PHARMACOLOGY

EFFECT OF AMINAZINE ON SKELETAL MUSCLE AND NEUROMUSCULAR CONDUCTION

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Changes in motor activity are among the earliest manifestations of the action of aminazine on experimental animals [1]. After introduction of doses of 2-5 mg/kg the animals (dogs, rabbits, rats) become limp and inactive, their legs spread apart when they try to walk, and the neck muscles are enfeebled. There is very little published work on the elucidation of the mechanism of the action of aminazine on motor activity. Courvoisier et al [4] have shown that administration of Largactil (identical with aminazine) lowers the minimum dose of Flaxedil (Pirolakson) needed to cause drooping of the head of rabbits, and prolongs the duration of muscle relaxation observed after administration of this curariform drug. Baxter et al [2] also report that Largactil reinforces the action of curariform drugs; according to these authors it is not clear whether this effect is connected with the central or the peripheral action of the drug.

Kopera and Armitage [5], working in Burn's laboratory, studied the effect of Largactil on contraction of the sartorius muscle of cats; they found that when it was administered intravenously contraction of the muscle in response to direct or indirect stimulation was weakened. Burn hence concluded that it has a direct paralyzing action on skeletal muscles, and that its hypothermic action may be ascribed largely to this effect [3].

In view of the considerable importance of the effect of aminazine on muscles and on neuromuscular transmission, and of its joint action with curariform drugs, we thought it desirable to undertake detailed studies of these problems.

The experiments were performed on rabbits, cats, and rats, and on the isolated rectus abdominis muscle of frogs.

Our experiments were designed to elucidate whether aminazine has any curare-like action. In the first series of experiments aminazine was injected into an ear vein of rabbits (weight 2-2.5 kg) without anesthesia, and the rabbits were watched to establish whether head drooping followed; this was very pronounced, and the effect resembled that following administration of curare or its synthetic substitutes. The smallest effective dose is 1 mg per kg., which causes head drooping of short duration in most of the test animals; some individuals exhibit this symptom after doses of 0.5 mg per kg. Administration of 2-3 mg per kg is followed within 40-50 seconds by appearance of the initial signs of muscle relaxation, and after 1-2 minutes the neck muscles are fully relaxed, and head droop is fully developed, persisting for 1.5-2 hours (see Fig. 1). The effect develops sooner, and is more persistent, lasting for several hours, when the dose is raised to 5 mg per kg. The action of aminazine differs from that of curariform drugs (Diplatsin) in that relaxation of the neck muscles develops more slowly, and head droop is associated with drowsiness or sleep; recovery of the ability to raise the head regularly coincides with termination of the somnolent state. Furthermore, relatively large doses of aminazine (5-10 mg per kg), which cause prolonged head droop, do not cause the depression of respiration characteristic of the curare group of drugs.

In order to establish whether the symptom of head droop is due to a curare-like action of aminazine, a second series of experiments was performed on cats, in which we made a direct study of neuromuscular transmission. The cats were anesthetized with urethane (1 g per kg) and nembutal (15 mg per kg), and contraction of the sartorius muscle was registered, in response to stimulation of the peripheral end of the severed sciatic nerve, using square wave impulses at frequencies varying from 1 per 2 seconds to 1 per 10 seconds.

These experiments showed that intravenous injection of aminazine even in relatively high doses (5-10 mg per kg) does not reduce the amplitude of muscle contraction.

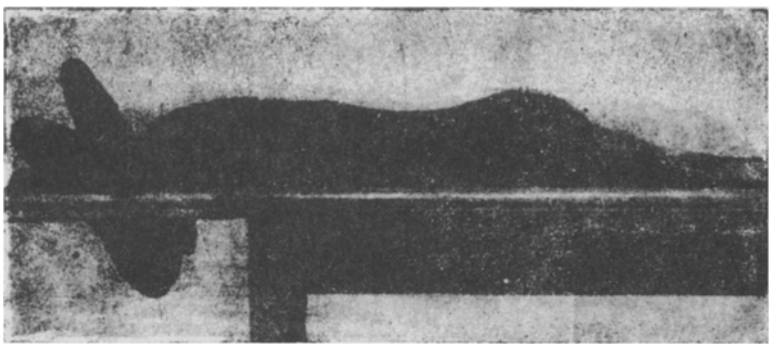

Fig. 1. Relaxation of the neck muscles of a rabbit after intravenous injection of aminazine (2 mg per kg).

In a number of experiments we found a transient increase in the amplitude of contraction immediately following the injection, after which it reverted to the initial value, at which it remained for a long time (observations were made over periods of 1-1.5 hours) (see Fig. 2). It may be concluded that aminazine does not, even in high doses, inhibit neuromuscular transmission, as do curare-like drugs, and that the myasthenic effect is not connected with its action on the neuromuscular junction.

Experiments with the rectus abdominis muscle of frogs showed that the action of aminazine differs from that of agents of the curare group, and that it has no direct inhibitory effect on muscle tissue. We found no significant change in the sensitivity of the muscle to acetylcholine in the presence of aminazine, in concentrations of 10^{-6} to 10^{-5}. Relaxation of the muscle was not found in the presence of aminazine; on the contrary, a gradually increasing persistent contraction was observed.

We were also unable to demonstrate any significant effect of aminazine (or in some experiments the identical drug Megaphen) on muscular excitability, in rats.

As with cats, we recorded the amplitude of contraction of the sartorius muscle, in response to stimulation (1 stimulus per 10 seconds) of the peripheral end of the severed sciatic nerve, after subcutaneous injection of 10 mg of aminazine per kg body weight. We found no decrease in the amplitude of contraction of the muscle over a period of observation of 3-4 hours. It should be noted that at the given dosage aminazine (or Megaphen) caused a marked fall in body temperature. The rectal temperature fell by 1.5-2° one hour after the injection, and by 3-4° after 2 hours. Having established that aminazine does not, at the very high dosage levels applied by us (these dosages must be regarded as high, both from the point of view of the experiment, and from that of clinical application), exert any curare-like action on transmission of stimuli at the neuromuscular junction, and has no effect on the excitability of skeletal muscle, we proceeded to investigate its action in reinforcing the effects of curariform agents.

The experiments were performed with unanesthetized rabbits and anesthetized cats. We used Diplatsin as a representative of the pachycurare class, and Ditilin for the leptocurare class of relaxants. The curariform drugs were injected into large skin veins of rabbits, in doses sufficient to cause head droop of short duration (a few minutes; Diplatsin 0.7-0.85, Ditilin 0.12-0.25 mg per kg). After 2-2.5 hours aminazine was injected intravenously in doses of 1 mg per kg (as shown above, this dose causes relaxation of the neck muscles, of short duration), followed by a second injection of the curariform drug, in the same dosage as before.

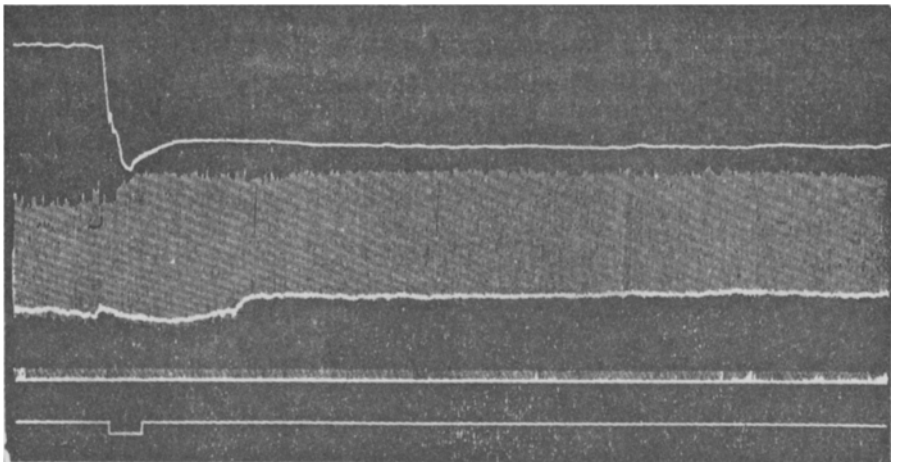

Fig. 2. Effect of aminazine on contraction of muscle in response to stimulation of the peripheral end of a severed sciatic nerve. The experiment was done on a cat, weighing 3.6 kg, anesthetized with 1 g of urethane per kg and nembutal 20 mg per kg. A dose of 5 mg of aminazine per kg body weight was injected intravenously. Explanation of tracings (from above down): blood pressure, contraction of the sartorius muscle, time base (5 seconds), signal marking injection of aminazine.

We did not find that aminazine shortened the time of onset of head droop, or prolonged its duration, in these experiments. We similarly found no evidence from experiments on contraction of cat sartorius muscle, in response to stimulation of the sciatic nerve, that aminazine causes prolongation of duration of action of curariform drugs. Aminazine, in doses of 5 mg per kg, similarly had no effect on the action of Diplatsin, administered in doses of 1.2-1.8 mg per kg., sufficient to cause considerable depression of neuromuscular transmission, or even total block. The curare-like action of Ditilin (0.01-0.03 mg per kg) was not enhanced by aminazine; in some experiments we even found some decrease in inhibition of neuromuscular transmission (Fig. 3). In view of the possibility of the second injection of Diplatsin reinforcing the first, we waited for 2.5 hours before repeating the injection.

In addition to the above experiments, we also investigated the effect of aminazine on contraction of the sartorius muscle of decerebrate cats, in response to electrical stimulation of the tibialis minor nerve. Administration of aminazine in doses of 0.1 to 7 mg per kg did not significantly affect the amplitude of the contractions.

Our experiments show that relatively large doses of aminazine have no perceptible effect on neuromuscular transmission, and do not reinforce the action of curariform agents on the neuromuscular junction. Nor could we find any inhibitory effect of aminazine on skeletal muscle. Although Kopera and Armitage [5] found a fall in the amplitude of contraction of the sartorius muscle after injection of Largactil into the iliac artery in doses of 4.6 mg per kg (and Burn with doses of 3 mg per kg), we were unable to find any such effect after intravenous injection into cats, or subcutaneous injection into rats, at doses of 10 mg per kg. Admittedly the conditions of action of the drug when it was introduced directly into the artery supplying the given muscle differ from those obtaining when it is given intravenously or subcutaneously. It should, however, be pointed out that the conditions prevailing after intravenous or subcutaneous injections are closer to those encountered in practice when aminazine is used. Our results show that aminazine, when given in doses sufficient to produce all the specific pharmacological effects of this drug, including marked lowering of body temperature, has no direct paralyzing action on skeletal muscle.

We conclude from our experiments that the general relaxation of muscles observed after administration of aminazine, including the symptom of head droop, can be ascribed chiefly to the action of the drug on the central nervous system.

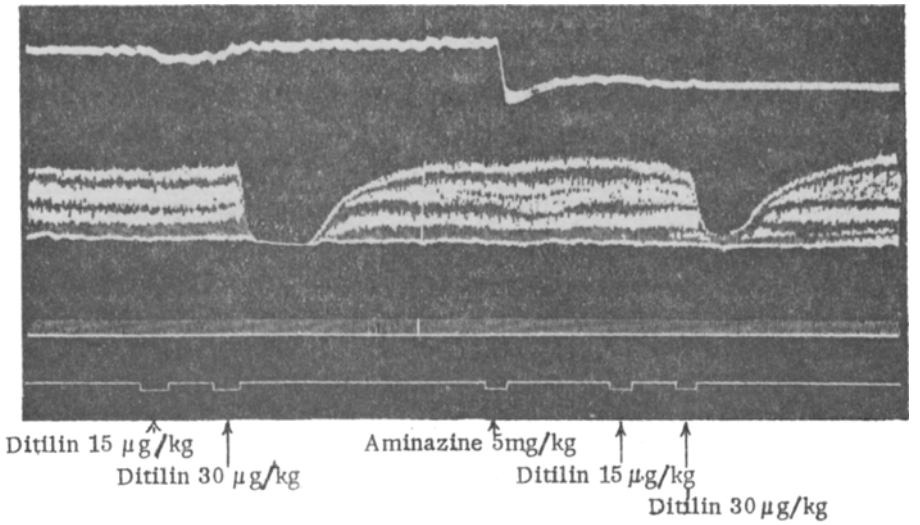

Fig. 3. Effect of aminazine on the curare-like action of Ditilin. The experiment was done on a cat, weighing 3.4 kg, anesthetized with 1 g of urethane per kg + 20 mg of nembutal per kg. Ditilin was injected intravenously before and after an injection of aminazine (5 mg per kg). Explanation of tracings (from above down): blood pressure, contraction of the sartorius muscle, time base (5 seconds), signals marking injections of Ditilin and aminazine.

As for the reinforcing action of Largactil on that of curariform agents (Flaxedil), reported by Courvoisier et al [4], this should also be related to its action on the central nervous system, and not to reinforcement of blockage of transmission at the neuromuscular junction. It should be remembered that Courvoisier gave Largactil in doses of 10 mg per kg., which are sufficiently high to cause prolonged relaxation of the neck muscles of rabbits.

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