THE INFLUENCE OF PHENOTHIAZINE DERIVATIVES ON THE ACTION OF ANALGESICS

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The literature contains several articles on the use of phenothiazine derivatives in combination with various medicinal substances: analgesics [5], somnifacients and narcotics [1, 3] muscle relaxants and anesthetics [2, 4]. However, opinion on the interaction of neuroplegic with analgesic agents is divided. Some authors note that potentialization occurs when phenothiazine derivatives are used in combination with analgesics [5, 8], while others deny this.

In order to determine how phenothiazine derivatives intereact with analgesics, we studied various combinations of Mepazine [10-(1'-methylpiperidyl-3-methyl) phenothiazine acetate; Pacatal], Aminazine [chlorpromazine] and Propazine [10-(2'-dimethylaminopropyl) phenothiazine hydrochloride; promazine] with morphine, Promedole [4-phenyl-4-propoxy-1,2,5-trimethyl-piperidine hydrochloride; Trimeperidine] and Phenadone [methadone].

The experiments were performed on white rats by determining the absolute threshold of the animals to faradic current. Stimulation was applied by needle electrodes inserted under the skin of the tail. Since our observations have given us excellent reasons to believe that a squeak from these animals is a sign of pain, the squeak was used as the index of the reaction.

Statistical processing was carried out in order to determine the authenticity of the difference between the arithmetic means of the control (maximal effect of the individual ingredients in double doses) and the experiment (maximal effect of the pharmacological combination).*

Effect of Mepazine combined with analgesics: For combination with analgesics, Mepazine was used in a dose of 50 mg/kg; neither this dose nor double its amount produced an analgesic effect (Fig. 1). The administration of 5 mg/kg morphine caused a marked decrease in the pain sensitivity of the rats. This effect was considerably enhanced on a background of Mepazine administration. The mixture of the two substances had an effect which was not only stronger than the sum of the effects of its ingredients, but was also stronger than that of double the morphine dose.

The most effective combination was Mepazine and Promedole. Promedole was used in a dose of 2 mg/kg in this combination. The efficiency of Promedole was more than quadrupled after the preliminary administration of Mepazine; this combination also produced a stronger analgesic effect than double the Promedole dose. The absolute threshold became over 10 times higher in a few animals.

We tested two combinations of Phenadone and Mepazine. The first combination used a 1.25 mg/kg dose of Phenadone; the second, double this dose. The absolute pain threshold of the animals increased 4.5 times with the use of the first combination, but only 2.5 times with the second combination using the double Phenadone dose. The intensification of the analgesic effect obtained with the use of the second combination was less significant.

* The authenticity criterion was D = 0.05.

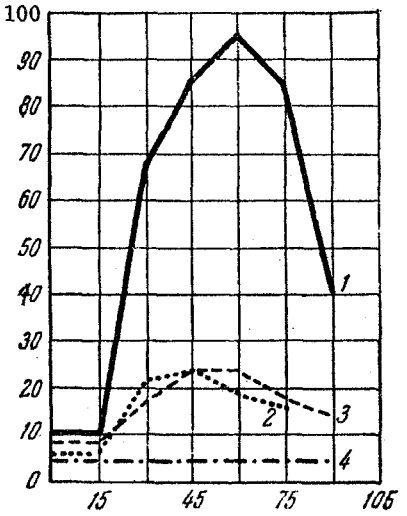

Fig. 1. Effect of Mepazine-Promedole combination on the pain sensitivity of white rats. Change in pain sensitivity after administration of: 3) 2 mg/kg Promedole; 2) 4 mg/kg Promedole; 4) 50 mg/kg Mepazine; 1) 50 mg/kg Mepazine and 2 mg/kg Promedole. Ordinate axis: absolute threshold of electric stimulation (in volts); abscissa axis: time of experiment (in minutes).

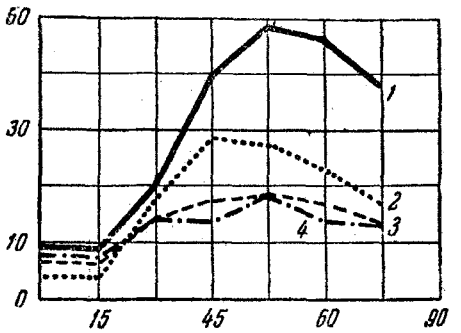

Fig. 2. Effect of simultaneous use of Aminazine and morphine on the pain sensitivity of white rats. Change in pain sensitivity after administration of: 3) 5 mg/kg morphine; 4) 5 mg/kg Aminazine; 2) 10 mg/kg morphine; 1) 5 mg/kg Aminazine and 5 mg/kg morphine. Ordinate axis: absolute threshold of electric stimulation (in volts); abscissa axis: time of experiment (in minutes).

The effect of the Mepazine-Phenadone combination was three times as strong as that of Phenadone alone, but in comparison with the efficiency of the latter preparation in a dose of 5 mg/kg, the difference was statistically unreliable.

Combined effect of Aminazine and analgesics: In a dose of 5 mg/kg, Aminazine caused a substantial decrease in the pain sensitivity, approximately equal to that effected by a like amount of morphine. A combination of these preparations was even more effective (Fig. 2). The effect of this combination was not only stronger than that of the sum of its ingredients, but also stronger than the effect of twice the dose of its most active component, morphine. The most active combination was found to be that with Promedole, as in the experiments with Mepazine. Promedole was used in a dose of 2 mg/kg in the combination. After the administration of this mixture, the pain sensitivity of the animals decreased to less than 1/6 the original. The effect obtained from a combination of the two preparations was 1.5 times stronger than the analgesic effect of twice the dose of Promedole.

A dose of 2.5 mg/kg Phenadone was used in combination with Aminazine. This combination reduced the sensitivity to painful stimulation 7.4 times. The effect of this mixture was considerably stronger both than the sum of its ingredients' effects and than the effect of double the Phenadone dose.

Combined effect of Propazine and analgesics: A 10 mg/kg dose of Propazine caused a sharp decrease in the pain sensitivity of the rats, equal to that caused by 5 mg/kg morphine (Fig. 3). After the preliminary administration of Propazine in this dose, morphine, Promedole and Phenadone (used respectively in doses of 5, 2 and 2.5 mg/kg) produced an analgesic effect considerably stronger than that of double the dose of each analgesic agent, used alone.

An especially enhanced effect was produced by the combinations with Promedole and morphine, while the combination with Phenadone was less active.

Narcotic effect of phenothiazine derivatives combined with analgesics: The use of neuroplegic agents in combination with analgesics also exhibited reciprocal enhancement of effect in relation to the sleep phenomenon. When the analgesics were administered to mice, the development of the effect was not attended in any case by loss of the "righting reflexes" or by a passive dorsal position of the animals. In these experiments, Promedole, Phenadone and morphine were used respectively in doses of 10, 20 and 40 mg/kg intraperitoneally administered.

Experimental Results Showing the Analgesic Activity of Pharmacological Combinations and Their Components

Pharmacological agents (in mg/kg)	Number of observations	Threshold voltage after administration of preparations
Morphine, 5 mg/kg	18	18 ± 2.6
Morphine, 10 mg/kg	10	27 ± 4.3
Promedole, 2 mg/kg	11	132 ± 4.1
Promedole, 4 mg/kg	8	150 ± 3.3
Phenadone, 2.5 mg/kg	9	87 ± 2.6
Phenadone, 5 mg/kg	15	29 ± 5
Aminazine, 5 mg/kg	27	75 ± 1
Aminazine, 10 mg/kg	10	18 ± 0.08
Propazine, 10 mg/kg	32	16 ± 1.8
Propazine, 20 mg/kg	10	25 ± 2.4
Aminazine, 5 mg/kg + morphine, 5 mg/kg	16	42 ± 5.6
Aminazine, 5 mg/kg + Promedole, 2 mg/kg	16	78 ± 10.8
Aminazine, 5 mg/kg + Phenadone, 2.5 mg/kg	15	48 ± 10.6
Propazine, 10 mg/kg + morphine, 5 mg/kg	10	87 ± 15.4
Propazine, 10 mg/kg + Promedole, 2 mg/kg	9	87 ± 15.7
Propazine, 10 mg/kg + Phenadone, 2.5 mg/kg	14	56 ± 6
Mepazine, 50 mg/kg + morphine, 5 mg/kg	10	41 ± 9.7
Mepazine, 50 mg/kg + Promedole, 2 mg/kg	15	90 ± 13.8
Mepazine, 50 mg/kg + Phenadone, 1.25 mg/kg	10	26 ± 3.1
Mepazine, 50 mg/kg + Phenadone, 2.5 mg/kg	10	29 ± 4.7

With the use of 40 mg/kg Aminazine or of the same dose of Propazine, none of the animals remained in the dorsal position for long. As in the other experiments, the phenothiazine derivatives were injected subcutaneously into the animals. Not more than 0.6 ml of the solutions of the preparations was administered. In these experiments, not one (out of 20) animals was observed in the dorsal position after the administration of Propazine. One out of ten mice maintained the dorsal position for 15 minutes after the administration of Aminazine.

A somnifacient effect was induced by the aministration of 20 mg/kg Aminazine in combination with 5 mg/kg Promedole, 1.25 mg/kg Phenadone or 10 mg/kg morphine. All the experimental mice remained in the dorsal position. Aminazine used with morphine induced sleep lasting an average of 126 ± 16 minutes; with Promedole, the sleep lasted an average of 112 ± 13 minutes;and with Phenadone, 106 ± 10 minutes.

When the same doses of the analgesics were combined with 40 mg/kg Propazine, the somnifacient effect induced was shorter and less constant.

Propazine in combination with Phenadone, for example, induced sleep lasting an average of 54 ± 11 minutes in nine out of ten animals. The combinations with Promedole and morphine were less active. After the administration of Propazine combined with Promedole, the dorsal position was observed in four out of ten mice, and the effect lasted an average of 95 ± 20 minutes. The combined administration of Propazine and morphine caused a somnifacient effect in only three out of ten animals, lasting an average of 106 ± 43 minutes.

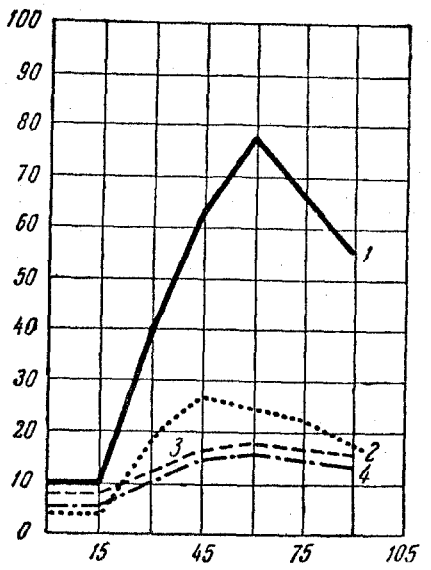

Fig. 3. Effect of Propazine-morphine combination on the pain sensitivity of white rats. Change in pain sensitivity after administration of: 3) 5 mg/kg morphine; 2) 10 mg/kg morphine; 4) 10 mg/kg Propazine; 1) 10 mg/kg Propazine and 5 mg/kg morphine. Ordinate axis: absolute threshold of electric stimulation (in volts); abscissa axis: time of experiment (in minutes).

Analogous results were observed in experiments conducted on rats, although larger doses of the analgesics were required in these experiments, and the effect was less constant. For example, the administration of 20 mg/kg Aminazine combined with 20 mg/kg morphine caused a lateral position lasting 27 ± 4.5 minutes in six out of ten rats. When the same dose of Aminazine was combined with 5 mg/kg Promedole, a somnifacient effect lasting 33 ± 5.6 minutes was observed in seven out of ten animals. Phenadone was found to be somewhat more active. The combination of 20 mg/kg Aminazine and 5 mg/kg Phenadone caused a condition of sleep lasting an average of 99 ± 4.5 minutes in all the animals.

The observations conducted have shown that an enhanced analgesic effect is obtained with the use of phenothiazine derivatives in combination with analgesics, although the effect is not equally enhanced by all the experimental combinations. For example, a combination of Mepazine and Phenadone (in a ratio of 1: 0.05) produced an only slightly enhanced effect which was no stronger than that obtained with the use of double the dose of the mixture's most active compound, Phenadone. It should be remembered, however, that Mepazine had no analgesic effect in either the dose used in the combination with the analgesic or in twice this dose.

In judging the efficiency of this mixture, therefore, the efficiency of the "most active" compound is no criterion, since only one of the preparations in this combination is active, i.e., Phenadone, and the increased activity observed can only indicate potentialization. In the other experiments, the difference between the activity of the pharmacological combinations and that of their ingredients (in double doses) was statistically significant.

The development of the narcotic effect also testified to the mutual potentialization of effect obtained with the combined use of phenothiazine derivatives and analgesics.

SUMMARY

The analgesic effect of the phenothiazine series derivatives (Mepazine, Aminazine and Propazine) and of analgesics (morphine, Promedole and Phenadone) was studied by the method of electric pain stimulation.

The presence of analgesia potentiation was established. Combinations of phenothiazine derivatives with Promedole proved most effective. Bilateral potentiation during concurrent use of phenothiazine derivatives and analgesics is also manifest in the appearance of hypnotic effect.

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