Development History of the TES Waveform Parameters in the Nexalin Technology

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Optimal Characteristics of Impulse Current and Frequency for Transcranial Electrical Stimulation (TES).

Introduction

Because analgesia was one of the most important focuses of the direct stimulation of the antinociceptive system, the reduction of pain was used as an indicator of its activation during and after TES. Quantitative estimation of acute pain level and pain tolerance and its reduction were performed in screening experiments with different animal species (rat, mice, rabbit, turtle) and volunteers by means of registration of emotional, autonomic, motor escape reactions, and verbal report. The optimal characteristics of impulse current were found, and relations "effect - frequency of impulses" and "effect - impulse width" resembled rather sharp quasi-resonance curve (Fig.1). As revealed in cross-over experiments the regimen elaborated is much more effective than one described by Limoge [1].

The main experimental series for selection of electroanesthesia parameters was carried out in rabbits to which electric stimuli were delivered through subcutaneous needle electrodes (cathode was placed at the forehead and two anode electrodes were inserted behind the ears). Efficiency of the chosen electroanesthesia parameters was subsequently controlled in the course of experiments in cats and dogs into which subcutaneous lamellar electrodes had been grafted in advance. Effect was assessed the same way as in rabbits, while analgesia was evaluated according to the change in motor response to mechanical nociceptive stimulation.

The experimental estimation of the analgesic effect manifestation was carried out in tests performed on different species of animals using the same quantitative procedures utilized when determining the analgesic effect of pharmacological agents.

The procedures are based on the measurement of time from the beginning of the pain stimuli until the appearance of motor response of avoidance or measurement of the intensity of autonomic response (e.g. increase of arterial pressure) at standard pain stimuli. The use of quantitative methods enabled comparisons with sufficient precision to identify the analgesic effects of various components to evaluate the optimal parametric values.

To define the parameters for pronounced analgesia, extensive screening studies of electrical components was performed. During these studies the impulse frequency, the duration of impulses, and the combination of pulsed and direct currents in various proportions were all studied.

Experimental Series to Determine TES Frequency and Impulse Duration/Direct Current.[2]

First Experimental Series: The effects of rectangular impulses within the frequency range of 50-Hz to 3,000-Hz, impulse duration from 0.1 to 1-ms, with gaps up to 0.5-ms and average current from 0.4-mA to 1-mA, were studied. Frequency was increased in steps of 10-Hz to 100-Hz and of 250-Hz to 3-kHz. Impulse duration steps were 0.1-ms and current steps were 0.05-mA. In the course of experiment, the complications which had been reported by other authors occurred in rabbits, i.e., arterial hypertension, tachycardia, tachypnea, and cramps which often caused animal death. At the same time, no electroanesthesia was observed.

Second Experimental Series: The delivery of similar impulse durations from 0.1 to 1-ms was preceded by direct current supplied through the same electrodes. Direct current was delivered from 0.5-mA to 2-mA in 0.5-mA steps. The first sign of anesthesia was observed, in some cases, when the direct current
component of 1 mA was combined with an impulse duration of 1-ms at a frequency of 80-Hz, with an average current of 0.4-mA to 0.55-mA.

Increasing the direct current value to 2-mA while maintaining the impulse duration of 1-ms at a frequency of 80-Hz with the average impulse current between 0.8-mA to 1.0-mA above the direct current, electroanesthesia (EA) developed in 68% of cases, in 20% of which cramps occurred 10 to 12-minutes after the development of EA. In the remaining 32% of cases there was no EA, and the primary effect was represented by cramps. At the same time, isolated action of direct current with similar characteristics did not result in any perceivable response, with the exception of alert reaction at the moment of switching-on. This could be avoided by gradually increasing direct current supply to the required level within 2 to 3-minutes.

These findings have clearly demonstrated that complications occurred; however, in many cases, electroanesthesia could be achieved with the combined effects of direct and impulse currents at the ratio of 2:1, impulse frequency of 80-Hz, and impulse duration time of 1-ms. It was noted that these current and duration characteristics were the highest ones obtainable using the industrially produced “Electronarcon-1” apparatus.

**Third Experimental Series:** The first evaluation of this series was to vary the impulse frequency starting at 80-Hz in steps of +1 Hz and -1 Hz. These frequency variations were then combined with an increase in the combined current values while maintaining the same direct current/average impulse current ratio of 2:1, and increasing the impulse duration beyond the 1-ms value. The results of this experimental series indicated that with the direct current component of 4-mA to 6-mA and the average impulse current between 2-mA to 3-mA above the direct current (2:1 ratio) with impulse durations of 3-ms to 5-ms, the greatest EA developed at frequencies of 77 and 78 Hz without any complications virtually in all cases.

Final current density that measured 3 to 5-mA/cm² resulted in complete disappearance of motor pain response to nociceptive skin stimulation and suppression of arterial blood pressure response to nerve stimulation were characteristic of EA condition in rabbits. At the same time, spontaneous breath was maintained, the rhythm of which slowed down, while arterial blood pressure remained unchanged. After switching-off the electrostimulation, no anesthetic after effects were observed in rabbits, and their motor activity and pain responsiveness were restored.

The anesthetic effect could be reproduced in the course of repeated electrostimulations. Similar results were obtained in cats and dogs with the same current parameters. Repeated severe pain stimulations of animals during EA did not result in any defense reflexes, which suggested the development of a kind of amnesia.

**Summary**

The combined application of direct and impulse currents provided a stable and reproducible condition of EA in laboratory animals (rabbits, cats, and dogs), which was characterized by the presence of spontaneous breathing and the stability of arterial blood pressure.
Transcranial electroanalgesia as a component of general anesthesia and method of treatment for pain syndromes’
Abstract of PhD dissertation by Yakov Katsnelson MD - PhD, was published Leningrad 1985

Experiment Using Human Subjects

Elaborated type of stimulation increased consumption of [3H]-deoxyglucose (increase of carbohydrate metabolism of neurons correlates with increase of neuronal activity) in periaqueductal grey and decreased it in relay nuclei, which participated in the ascending nociceptive impulses and in somatomotor cortex. [3]

Fig. 2. Plasma beta-endorphin level after TES with different frequencies in three groups of volunteers after one 30 min TES session. C – Control level.

Neurotransmitter mechanisms involved in TES effects. TES with elaborated regimen activated endorphinergic and serotoninergic mechanisms. The increase of β-endorphin concentrations in the brain stem, spinal dorsal horns, in Cerebral Spinal Fluid (CSF), and met-enkephalins - in CSF were demonstrated. The maximal β-endorphin release coincided with the optimal frequency and impulse
duration of the regimen of transcranial electrostimulation (Fig.2). In correspondence with CSF opioid concentration growth, the decrease of substance P in CSF was observed and elicited pain relief. Serotonin (5-HT) level in CSF was also increased. The effects of the TES were blocked by naloxone (opioid receptors blockers).

Discussion and Conclusions

The data devoted to elaborate the critical regime of TES based on the contemporary physiological and neurochemical data on the brain system showed effectiveness of TES in a very narrow set of electrical parameters of stimulation including the impulse frequencies of 77-78-Hz.

References

