THE EFFECT OF NOVOCAIN BLOCK ON THE CATALYTIC BREAKDOWN OF NOVOCAIN IN ENDARTERITIS OBLITERANS

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The wide use of novocain as a local anesthetic and therapeutic agent gives rise to many problems requiring investigation.

It has been shown that after intravenous or subcutaneous injections of novocain in animals [5, 8, 9] and man [7, 10] there is a rapid breakdown into paraaminobenzoic acid and diethylaminoethanol. Both these products of hydrolysis are less toxic than novocain itself [6, 19]. The paraaminobenzoic acid is almost completely eliminated from the organism in the urine, 20-30% of the diethylaminoethanol is excreted, and the fate of the remainder is unknown. There is some evidence that it is absorbed by the tissues – mostly by the spleen, and least by the skeletal muscles and blood plasma [19]. The length of time for which it remains in the body is unknown. There is some evidence that its presence increases the toxicity of novocain, lowering the value of the lethal dose by approximately 35% [11, 12, 23].

We have previously shown that the amount of unchanged novocain excreted in the urine depends upon the type of block (whether a paranephric or a nerve block), and that it is less in patients receiving repeated blocks at intervals of one to four weeks. These results indicate a variability in the activity of the novocainesterase in the organism, and show the need for investigation of the variability of the enzyme systems responsible for the breakdown of novocain.

It has been shown recently that novocainesterase is present in all tissues, but that its activity depends upon the particular tissue in which it is found. The greatest novocainesterase activity is found in the liver, while in the spleen and brain it has practically no activity. There is also considerable variation in the activity from one animal to another. The novocainesterase of skeletal muscle is particularly inactive [1, 22].

R. Hazard and his co-workers [13] have studied the activity of novocainesterase in blood serum in vitro in man and in various animals, including birds. These authors consider that the activity of this enzyme in man is such as to cause 80-100% hydrolysis of novocain in a 30-minute incubation period. Rodent blood has a higher activity than this, while canine blood has a very low value.

The long-maintained excretion of unchanged novocain in the urine in dogs [1] is some evidence for the low novocainesterase activity, though this has a higher value than was found by Hazard in his experiments in vitro. Evidently the enzyme is very labile, and the action may depend on whether it is in vitro or in vivo.

P. Hazard [13, 14, 15] considers that the determination of the novocainesterase activity of blood may be used as a diagnostic and prognostic test in several diseases. From a wealth of clinical material, he and others have shown that the novocainesterase activity of blood serum is lowered in conditions affecting the liver and thyroid. A particularly low value is found in cirrhosis and cancer of the liver [16, 20] and the activity is lowered for a considerable time in man after cranial trauma [21].

If, as we may suppose, there are individual differences in the activity of the enzymes responsible for the breakdown of novocain, then its rate of destruction will vary from one individual to another.

It is possible that the death of the patient following local novocain anesthesia described by L. G. Kaganova [2] can be explained in this way, as can the dizziness and vomiting in several patients after injections of novocain.

We have investigated the activity of novocainesterase in the hydrolysis of novocain, as well as that of the enzyme causing the acetylation of paraaminobenzoic acid, which is probably a product of this hydrolysis.

EXPERIMENTAL METHODS

The novocainesterase activity of the blood serum was determined in blood taken from patients before starting any treatment, as well as 4-5 days after the first novocain block; we used the method of R. Hazard [10], as modified by us [1].

The activity of the novocainesterase was determined by mixing 100 γ of novocain with 1 ml of blood serum and finding how much was hydrolyzed during a five-minute incubation period at 37°C; a determination of the amount of novocain hydrolyzed during a 30-minute incubation period was also made, and this gave additional information about the extent to which the novocain was broken down.

A quantitative estimation of the action of the enzyme systems causing the hydrolysis and acetylation of paraaminobenzoic acid in vivo was made by determining the amount of unchanged novocain and free and acetylated paraaminobenzoic acid excreted in the urine after novocain block. The novocain and its hydrolysis products present in both blood and urine were determined by the method previously described [1].

Altogether, investigations were made in 34 human subjects; the experimental group consisted of 18 patients with endarteritis obliterans, and the control group consisted of 16 subjects suffering from various other diseases, including: abscesses, carcinoma of the stomach, pyloric stenosis, cicatrization of the esophagus, duodenal ulcer, tuberculosis of the joints, and deformation of the hip joint. All subjects were of approximately the same age. There are various classifications of the types and phases of endarteritis obliterans. We used two classifications, the first being that used in the A. V. Vishnevsky Surgical Institute, and the second that proposed by I. G. Rufanov.

In the first classification, the subjects were divided as follows: 7 subjects (Group I) with atonic, 6 subjects (Group II) with spastic, and 5 subjects (Group III) with mixed forms of the disease.

In the second classification, the subjects were divided as follows: the second period of disease – 5 subjects (Group IV), third period – 9 subjects (Group V).

Patients in whom a sympathectomy had been performed were referred to a separate group, Group VI.

EXPERIMENTAL RESULTS

The percentage amounts of novocain hydrolized in the five-minute incubation period in the case of patients with endarteritis obliterans were: for Group I, 23-56%; for Group II, 28-61%; and for Group III, 42-55%.

These results demonstrate the individual differences in the activity of novocainesterase. The average values for the results for activity changes in endarteritis obliterans patients are shown in Fig. 1.

It can be seen from these results that in all cases the activity of the novocainesterase of the blood serum is below normal. The amount of novocainesterase broken down during a 30-minute incubation period is below normal in half of the cases. In all patients with endarteritis obliterans, the activity of the novocainesterase of the blood system shows scarcely any reduction after novocain block. Normally, injections of novocain increase the novocainesterase activity of blood serum, and this was observed in the control group.

We also found the length of time for which novocain and its hydrolysis products were excreted in the urine after novocain block (Figs. 2 and 3).

In patients with endarteritis obliterans, the unchanged novocain is excreted in the urine for longer periods than in the control group. In patients in Groups I and V, the excretion of unchanged novocain in the urine continues as long as eight hours after the block (Fig. 2, a, b), but does not exceed the amount excreted in the control group (Fig. 2, c). This indicates a reduced rate of hydrolysis of novocain in the body, and agrees with the results found for novocainesterase in blood serum in vitro.

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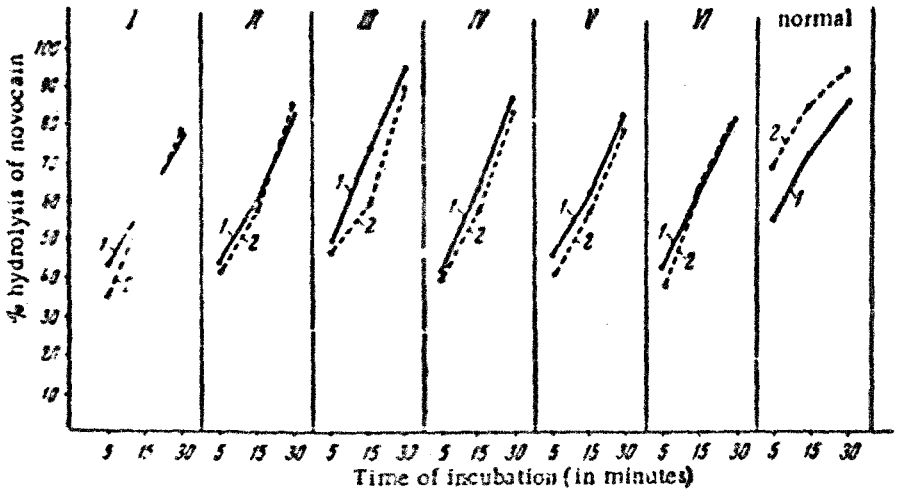

Fig. 1. The effect of novocain block on the activity of novocainesterase blood serum in patients with endarteritis obliterans. Groups I to VI patients with endarteritis obliterans. 1) before block, 2) after block.

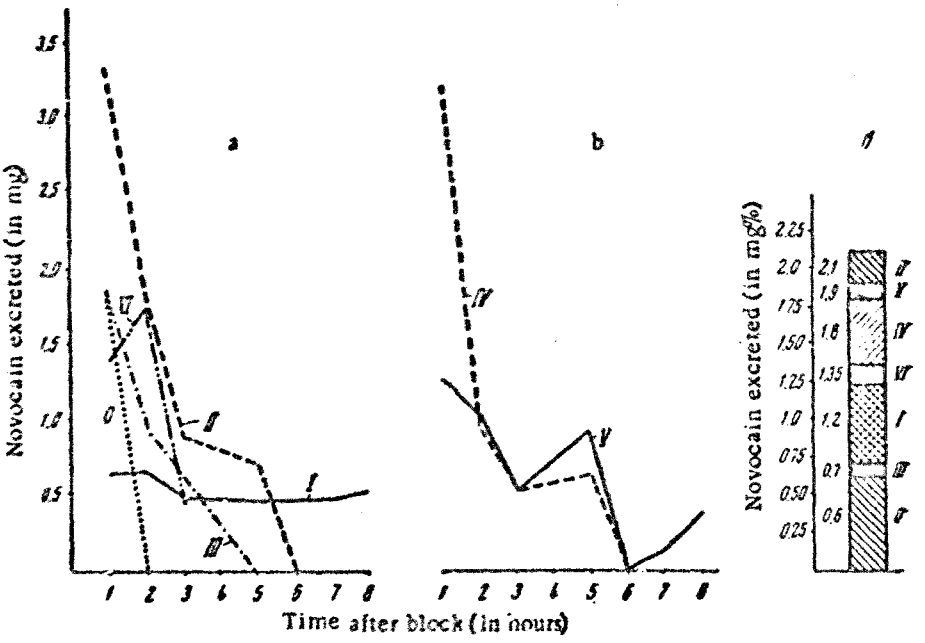

Fig. 2. Rate of excretion of unchanged novocain from the urine after block in patients with endarteritis obliterans, patients of Groups I-VI.
0) Control group; a) groups of endarteritis obliterans patients according to the first classification; b) groups of patients according to the second classification; c) amount of novocain excreted during the whole time after the block.

The results for the atonic forms of the disease must be noted (Group I). The rate of excretion of unchanged novocain is constant for a considerable time, as though a novocain renal threshold had been reached which was independent of the novocain concentration in the body. This effect is clearly associated with changes in the

permeability of the blood vessels. In patients with spastic and mixed forms of the disease (Groups II and III), most of the unchanged novocain is excreted in the first two hours after the block when its concentration in the body is highest; after this the excretion rate becomes considerably reduced, though it continues longer than in patients of the control group. In these, the unchanged novocain is excreted only for one hour after the block, and in very small quantities.

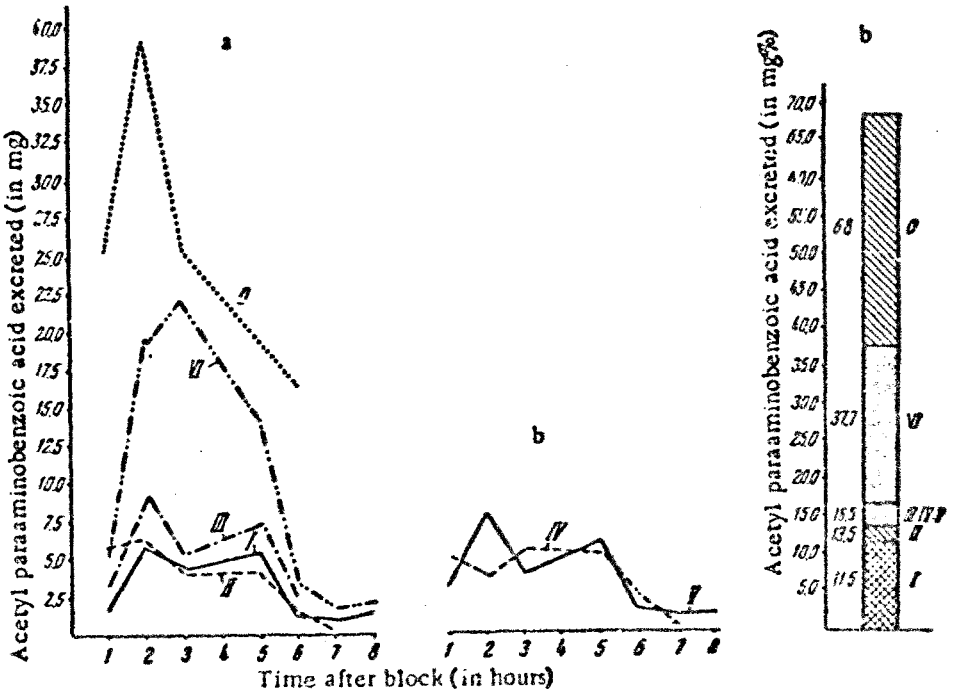

Fig. 3. Excretion of acetyl paraaminobenzoic acid from the urine after novocain block in patients with endarteritis obliterans (legend as in Fig. 2).

Figur 2, c shows details of the excretion of unchanged novocain in the urine for the whole period after the block. The smallest quantity is excreted in the control group, and the greatest amount in patients with the spastic form of endarteritis obliterans (Group II), but in patients with the atonic form of the disease, a smaller percentage of the novocain is excreted, since the investigation was limited to eight hours after the block, and the excretion of unchanged novocain not only had not finished by this time, but the concentration in the urine had not even begun to fall.

Paraaminobenzoic acid, one of the hydrolysis products of novocain, is excreted in the urine of patients with endarteritis obliterans in 2-3 hours, while in the control group the same amount is excreted in the first hour after the block. The amount of the acid secreted does not exceed 4 mg %. A considerable amount of another novocain breakdown product – acetyl paraaminobenzoic acid – is also excreted in the urine, and most of the novocain is excreted from the body in this form (Fig. 3).

The excretion of acetyl paraaminobenzoic acid in patients of Groups I, V and VI, lasts longer than in the control group. In the first groups, the excretion of the acid continues for eight hours after the block, while in the control group it is complete in six hours (Fig. 3, a, b). In all the endarteritis obliterans patients the percentage of acetyl paraaminobenzoic acid excreted is considerably less than normal (Fig. 3, c).

Thus, there are individual differences in the ability to break down novocain, but in endarteritis obliterans patients hydrolytic enzyme activity is reduced, and there is also a considerable reduction in the amount of acetyl paraaminobenzoic acid excreted after the block. This latter effect may be due to a change in the permeability of the blood vessels. However, it could be due to a general reduction in the processes of acetylation in the patients, and this in turn may be associated with a lack of pantothenic acid or coenzyme A. When, as a result

of the hydrolysis of novocain, more than the normal amount of paraaminobenzoic acid is formed, the lack of pantothenic acid may result in a reduced amount of acetylation. This has been shown by T. Riggs and D. Hegsted [17, 18]. Determination of the novocainesterase activity of the blood indicates how a patient will react to novocain, and according to certain investigators, when the activity is low it may be possible to effect an adaptation of the enzyme by a preliminary injection of small doses of novocain [4, 21]. In Hungary, novocainazoprotein immune sera have been prepared, which, on injection, raise the lethal dose of novocain for rabbits from 60 to 80 mg/kg.

Thus, according to our observations, in endarteritis obliterans patients the novocainesterase blood serum activity is less than normal, and after novocain block it tends to become lowered further still.

In patients of Groups I and V, the excretion of unchanged novocain in the urine after the block continues for more than eight hours. The amount of excreted novocain is very small, and is independent of the concentration of novocain in the body.

In patients with endarteritis obliterans in all forms and phases of the disease, with the exception of sympathectomized patients, the excretion of paraaminobenzoic acid formed by breakdown of novocain is considerably reduced.

SUMMARY

In vitro and in vivo experiments have demonstrated a fall in novocainesterase activating the destruction of novocain in the blood of patients with endarteritis obliterans.

The activity of the enzymatic system catalyzing acetylation of paraaminobenzoic acid – one of the products of novocain metabolism – is as well inhibited.

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