

# PHARMACOLOGY

## APPRAISAL OF THE TRANQUILIZING ACTION OF PHENAZEPAM AND MEBICAR BY THE AVERAGED CORTICAL EVOKED POTENTIALS METHOD DURING PERCEPTION OF EMOTIONALLY MEANINGFUL WORDS

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One of the principal psychophysiological mechanisms of the action of tranquilizers is their effect on perception and information processing [1, 4]. It has been shown [7, 8], that averaged evoked potentials (AEP) in the cerebral cortex of patients with pathological emotional reactivity differ depending on whether emotionally neutral or emotionally meaningful words, associated with some object in the experience of the persons concerned, are presented.

This paper describes an attempt to appraise objectively the tranquilizing effect of drugs by analysis of the time course of AEP during perception of emotionally meaningful words and to determine whether tranquilizers may have a selective action on the perception and processing of emotionally meaningful information.

### EXPERIMENTAL METHOD

Emotionally meaningful or emotionally neutral words were displayed on an electroluminescent screen located 180 cm from the eyes of the semirecumbent subject, with his eyes open, in a soundproof, screened chamber. The letters measured 32 × 25 mm, the duration of exposure was 100 msec, and the intensity of illumination 0.1 lx. Cortical electrical activity was derived by a monopolar technique. The active electrode was located 2 cm laterally and superiorly to the external occipital protuberance, and the reference electrode was secured to the mastoid process. Evoked potentials (EP) were averaged and processed on an apparatus based on a Nova 2/10 minicomputer (USA). Electrical activity from the outputs of the electroencephalograph (Nihon Kohden, Japan) was led to the inputs of an analog-to-digital converter (Datel Systems 256) of the computer system. Programs were devised by engineer S. A. Pogrebinskii.

The subjects were 10 men admitted to hospital for treatment of psychoemotional disorders (psychopathia, acute psychopathic decompensation). The response of such patients to an emotional stimulus does not decay during repeated presentation [8]. Emotionally meaningful words were chosen individually on the recommendation of the psychiatrist in charge of the case. EPs to emotionally meaningful and emotionally neutral words were averaged separately in groups of 50. AEP were recorded 3 times in the course of 5 days. Each investigation consisted of two parts: 1) EPs to presentation of two emotionally neutral words in random order were averaged, 2) EPs to presentation of two words in random order, one emotionally neutral, the other emotionally meaningful, were averaged. On the 2nd day of the investigation AEP were recorded by the program described above 40 min after enteral administration of tranquilizers (phenazepam,\* in a dose of 1 mg, mebicar,† in doses

\*7-Bromo-1,3-dihydro-5-(2'-chlorophenyl)-2H-1,4-benzodiazepin-2-one.  
†2,4,6,8-Tetramethyl-2,4,6,8-tetra-azobicyclo-(3,3,0)-octadione-3,7.

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TABLE 1. Changes in Amplitude and Temporal Parameters of P300 Wave of AEP to Emotionally Neutral (I) and Emotionally Meaningful (II) Words after Administration of Tranquilizers (M + m)

Characteristics of P300 wave	Control		After tranquilizer		After placebo	
	I	II	I	II	I	II
<b>Phenazepam, 1 mg</b>						
Latent period, msec	272±11	252±12*	259±13	274±16	278±14	261±16
Amplitude, $\mu V$	7,2±2,1	10,4±1,7*	7,5±1,0	6,8±1,3	7,3±1,4	8,8±1,2*
<b>Mebicar, 1200 mg</b>						
Latent period, msec	280±16	253±15*	267±14	267±14	260±19	250±16
Amplitude, $\mu A$	5,7±0,9	7,9±0,7*	7,6±1,8	6,5±1,9	7,7±1,0	9,1±1,7*

\*P < 0.05 (Student's paired t test).

of 600 and 1200 mg). On the 3rd day a control investigation was undertaken after administration of a placebo. All measurements were made in the first half of the day. The latent period and amplitude (peak-peak) of the P300 wave of the AEP were calculated. The results of the investigations were subjected to statistical analysis and the significance of differences was determined by Student's paired t test.

#### EXPERIMENTAL RESULTS

On presentation of emotionally meaningful words characteristic changes were observed in the amplitude and latent period of the P300 wave compared with AEP to emotionally neutral words. On average for all investigations the amplitude of the P300 wave increased from  $6.5 \pm 1.5 \mu V$  (emotionally neutral words) to  $9.2 \pm 1.2 \mu V$  (emotionally meaningful words). Changes were significant at the  $P < 0.05$  level. The latent period of the P300 wave was shortened from  $276 \pm 13$  to  $252 \pm 12$  msec respectively ( $P < 0.05$ ). Typical changes in AEP in one subject are illustrated in Fig. 1.

Subjectively, phenazepam (1 mg) induced sleepiness and apathy. After administration of the drug the amplitude of the P300 wave of the AEP to emotionally meaningful words decreased (from  $10.4 \pm 1.7$  to  $6.8 \pm 1.3 \mu V$ ,  $P < 0.05$ ). The latent period of the wave increased from  $252 \pm 12$  to  $274 \pm 16$  msec ( $P < 0.05$ ). Equalization of the amplitude and temporal parameters of the P300 wave of the AEP to emotionally meaningful and emotionally neutral words took place (Table 1). The experimental [5] and clinical [9] data are evidence that phenazepam (a benzodiazepine derivative), in the dose used, had a marked tranquilizing effect. Since the decrease in amplitude and increase in latent period of the P300 wave of the AEP after administration of phenazepam were observed only on presentation of emotionally meaningful stimuli, this effect can be interpreted as the result of a change in appraisal of the emotional significance of the stimulus.

After administration of mebicar in doses of 600 and 1200 mg, the patients were not subjectively aware of any change in the level of wakefulness. Administration of mebicar in a dose of 600 mg did not lead to any significant changes in the amplitude and temporal parameters of the P300 wave of the AEP on presentation of emotionally meaningful words. A decrease in the amplitude and temporal parameters of the P300 wave of the AEP to emotionally meaningful words (from  $7.9 \pm 0.7$  to  $6.5 \pm 1.9 \mu V$ ,  $P < 0.05$ ) and an increase in the latent period of the peak of the wave (from  $253 \pm 15$  to  $267 \pm 14$  msec) were observed. Mebicar (a bicyclic bis-urea derivative), as the results of experimental [3] and clinical investigations [1] have shown, is effective in neurotic states. However, the results are evidence that the doses recommended by the instruction are not optimal. Objective changes in the amplitude and temporal parameters of the P300 wave of the AEP during presentation of emotionally meaningful stimuli took place after administration of higher doses of this drug (1200 mg).

Restoration of the original relationships of the P300 wave of the AEP to emotionally meaningful and emotionally neutral words, observed in the control, also was found 1 day after administration of the tranquilizers. This is evidence of the specificity of the tranquilizing action of the drugs.

In the doses used, neither phenazepam nor mebicar had any effect on the amplitude or latent period of the P300 wave of the AEP to presentation of emotionally neutral words.

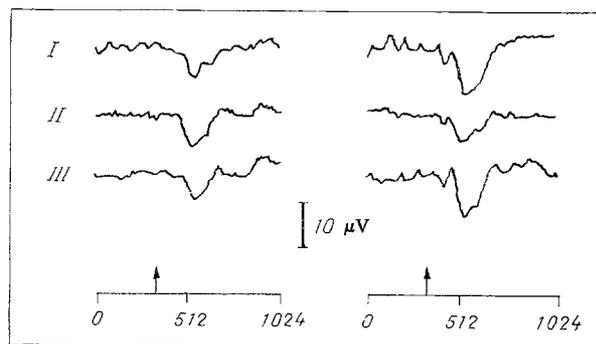


Fig. 1. Effect of phenazepam on AEP on presentation of emotionally neutral (left) and emotionally meaningful (right) words. I) Control; II) after administration of 1 mg phenazepam; III) after administration of placebo. Arrow indicates beginning of stimulation.

These findings indicate indirectly that the tranquilizers did not affect the genesis of cortical EP.

The results of these investigations thus showed that the tranquilizers induce a selective change in the appraisal of emotionally meaningful stimuli. The change in the amplitude and temporal parameter of the P300 wave of the AEP during presentation of emotionally meaningful words correlates with a change in the autonomic parameters (heart rate, psychogalvanic reflex) and is an electrophysiological manifestation of the emotional response [7]. Changes in the P300 wave of the AEP on presentation of emotionally meaningful words are due to an additional increase in excitability of cortical neurons on account of corticofugal activation from structures of the limbic system concerned in the appraisal of the emotional significance of a stimulus [6, 7]. The action of tranquilizers in an emotional stress situation consists essentially of depression only of the additional activation connected with evaluation of the stimulus as emotionally meaningful, without any disturbance (within a definite dose range) of the processes of stimulus appraisal, for information on the physical properties of the stimulus is undisturbed.

The method of recording AEP during presentation of emotionally meaningful words to patients with pathology of the psychoemotional sphere can be regarded as a convenient criterion in the choice of optimal doses of tranquilizers in the stage of clinical study of new drugs of this class.

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