THE ANALGESIC PROPERTIES OF CERTAIN PHENOTHIAZINE DERIVATIVES

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Among the published work relating to the study of the analgesic properties of the phenothiazine derivatives, there are several contradictory statements. Some workers consider that the possession of analgesic properties by the phenothiazine derivatives is a proven fact [4, 10], whereas others [3, 11] deny that this is so. It must be emphasized that different authors used different methods in their investigations. We accordingly deemed it necessary to study the analgesic properties of the phenothiazine derivatives, using the greatest variety of methods of pain stimulation. It was shown by means of electrical stimulation that aminazine, propazine and mepazine possess an analgesic action.

In the present article we describe the results of experiments using thermal pain stimulation by the methods of Boreus and Sandberg [6] and of D'Amour and Smith [7].

METHOD

Experiments were carried out on rats. For the Boreus and Sandberg method, the source of stimulation was the infrared rays from a Sollux lamp with a power of 500 w. The pain reaction was judged by the time of onset of the twitch reflex, and the range of measurements was confined to 15 seconds. When the method of D'Amour and Smith was used, the reaction of the animals was estimated by measurements of the reflex time (withdrawal of the tail). Stimulation was by means of focussed infrared rays from a 500 w lamp, projected through the diaphragm of a heat-insulating screen onto the blackened surface of the rat's tail. The maximum exposure was 15 seconds. Derivatives of the phenothiazine series (mepazine, aminazine and propazine) were injected subcutaneously. For purposes of comparison, the same tests were carried out with morphine, promedol and phenadon. These analgesics were injected intraperitoneally. The criterion of significance of the changes recorded was selected to correspond to $P = 0.05$.

RESULTS

In the investigations by the method of Boreus and Sandberg, after injection of aminazine, propazine and mepazine (in doses of 5, 10 and 50 mg/kg respectively) an increase in the reflex time was observed (Fig. 1). Doubling of the doses was followed by a significant increase in the effect only in the case of aminazine; in relation to mepazine and propazine these proportions were ill-defined. The maximum reaction was observed 60-90 minutes after injection of the drugs.

In the series of experiments carried out by the method of D'Amour and Smith, aminazine, propazine and mepazine (in doses of 1.25, 2.5 and 100 mg/kg, respectively) caused an increase in the reflex time; a further increase in the dose (aminazine – 10 mg/kg, propazine – 20 mg/kg and mepazine – 200 mg/kg), however, in contrast to all the preceding experiments, led to a shortening of the reflex time (Fig. 2). In order to explain this finding, we carried out an additional series of experiments. The pain reaction was judged by the animal's squeak; the strength of stimulation was increased, and the whole surface of the tail, fixed to the screen, was irradiated. In this way it was found that injection of all the phenothiazine derivatives under study (aminazine – 10 mg/kg, propazine – 20 mg/kg and mepazine – 400 mg/kg caused a clear-cut increase in the reflex time.

By their analgesic activity, morphine, promedol and phenadon were considerably stronger than the phenothiazine derivatives studied, in the experiments using the methods of both Boreus and Sandberg, and D'Amour and Smith.

As a result of the observations using the Boreus and Sandberg method it was found that aminazine, propazine, and mepazine possess the ability to depress pain reactions in experimental animals. When the method of D'Amour and Smith was used, it was found that the phenothiazine derivatives, in certain doses, lead to increased sensitivity to pain stimulation. This phenomenon may be explained

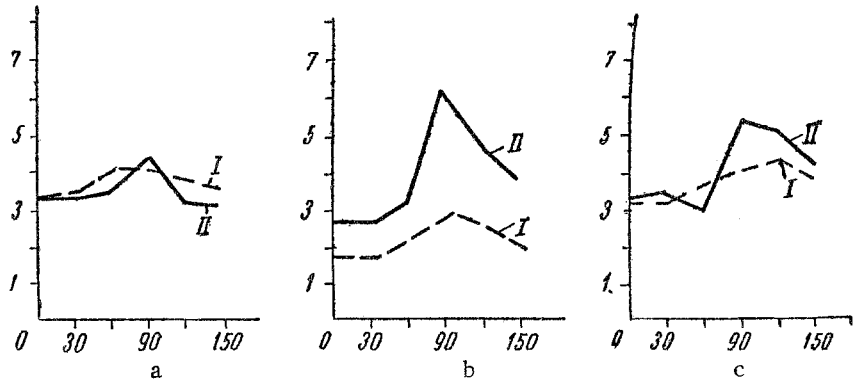

Fig. 1. Effect of mepazine, aminazine and propazine on the pain sensitivity to thermal stimulation (method of Boreus and Sandberg). Along the axis of ordinates – reflex time in seconds; along the axis of abscissas – – time of experiment in minutes; a – mepazine: I – 50 mg/kg subcutaneously, II – 100 mg/kg subcutaneously; b – aminazine: I – 5 mg/kg subcutaneously, II – 10 mg/kg subcutaneously; c – propazine: I – 10 mg/kg subcutaneously, II – 20 mg/kg subcutaneously.

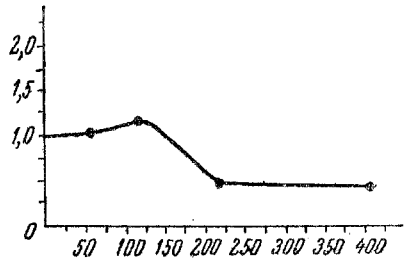

Fig. 2. Effect of mepazine on the pain sensitivity to thermal stimulation (method of D'Amour and Smith). Along the axis of ordinates – time of change of reflex (in conventional units); along the axis of abscissas – dose of drug (in mg/kg body weight).

if certain statements in the literature are borne in mind. The method of D'Amour and Smith cannot be considered to reproduce a purely pain reaction, for the reflex responsible for the defensive reaction in this method may be effected by neurons lying within the confines of the spinal cord. In experiments on spinal rats, for example, it was shown by Irwin and co-workers [8] and by Bonnycastle et al. [5] that the arc of the reflex, used as a test of the pain reaction in the method of D'Amour and Smith, may also be completed in the spinal cord. By this test, the depressing action of morphine may also be demonstrated in spinal rats [7].

The shortening of the reflex time observed after administration of the phenothiazine derivatives may possibly be due to the fact that under the influence of these drugs – besides depression of the sensitivity to pain, excitation of the spinal cord takes place, preventing manifestation of the analgesic effect.* It is obvious that this method cannot be used as a model for the study of the analgesic action of neuroplegic drugs. For this purpose a reaction must be selected which does not depend on spinal reflexes for its performance. When, for instance, we used the animal's squeak as the test of the reaction, we observed depression of the sensitivity to pain under the influence of mepazine, aminazine and propazine.

If the results of the present experiments are compared with our previous findings, it may be seen that the choice of a suitable test object plays a most important role in the search for analgesic drugs. From a comparison of the various methods of pain stimulation during the trial of typical analgesic drugs and of preparations with an ill-defined analgesic action, it may be considered that the method of D'Amour and Smith, which is widely used, is unsuitable for this purpose. The limitations of this method are due to the fact that it can only be used to determine the analgesic action of drugs which have a depressing influence on the synaptic formations of the spinal cord, whereas the analgesic properties of substances, with their point of application in the suprasegmental apparatus, may remain undetected.

It must be emphasized that the degree of stimulation plays an important part here. As shown by experiments

* This excitation is evidently not the result of the direct action of aminazine, propazine and mepazine on the elements of the spinal cord, but may be associated with depression of the tonic centers in the region of the reticular formation. It has been shown in V. V. Zakusov's laboratory that aminazine and mepazine have no direct influence on the transmission of impulses in the spinal cord [2]; at the same time phenothiazine derivatives are known to have a depressing action on the reticular formation [9].

using thermal stimulation, and with measurement of the threshold of sensitivity to an electric current, when the pain reaction was determined by the animal's squeak (intensive stimulation), an analgesic action of the phenothiazine derivatives was observed; in those experiments in which the test was movement of the tail (in response to less intensive stimulation), the results were negative. It is obvious that the animal's squeak in response to stimulation may, with greater justification, be regarded as the manifestation of a pain reaction, for it arose after more intensive stimulation than did the other motor reactions.

When the method of Boreus and Sandberg was used, a weakening of the sensitivity to pain could also be determined under the influence of neuroplegic drugs. In this case, too, the stimulation was so intensive that the pain stimuli evidently passed into the higher divisions of the central nervous system. In contrast to the method of electrical pain stimulation, an essential failing of the Boreus and Sandberg method is the small parameter of the measurements: a three- or fourfold fall in sensitivity is the maximum change that can be estimated in these experiments.

SUMMARY

The analgesic effect of mepazine, aminazine and propazine was studied with the aid of thermal methods of pain stimulation. Aminazine was found to be the most active of the preparations investigated. According to observations carried out earlier, and to the data contained in the present work, the electrical method of pain stimulation proves best for studying the analgesic effect of neuroplegic substances, provided squeaking of the animals is to be regarded as an indicator of the reaction.

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