THE ANTAGONISTS OF AMINAZINE IN RELATION TO ITS HYPOTENSIVE AND ADRENOLYTIC ACTION

B.I. Liubimov

From the Laboratory of Special Pharmacology (Chief – Active Member Acad. Med. Sci. USSR, V.V. Zakusov) of the Institute of Pharmacology and Chemotherapy (Director – Active Member Acad. Med. Sci. USSR, V.V. Zakusov), Acad. Med. Sci. USSR, Moscow

(Received September 14, 1957. Presented by Active Member Acad. Med. Sci. USSR, V.V. Zakusov)

Because of the widespread clinical use of aminazine, and its side-effects which are especially obvious with overdoses, the question of antagonists or "correctors" of this drug acquires great practical significance. The literature lists caffeine, theophylline and euphylline [2] as antagonists of aminazine. However, it still has not been established whether these substances antagonize all the aminazine effects or only several.

One of the factors limiting the use of aminazine is its property of inducing a prolonged depression of arterial pressure [1, 5]. The danger of such an effect is increased by the fact that, as one of its other properties, it has an adrenolytic effect so that the attempt to employ adrenalin and other such pressor substances against this aminazine background can lead to perverted effects.

There have been experimental studies [3, 4] devoted to the investigation of the hypotensive actions of aminazine and the use of substances raising the arterial pressure depressed by aminazine. These authors included among such substances noradrenalin, mesaton, phenamine and pervitin. However, the findings of these authors are contradictory, diametrically opposing statements being made at times. Thus, for example, Krause and Schmidtke-Ruhnan, studying the sympatholytic action of megaphen (aminazine) stated that the arterial pressure depressed by megaphen administration can be raised with phenamine or pervitin. Marquardt and his co-workers indicated [4] that phenamine and pervitin not only did not raise the arterial pressure depressed by megaphen but that there is actually a perversion of their normal action.

For all these reasons we believed it advisable to search for antagonists of the hypotensive and adrenolytic effects of aminazine.

EXPERIMENTAL METHOD

The experiments were performed on cats under urethane, chloralose or nembutal narcosis as well as on decerebrate cats and intact rabbits. The arterial pressures were measured with a mercury manometer connected with the carotid artery. Respirations were recorded with the aid of a Marey tambour connected with a tracheal cannula.

The adrenolytic action of the aminazine was determined using Marquardt's method. Before beginning the experiment, the minimal intravenous pressor dose of adrenalin was determined. As a rule, this was 5-20 μg of adrenalin. After the introduction of aminazine, because of its adrenolytic effect, this dose of adrenalin no longer produced a pressor effect. We recognized two degrees of adrenolysis: in the first stage, the injection of adrenalin failed to produce a pressor effect; in the second, adrenalin injection led to a definite depressor effect. This method was most suitable for the purposes of the present investigation as the difficulties in elevating the arterial

pressure depressed by aminazine arise in the first and especially in the second stage of adrenolysis.

Aminazine was employed in intravenous doses of 0.5 to 35 mg/kg.

As possible aminazine antagonists we studied the following: noradrenalin (5-20 μg), mesaton (10-15 μg), ephedrine (1-5 mg/kg), phenamine (1-2 mg/kg), pervitin (2 mg/kg), corazole (2 mg/kg), cordiamine (10-15 mg/kg), strychnine (0.1 mg/kg), caffeine (0.1 mg/kg), picrotoxin (0.2-0.45 mg/kg), lobeline (0.25-0.30 mg/kg), euphylline (20 mg/kg), β-tetrahydro-naphthylamine (0.5-15 mg/kg), pituitrin (0.1-1 units/kg), pyrogenal (10-20 units), as well as 10-allyl-phenothiazine and 10-allyl-2-chlorphenothiazine (5-10 mg/kg).

All the substances were introduced intravenously, the only exception being the insoluble allyl derivatives of phenothiazine which had to be given intra-abdominally as part of a starch suspension.

EXPERIMENTAL RESULTS

a) Search for Antagonists of the Hypotensive Effect of Aminazine

In the experiments on cats under urethane and nembutal narcosis as well as on the decerebrate cats and intact rabbits, it was established that of all the tested substances only noradrenalin and pituitrin are capable of elevating the blood pressure depressed by aminazine. Noradrenalin against an aminazine background is almost as effective as before aminazine, while adrenalin after aminazine does not show a pressor effect (Figure 1a).

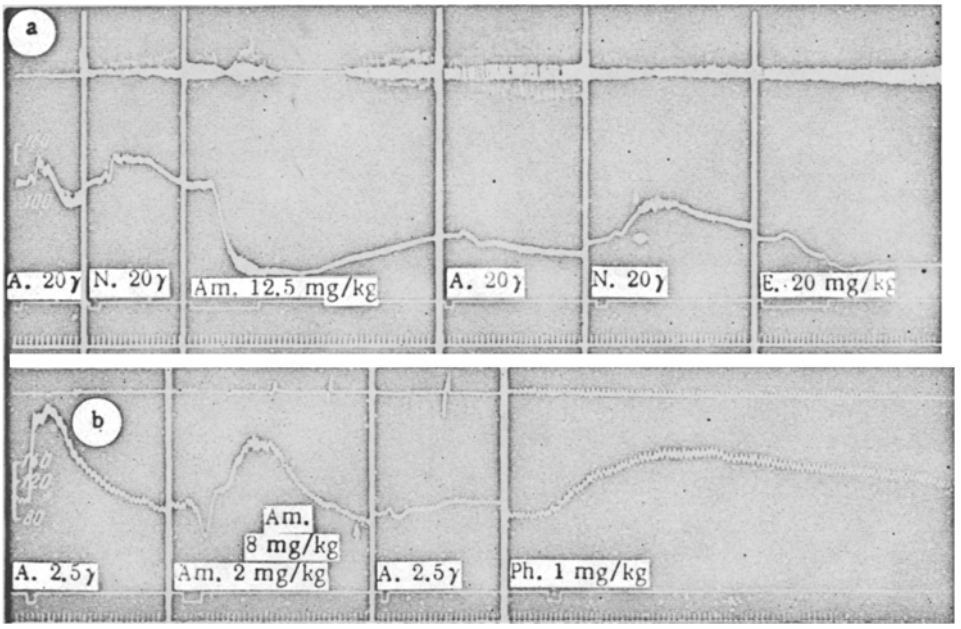

Fig. 1. Pressor action of noradrenalin and phenamine against the background of aminazine. Significance of curves (from above down): respiration; application of stimulus; A) introduction of adrenalin; N.A.) introduction of noradrenalin; Am) introduction of aminazine; E) introduction of euphylline; Ph) introduction of phenamine; a) under urethane narcosis; b) under chloralose narcosis. Time marker – five seconds.

The action of noradrenalin is relatively fleeting. To prolong the pressor effect of noradrenalin, it should be introduced by the drop method. At times, the pituitrin effect is re-enforced and prolonged by the antecedent injection of aminazine. This is especially noticeable when pituitrin is introduced by the drop method (Figure 2). Before the introduction of aminazine, the drop injection of 1 unit/kg of pituitrin in 10 ml of physiological saline over an eight-minute period produces only an insignificant rise in arterial pressure while, after the introduction of aminazine, even against a second degree adrenolytic effect, the same amount of pituitrin introduced in a similar manner produces a marked, almost instantaneous arterial rise (in order to avoid manifestations of tachyphylaxis, the second pituitrin injection was not given until at least $1\frac{1}{2}$ hours after the first).

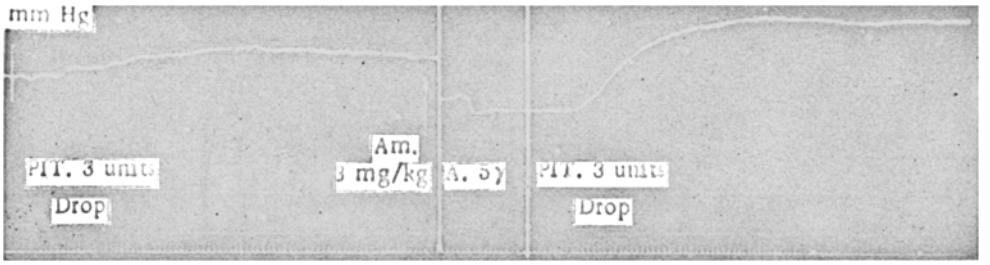

Fig. 2. Pressor action of pituitrin against an aminazine background. Significance of curves (from above down): blood pressure, stimulus marker; P) drop introduction of pituitrin (1 unit to 1 kg weight in 10 ml of physiological saline for eight minutes); Am) introduction of aminazine; A) introduction of adrenalin. Time marker – five seconds.

When the animals received larger doses of pituitrin (1 unit/kg) coronary spasm developed with upsetting of the cardiac rhythm which had to be restored with the use of papaverine.

The other substances, tested in the doses indicated, produced uncertain effects. For example, cordiamine in some instances produced insignificant fleeting arterial pressure rises, while, in other instances, the pressure either did not rise or actually became depressed.

Euphylline (Figure 1a) and lobeline against a background of aminazine action, as a rule gave markedly pronounced depressor effects.

Thus, the antagonists to the hypotensive action of aminazine are noradrenaline and pituitrin. At this point it should be repeated that our results were obtained in experiments on cats under urethane and nembutal narcosis as well as on decerebrate cats and intact rabbits.

During the course of our experiments we showed that chloralose narcosis materially alters results, for, in order to obtain adrenolysis by the use of aminazine under chloralose narcosis, quite large doses had to be employed so that second degree adrenolysis occurred much less often. In addition, chloralose narcosis muted the hypotensive effects of aminazine markedly. Even the arterial pressure reaction in response to aminazine introduction under chloralose narcosis is different from that observed when other anesthesia methods are employed. Introduction of aminazine under this type of narcosis results in an arterial pressure rise succeeding a fleeting depression (Figure 1b). In experiments conducted under urethane narcosis introduction of aminazine produces an immediate profound depression of the arterial pressure (Figure 1a).

In the experiments conducted under chloralose narcosis the arterial pressure, depressed by aminazine, rises after the introduction of noradrenalin and pituitrin just as it does in the experiments employing other methods of narcosis.

In addition to these substances, phenamine is capable of elevating the arterial pressure in experiments conducted under chloralose narcosis. Phenamine in doses of 1-2 mg/kg (Figure 1b), introduced after aminazine, results in a considerable, prolonged rise of pressure, a phenomenon not obtained with phenamine when other methods of narcotization are used.

b) Search for Antagonists of the Adrenolytic Effect of Aminazine

It is more difficult to remove the adrenolytic effect of aminazine than it is to remove the hypotensive action. Of all the substances examined ephedrine only, and then for a short time and with chloralose narcosis only, would restore the pressor reaction of adrenalin (Figure 3a). With time the pressor response to adrenalin continued to diminish so that within 10-15 minutes adrenolysis occurred again. However, another injection of ephedrine restored the pressor response to adrenalin. With other narcotizing agents and in intact rabbits ephedrine failed to produce such an action.

The special characteristics of these experiments under chloralose narcosis made us believe that chloralose

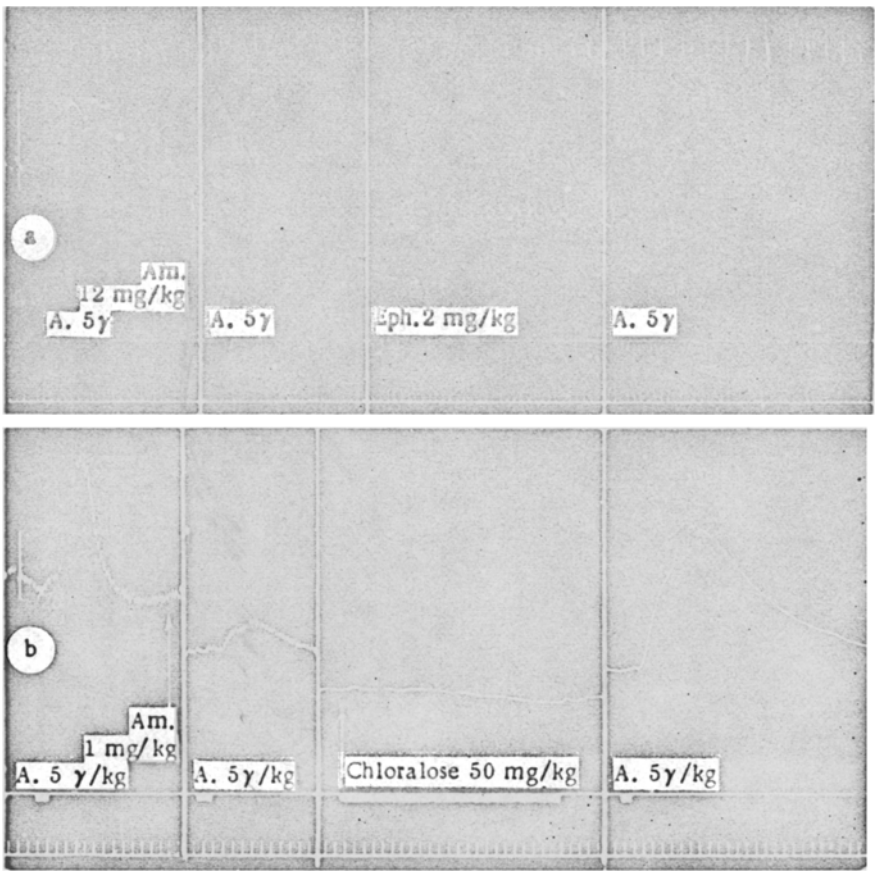

Fig. 3. Restoration of the pressor reaction of adrenalin by the use of ephedrine and chloralose against a background of aminazine. Significance of curves (from above down): blood pressure, stimulus marker; A) introduction of adrenalin; Am) introduction of aminazine; Eph) introduction of ephedrine; a) chloralose narcosis; b) with decerebration. Time marker – five seconds.

itself might have an influence on the adrenolytic properties of aminazine.

In order to answer this question, we did a few experiments on cats under urethane and ether narcosis as well as on decerebrate cats and used chloralose as a possible aminazine antagonist.

After giving the animals aminazine and obtaining adrenolysis, we injected chloralose intravenously in doses of from 50 to 100 mg/kg but this failed to produce arterial pressure levels. In cases in which the aminazine dose had been as small as 1 mg/kg, the pressor response to adrenalin was temporarily restored to almost the initial levels (Figure 3b).

It appears that, on the basis of our experiments, the antagonists of the hypotensive action of aminazine are noradrenalin and pituitrin.

Under conditions of chloralose narcosis, phenamine is also an antagonist of aminazine. Ephedrine is an antagonist of the adrenolytic effect of aminazine only when chloralose narcosis has been used. Chloralose by itself is not capable of decreasing the adrenolytic action of aminazine.

Arterial pressure, depressed by aminazine, may be raised by the introduction of noradrenalin and pituitrin. The drop introduction of these substances seems the most practical method.

Practically speaking, not one of the substances tested removed the adrenolytic effect of aminazine.

The conflicting opinions of various investigators working with aminazine antagonists are explained by their use of different narcotizing agents.

SUMMARY

Acute experiments were performed on cats anesthetized by different methods, as well as on intact rabbits. Noradrenalin, mesaton, phenamine, picrotoxin, lobeline, euphylline, β-tetrahydronaphthylamine, pituitrin, pyrogenal, allyl-phenothiazine, allyl-2-chlorphenothiazine were tested as possible antagonists of the hypotensive and adrenolytic effect of aminazine. Only pituitrin and noradrenalin caused the rise of arterial blood pressure, decreased by aminazine. Phenamine had the same effect as these two substances in experiments performed on cats under chloralose anesthesia. Adrenolytic effect of aminazine could be removed by injection of ephedrine only in experiments where chloralose anesthesia was employed. In connection with the fact that chloralose anesthesia had a pronounced effect on the pharmacological properties of aminazine, chloralose was tested as a possible antagonist of aminazine. It appeared that it decreases the adrenolytic effect of aminazine but slightly.

LITERATURE CITED

[1] M.D. Mashkovskii, S.S. Liberman and A.I. Polozhaeva, Farmakol. i Toksikol. 18, 1, 14-22 (1955).

[2] N. Kopera, Wiener klinische Wschr. 67, 48, 867-874 (1955).

[3] D. Krause and D. Schmidtke-Ruhnan, Arch. exper. Pathol. u. Pharm. 226, 3, 243-254 (1955).

[4] P. Marquardt, H. Puppel and H. Schumacher, Klin. Wschr. 33, 9/10, 211-215 (1955).

[5] H. Spitzbarth, H. Bauer and H. Wegland, Deutsche med. Wschr. 80, 12, 406-409 (1955).