PHARMACOLOGY

THE INFLUENCE OF CHLORPROMAZINE AND PROMETHAZINE ON VISCERO-VISCERAL REFLEXES

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The study of substances which exert an influence on viscero-visceral reflexes is of great theoretical and practical importance.

In the literature there are communications which deal with the influence of certain pharmacological agents on these reflexes. N. V. Kaverina [1,2,3] found that local anesthetic (Novocaine, Dicaine, etc.) and narcotic substances (Medinal, urethane) and also glucose reduce the cardiovascular and respiratory responses to stimulation of the internal organs. R. P. Kruglikova-Lvova [4] observed that morphine and, to a lesser degree, Promedol intensify the pressor reflex from the urinary bladder and the large intestine.

Our object was to study the influence of chlorpromazine (Largactil, Megaphen) and promethazine (Phenergan) on the reflexes elicited by stimulation of certain internal organs.

Courvoisier et al., [6] report briefly on the suppressive effect of Largactil on the reflexes induced by occluding the common carotid artery and by stimulating the ischiatic nerve. Analogous observations have been made by M. D. Mashkovsky, S. S. Liverman and A. I. Polezhaeva [5]. Kalkhoff [7] noted suppression following administration of Megaphen of the pressor reflexes induced by occluding the carotid artery. There has been no study made to date on the influence of chlorpromazine on other interoceptor reflexes. We have been unable to discover any published findings on the effect of promethazine on viscero-visceral reflexes.

EXPERIMENTAL

The experiments were conducted on cats under deep urethane or urethane-Nembutal narcosis. Urethane was administered intraperitoneally in the majority of experiments, but in some it was injected intravenously or intramuscularly.

The doses of urethane varied from 1.3-1.5 g/kg depending on the individual sensitivity of the animals. In the experiments in which anesthesia was produced by urethane plusNembutal, urethane was administered at a dose of 1.0-1.1 g/kg together with 10 mg/kg Nembutal.

Stimulation of the interoceptors of the urinary bladder and small and large intestinal ansae was effected by inflating these organs with air at a pressure of 50-80 mm Hg. The ischiatic nerve was stimulated by a current from an induction coil, the distance between the primary and secondary coils being 11-13 cm. Stimulation of the baroceptors of the carotid sinus was induced by occluding the common carotid artery by means of a Dieffenbach clamp.

In all the experiments, blood pressure was recorded by means of a mercury manometer connected to the common carotid artery and respiration by a Marey capsule connected to the trachea.

Stimulation was applied both before administration of chlorpromazine and promethazine and the following

intrevenous injection of these substances, usually after a time lapse of 1-3, 5, 15, 30, 60 and 120 minutes, but in some experiments even after 3, 4, 5 or 6 hours. 60 animals were used in the investigation.

RESULTS

In the experiments in which the urinary bladder was stimulated, it was found that at doses of chlorpromazine as low as 0,05-0,1 mg/kg the reflex rise in blood pressure was reduced by 20-30% and in some animals by 50% as compared with the level of the original reflex. The duration of action of these doses of chlorpromazine was 1½ to 2 hours (Fig. 1).

The action of promethazine proved to be analogous in intensity and duration at doses of 1-5 mg/kg and at higher doses. Lower doses of promethazine often either exerted no effect or even produced increase in the reflex rise in blood pressure.

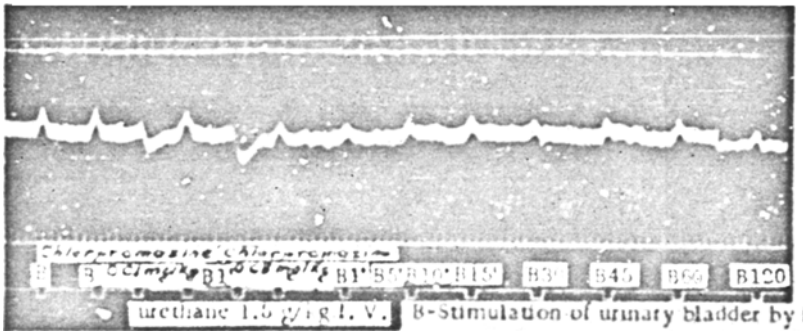

Fig. 1. Influence of chlorpromazine on vasopressor reflex with stimulation of urinary bladder. Cat 4 kg. Urethane 1,5 g/kg intravenously. Tracings from top to bottom: respiration, blood pressure, time (15 seconds), periods of stand-still of kymograph in minutes, stimulation of urinary bladder before administration and 1, 5, 10, 15, 30, 45 and 60 and 120 minutes after intravenous injection of chlorpromazine at dosage of 0,05 mg/kg.

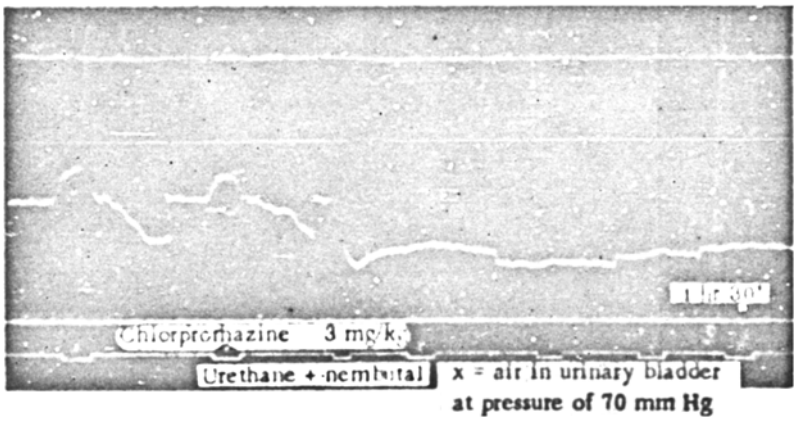

Fig. 2. Influence of chlorpromazine on vasopressor reflex with stimulation of urinary bladder. Cat 4,5 kg. Urethane 1,2 g/kg and Nembutal 10 mg/kg. Tracings as in Fig. 1. Time interval -5 seconds. Stimulation was applied 5, 20, 60 and 160 minutes after administration of chlorpromazine.

When the dosage of chlorpromazine was increased to 0,5-3 mg/kg, in the majority of experiments, there

was observed almost total suppression of reflex changes in arterial pressure, for a period of two or more hours. This was followed by slow restoration of the vasopressor reflex which did not return to the initial level for 5-6 hours (Fig. 2).

Promethazine did not exert such a powerful and prolonged effect even at a dosage of 10 mg/kg.

The respiratory changes on stimulation of the urinary bladder were in our experiments inconsistent and nonspecific. Nevertheless, it could be noted that in some experiments following administration of chlorpromazine or promethazine, the respiratory changes induced by stimulation of the interoceptors of the urinary bladder became less marked.

In the experiments with stimulation of ansae of the large and small intestines it was seen that chlorpromazine at a dose of 0.01 mg/kg, while not essentially influencing the magnitude of the pressore reflex, produced a change in its character: the rise and fall in blood pressure showed greater slope. Promethazine exhibited an action roughly similar in intensity at a dose of 1 mg/kg. Smaller doses of promethazine (0.1 mg/kg) produced a short (10-15 minutes) slight intensification of the pressor reflex.

Chlorpromazine, at doses of 0.05 - 0.1 mg/kg reduced the vasopressor reflex from the intestines by 20-40% and, at doses of 0.5-1.0 mg/kg, by more than 60%, for a long period (up to 2 hours); this was followed by a slow increase but complete restoration of the initial amplitude of the reflex was not observed in any experiment (Fig. 3).

Total suppression of the pressor reflex was seen lasting for 3-5 hours and longer with doses of 3-5 mg/kg chlorpromazine.

The respiratory changes on stimulation of the intestines were in our experiments inconsistent and it is therefore difficult to assess the effect of chlorpromazine and promethazine in this respect.

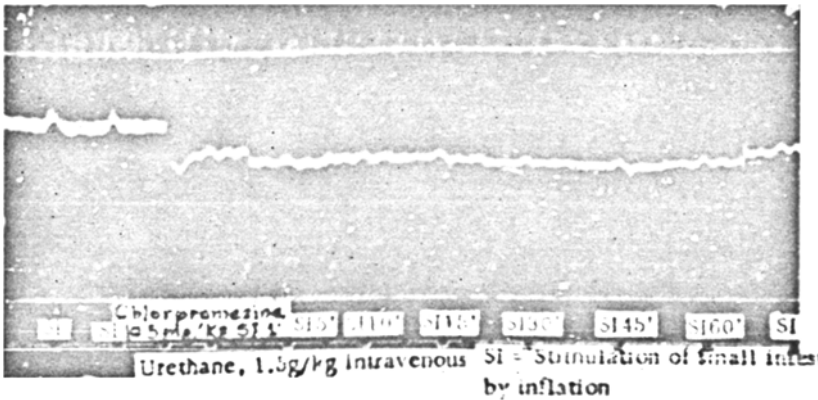

Fig. 3. Influence of chlorpromazine at dose of 0.05 mg/kg on vasopressor reflex with stimulation of small intestine. Cat 3.35 kg. Urethane 1.5 g/kg. Tracings as in Fig. 1.

Stimulation of the ischiatic nerve by an induction current in the control experiments produced a rapid rise in arterial pressure, increased frequency and a sharp increase in the depth of respiration.

Following administration of chlorpromazine at doses of 0.05-0.1 mg/kg a reduction in the pressor reflex response of approximately 50% was observed for 1-2 hours.

Promethazine exerted an action analogous in strength only at doses of 5-10 mg/kg; low doses of 0.1-0.5 mg/kg causing a distinct increase in the reflex response for 1-1½ hours following administration.

With increased dosage of chlorpromazine the vasopressor reflex decreased and at doses of 3-5 mg/kg was completely absent for several hours.

In experiments with stimulation of the ischiatic nerve in which the respiratory response was always dis-

tinctly manifest, chlorpromazine and promethazine exerted a very marked influence on reflex changes in respiration.

Chlorpromazine at doses of 3-5 mg/kg shortened the duration of increased respiratory frequency and the amplitude of respiratory movements. Doses of 0,01-1,0 mg/kg exhibited a less clearly marked action.

The doses of promethazine required to produce an effect of similar intensity were about double those of chlorpromazine.

When the baroceptors of the carotid zone were stimulated by occlusion of the common carotid artery a decrease in the pressor reflex was also seen following administration of chlorpromazine. An initial effect was observed at doses of chlorpromazine as low as 0,01 mg/kg; increase in dosage to 0,05 mg/kg led to a 50-60% diminution in the vasopressor reflex for one hour.

An effect analogous in strength was seen with promethazine at a dose of 5 mg/kg. This preparation at doses below 0,1 mg/kg did not exert an appreciable influence on the magnitude of the reflex; at a dose of 0,1 mg/kg a distinct increase was produced in the vasopressor reflex (Fig. 4).

Chlorpromazine at a dose of 3 mg/kg suppressed the reflex from the carotid sinus for a long time (5-6 hours).

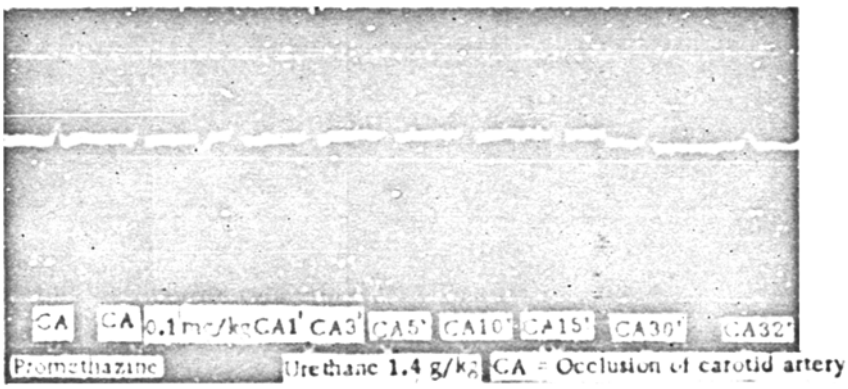

Fig. 4. Effect of promethazine at dose of 0,1 mg/kg on vasopressor reflex induced by occluding common carotid artery. Cat 4,1 kg. Urethane 1,4 g/kg. Tracings as in Fig. 1. Stimulation applied 1, 3, 5, 10, 15 and 30 minutes after administration of promethazine.

In our experiments changes in respiration with stimulation of the baroceptors of the carotid sinus were insignificant and no conspicuous effect on these changes was exerted by chlorpromazine or promethazine.

DISCUSSION OF RESULTS

Our findings demonstrate that the representatives of the phenothiazine series tested by us are able to decrease or suppress the reflex changes in blood pressure produced by stimulation in experimental conditions of internal organs.

This effect was particularly marked in the case of chlorpromazine which, at doses of 0,01 mg/kg and less, changed the character of the pressor reflexes and at higher doses either sharply reduced or completely removed them.

Promethazine also reduced the reflex blood pressure responses but its activity was ten to twenty times lower than that of chlorpromazine and the duration of its action was considerably less. Furthermore, with use of promethazine we observed a feature not seen with chlorpromazine, i.e., small doses of promethazine (0,1 mg/kg) produced intensification of the vasopressor reflex with significant regularity.

The compounds under investigation also exerted an influence on reflex changes in respiration, but this

effect could not be demonstrated so easily and was less uniform in character.

In comparing our results with published findings on substances which have been tested for influence on vasopressor reflexes, it will be seen that chlorpromazine shows significantly higher activity than do other substances. Thus, according to N. V. Kaverina Novocaine at doses of 2-3 mg/kg reduces vasopressor reflexes by 20-30% whereas an analogous effect is seen with chlorpromazine at doses of 0.05-0.1 mg/kg, i.e., doses at least 30-40 times less. Other compounds (glucose, urethane, Sovcaine, Dicaine, etc.), according to the same author, are either less active or produce a powerful toxic effect. Thus, at present chlorpromazine is apparently one of the most active substances known possessing the property of suppressing interoceptor reflexes.

The particular aspect of activity of chlorpromazine investigated by us is apparently to be explained by various factors.

First of all, it is necessary to take account of the blocking (neuroplegic) action of this compound. Its ability to exert an influence on the different links in the nervous system cannot but affect the conduction of excitation in the central link of the interoceptor reflex arc. However, of great importance in the action of chlorpromazine is the influence which it exerts on the peripheral links of the reflex arc, in particular, the blocking effect of the preparation on the adrenoreactive systems which receive the vasoconstrictor impulses. This is all the more likely since the doses of chlorpromazine at which the adrenolytic effect starts to manifest itself coincide with the doses which produce initial changes in the reflexes (0.01-0.05 mg/kg).

The lower activity of promethazine must, it seems, be explained by its less powerful central blocking (neuroplegic) and also its lower adrenolytic action as compared with chlorpromazine. Since the antihistaminic activity of promethazine considerably exceeds that of chlorpromazine it must be considered that this type of pharmacological action is not directly connected with influence on interoceptor reflexes.

SUMMARY

The effect of chlorpromazine and promethazine on viscero-visceral reflexes caused by stimulation of the interoceptors of the urinary bladder, intestine, sinus caroticus, as well as by stimulating the ischiadic nerve was studied. Both substances can inhibit these reflexes. Chlorpromazine is 10 to 20 times more active than promethazine. Small doses of promethazine can enhance vasopressor reflexes.

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