ANALYSIS OF THE BRADYCARDIC PHASE OF THE ACTION OF ATROPINE ON THE DOG'S HEART

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According to the existing view, atropine is a typical cholinolytic substance blocking the transmission of inhibitory impulses from the vagus nerves to the heart. Meanwhile, reports have been published indicating that in dogs and in man atropine initially causes bradycardia [7, 8, 9]. The cholinomimetic action of atropine on adult dogs has also been demonstrated in the authors' laboratory [2, 4].

The object of the present investigation was to analyze the bradycardic phase of the action of atropine on the dog's heart.

EXPERIMENTAL

Experiments were carried out on 20 puppies aged under 30-40 days and 25 adult dogs and puppies aged from 1.5 months. Atropine was injected subcutaneously in doses of 0.03-0.5 mg/kg. The animals were left unfixed in all the experiments. The ECG was recorded in lead II. The respiration rate was recorded by means of an electrolytic pick-up or counted visually. Some of the observations (on 6 adult dogs) were made in acute experimental conditions.

EXPERIMENTAL RESULTS

Injection of small doses of atropine (0.03 mg/kg) into adult dogs as a rule caused a prolonged bradycardic reaction. The heart rate diminished. The bradycardia was most pronounced 10-15 min after the injection of atropine. In most experiments the reaction ended by a return to the initial state, but in a few experiments the condition changed into the cholinolytic phase, shown by predominantly an increase in the heart rate (Fig. 1). It is clear from Fig. 1 that after injection of atropine the severity of the respiratory arrhythmia increased and the amplitude of the P_2 and T_2 waves was lowered. After 31 min, complete atrioventricular block developed (c). After 45 min, the cholinolytic phase supervened: the atrioventricular block and the respiratory arrhythmia disappeared while the amplitude of the P_2 and T_2 waves increased (d). After injection of larger doses of atropine (0.1-0.3 mg/kg) the cholinomimetic phase did not develop; roughly 5 min after injection of the drug a cholinolytic reaction appeared. When the cholinomimetic phase was more pronounced, the tone of the vagus nerve was higher, i.e., the slower the initial heart rate and the more marked the respiratory arrhythmia.

When the relationship between the degree of prominence of the bradycardic phase and the initial state of the vagal tone had been determined, a series of acute experiments was carried out on 6 adult dogs, to test the action of atropine after division of vagus nerves in the neck. Against this background, no cholinomimetic reaction could be found following administration of various doses of atropine (0.03-0.1 mg/kg), and in general no changes were observed in the rhythm of the heart. After injection of these doses of atrophine the heart could no longer respond by a negative chronotropic reaction to stimulation of the peripheral end of the divided vagus nerve. In the experiments on the younger group of puppies, starting with the first days after birth before vagal tone had appeared, no cholinomimetic phase of the reaction likewise was observed after subcutaneous injection of various doses of atropine. V. D. Rozanova [6] also found that in young puppies the blocking dose of atropine was many times smaller than for adult dogs. In the present experiments, the effect of doses starting from 0.01 mg/kg was tested. In the puppies the first signs of vagal tone appeared after 16-18 days, i.e., when the animal has learned to stand on all four limbs. However, the first signs of an ill-defined cholinomimetic reaction to injection of atropine were not observed

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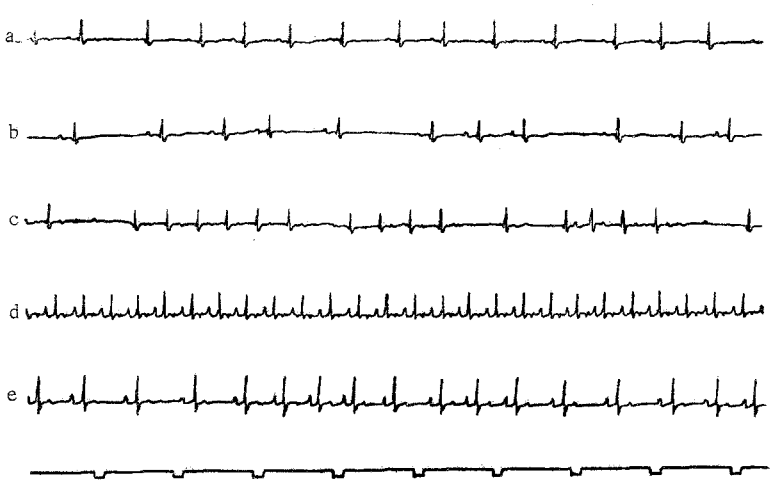

Fig. 1. ECG of an adult dog. a) Initial ECG (heart rate 100 beats/min); b) 10 min after injection of atropine (rate 75 beats/min); c) 31 min after injection of atropine (atrioventricular block); d) 1 h after injection (rate 200 beats/min); e) 2 h after injection (rate 125 beats/min, respiratory arrhythmia of the heart). Time marker below.

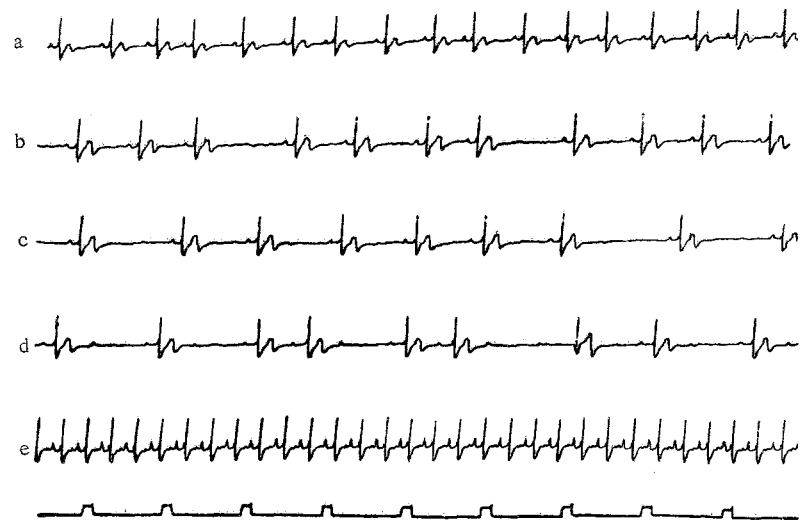

Fig. 2. ECG of a puppy aged 5 months. a) Initial ECG (heart rate 108 beats/min); b) 25 min after injection of morphine (rate 63 beats/min); c) 2 min after injection of atropine (rate 50 beats/min); d) 3 min after injection (atrioventricular block); e) 11 min after injection (rate 186 beats/min).

until 1.5 months, when the vagal tone of the puppies had become more pronounced. At 2.5-3 months the tone of the vagus nerves was almost as strong as in the adult animals. At this age the cholinomimetic phase of the reaction was like that in adult dogs.

In the next series of experiments the object was to produce additional strengthening of the vagal tone. Dogs aged 1.5 months and over received a preliminary injection of morphine (20 mg/kg), which increases the tonic excitation of the center for vagal innervation of the heart. Bradycardia developed 10-15 min after the injection of morphine. The heart rate in the adult dogs reached 45-55, and in the puppies aged 1.5-2 months – 85-90 beats/min, depending on the initial rhythm. The bradycardia was accompanied by marked polypnea. Atropine was injected, usually in a dose of 0.1 mg/kg, i.e., definitely a blocking dose, approximately twice the threshold level producing blocking in control animals, against this background of a low

heart rate. Despite this high dose, the dogs developed a clear cholinomimetic phase of the reaction: the bradycardia was increased and an atrioventricular block appeared. After 7-10 min the cholinomimetic phase was replaced by a typical cholinolytic phase: the heart rate increased to 200-300 beats/min, the atrioventricular block and arrhythmia disappeared, and the amplitude of the P_2 wave increased (Fig. 2). The cholinomimetic phase following injection in doses of 0.3-0.5 mg/kg. Naturally the threshold dose was also increased for the second, cholinolytic phase of the reaction. It is clear from Fig. 2 that the strengthening of the vagus effects by injection of morphine resulted in a more marked cholinomimetic action of atropine, even in doses at which no action was found against the natural background. With these doses, without previous injection of morphine, a cholinolytic reaction appeared at once.

What is the explanation of the paradoxical effect during the action of atropine, this classical cholinolytic drug? It has been suggested [7] that the first phase of the action of atropine is central in origin, while other writers [5] attribute it to the choline-sensitizing action. After subcutaneous injection of atropine in doses of 0.03-0.05 mg/kg, a well marked temporary and paradoxical phase of a parabiotic reaction may be observed in response to stimulation of the peripheral end of the divided right vagus nerve before complete block develops [4]. Taking these facts into consideration it may be assumed that atropine in the doses mentioned above, when acting on the muscarine-like cholinergic substance of the heart, initially causes the first, cholinomimetic phase, which passes through typical parabiotic stages into the second, cholinolytic phase. Mention must be made of common features in the chemical structure of the cholinolytic and cholinomimetic substances [1]. If this hypothesis is correct, it means that the cholinomimetic phase of the reaction to injection of atropine is peripheral and not central in origin. It is important to remember, however, that the reaction of the muscarine-like cholinergic receptor substance of the heart and its resistance to the action of atropine are directly dependent on the degree of tonic excitation of the vagal centers of the heart.

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