-arousal state. This latter phenomenon has not been seen with amitriptyline.

A double-blind study was believed to be unnecessary owing to the sensitivity of the FOBT method, and most of all because the patients were completely unaware that a drug was being administered to them. Each patient served as his own control.

The results obtained with the FOBT provide evidence of the sedative effect of intravenously administered amitriptyline and that the same degree of sedation by means of an intramuscular injection requires a larger dose. The mean anaesthesia recovery time was slightly shorter in patients premedicated with amitriptyline. However, it cannot be concluded that this drug shortens the duration of recovery after halothane anaesthesia because the anaesthesia administration time was also shorter in the group of patients premedicated with amitriptyline. It has been shown previously that the duration of recovery from halothane is a function of the duration of administration[11] and that amitriptyline does not alter the duration of recovery after halothane anaesthesia.

The sedative action and the mild pressor effect of amitriptyline are functions that permit adequate preoperative sedation without circulatory depression. Other significant effects are the mood-elevating properties which relieve apprehension. In view of these effective functions, amitriptyline deserves further extensive clinical trial as a pre-anaesthetic agent.

Summary

Amitriptyline (Elavil) was evaluated as a premedicant sedative and its effect upon recovery time following halothane anaesthesia was objectively quantitated

in man by means of the Free-Operant Behaviour Technique. Amitriptyline exerted a specific degree of sedation without prolonging recovery time following halothane anaesthesia. Following the intravenous administration of amitriptyline, the arterial blood pressure either was slightly elevated or was maintained at the resting levels.

RÉSUMÉ

Amitriptyline (Elavil) a été évalué pour son emploi comme médication pré-anesthésique, et son action sur le temps de recouvrement après anesthésie à l'halothane a été objectivement mesuré chez l'homme au moyen de la technique de comportement-opérant-libre (Free-Operant Behaviour Technique). L'amitriptyline produit une sédation qui ne fait aucun doute, sans pour cela prolonger le temps de recouvrement de l'halothane. Suivant l'administration intraveineuse d'amitriptyline, la pression artérielle était ou bien légèrement élevée ou était maintenue au niveau de control.

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