LOCAL ANESTHESIA IN IRRADIATED ANIMALS

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 55, No. 2,
pp. 63-67, February, 1963
Original article submitted February 4, 1961

Although the question of anesthesia in surgical diseases combined with radiation injuries is one of practical importance, it has not been studied experimentally. As a result of the widespread application of local anesthesia, the study of the effect of local anesthetics during the period of radiation sickness is of particular interest. No information on this subject is present in the literature. Only in a paper by P. V. Vasil'ev and P. P. Saksonov [1] is it stated that the anesthetic action of decicaine is shown more intensively on the cornea of animals irradiated with roentgen rays.

The aim of the present investigation was to study the special features of surface, nerve-block, and infiltration anesthesia in animals exposed to the action of ionizing radiation.

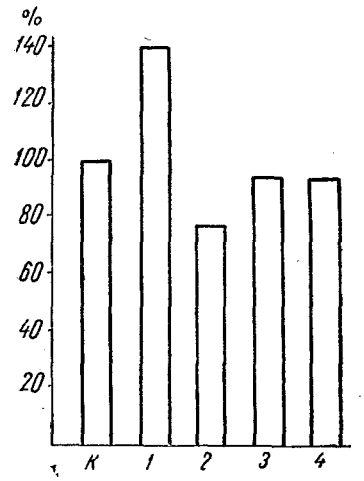
EXPERIMENTAL METHOD

Surface anesthesia was studied on the cornea of rabbits, by the use of 0.05 ml of 0.5% decicaine. The duration and depth of anesthesia were judged by the number of times that touching the center of the cornea with a fine hair caused blinking. The frequency of stimulation, applied every 5 min, was constant (100/min). Total anesthesia was taken to be a condition in which 100 touches did not produce a blinking reflex. The effect of decicaine in the irradiated and nonirradiated animals was compared from a consideration of the time taken to regain the original sensitivity of the cornea and of the duration of the total anesthesia. Between 5 and 7 determinations were made on each rabbit before irradiation. After irradiation, experiments were carried out during the first 1-2 hr and on the 1st, 3rd 5th, and 7th days. Altogether 126 experiments were conducted on ten animals.

Nerve-block anesthesia was studied on the sciatic nerve of spinal frogs (Rana temporaria) in 88 experiments. The nerve was stimulated by a sinusoidal current with a frequency of 100 cps, supplied by a type ZG-10 audiofrequency oscillator. Anesthesia was induced with 0.1% novocain, applied in a volume of 0.01 ml to the nerve proximally to the stimulating electrodes. Measures were adopted to prevent the rapid absorption of the anesthetic into the surrounding tissues. The effect of the novocain was judged by the magnitude and duration of the increase in the thresholds of the animal's general motor reaction to stimulation of the nerve. Experiments were carried out on the animals 1-3 hr and 1, 3, 7, and 15 days after irradiation.

Infiltraton anesthesia was studied on guinea pigs (20 animals). The anesthetics used were a 1% solution of novocain, a 1% solution of bencaine (an analog of novocain but without the NH_2 group in the benzene ring), and the new local anesthetic mesocaine (diethylaminoacetyl-2,4,6-trimethylaniline hydrochloride), recently synthesized at the Institute of Pharmacology and Chemotherapy of the USSR Academy of Medical Sciences, which was used as a 0.25% solution. The solutions of these anesthetics were injected intradermally in a dose of 0.25 ml. The anesthetized portion of skin was rhythmically stimulated by a fine needle every 5 min. Absence of the skin-muscle reflex after pricking the skin six times indicated total anesthesia; appearance of the reflex in response to the first prick indicated absence of anesthesia. The duration and depth of anesthesia in the irradiated and nonirradiated animals were compared. Before irradiation, the effect of novocain and bencaine was determined repeatedly in each animal, and the effect of mesocaine once (in two areas). After irradiation, experiments were performed after an interval of 30 min and on the 1st, 3rd, 5th, 7th, and 9th days.

The animals were irradiated with roentgen rays from the RUM-3 apparatus. The doses of irradiation were: for rabbits, 1000 r; for frogs, 5000 r; and for guinea pigs 350 r.



Duration of decicaine anesthesia of the cornea of rabbits before and after irradiation of the animals with roentgen rays in a dose of 1000 r. K) Nonirradiated; 1) 1-2 hr after irradiation; 2) 24 hr; 3) 3 days; 4) 5-7 days after irradiation.

EXPERIMENTAL RESULTS

In the irradiated animals the effect of decicaine on the sensory nerve endings of the cornea (terminal anesthesia) showed certain peculiarities. For 1-2 hr after irradiation, in all the animals the local anesthetic effect was considerably enhanced. Whereas before irradiation the total duration of anesthesia, i.e., the time from the injection of decicaine until restoration of the initial pain sensitivity of the cornea, varied from 70 to 104 min (average 86 min), during the first hours after irradiation this time varied from 93 to 160 min (average 121 min). The duration of anesthesia thus increased by 40%. A corresponding increase took place in the duration of total anesthesia, namely from 35-70 min before irradiation to 65-130 min after irradiation. When 24 hr had elapsed after irradiation, the anesthetic effect of decicaine was modified: the average duration of anesthesia was now 65 min (varying from 40 to 90 min), i.e., 25% less than in the controls. The depth of anesthesia was also decreased, and in some experiments total anesthesia of the cornea could not be obtained. The initial magnitude of the anesthetic effect in the great majority of the animals was restored during the 3rd day. At this period the duration of anesthesia was 79 min, i.e., 92% of the initial value. Subsequently the effect of decicaine on the irradiated animals was the same as on the controls (see figure). These results were statistically significant.

In order to study the nerve block anesthesia in the control and irradiated frogs, the degree of elevation of the thresholds of the animal's general motor reaction by the administration of novocain was determined from the readings of the ZG-10 oscillator, expressed in decibels, and the ratio between the threshold voltages before and after application of novocain to the nerve was determined from tables; these ratios were then converted into percentages (Table 1).

It will be clear from Table 1 that statistically significant differences in the degree of the novocain blocking of the sensory fibers between the irradiated and nonirradiated animals were found within a few hours after irradiation and persisted for one week. During this period, the thresholds of pain stimulation in the irradiated animals, causing general motor reaction of the animals, were increased three-fold or more after application of novocain, while the mean duration of the novocain effect was 63-89 min. In the group of control animals, these thresholds were doubled after application of novocain; restoration of their original magnitude occurred on the average after 46 min.

TABLE 1. Effect of Novocain on the Sensory Fibers of the Sciatic Nerve of Frogs Irradiated with Roentgen Rays (5000 r)

Interval after irradiation	Number of experiments	Average elevation of thresholds of general motor reaction after novocain injection (% of original)	t	Average time of restoration of original thresholds (in minutes)	t'
1-3 hours	16	326 ± 42	2.9	63 ± 6	2.4
1 day	13	288 ± 33	2.6	81 ± 10	3.4
3 days	18	336 ± 39	3.3	89 ± 5	7.4
7 days	10	314 ± 31	3.4	73 ± 7	3.7
15 days	13	179 ± 6	1.6	61 ± 9	1.6
Control	18	199 ± 9	–	46 ± 3	–

Note: t and t' are the ratio of the difference between the experimental and control values and its error. According to textbooks of statistics, if the differences between the experimental and control values are significant, this ratio should be not less than 2:1.

Hence, the effect of novocain on the sensory conductors of a peripheral nerve was manifested much more strongly in animals exposed to ionizing radiation. It should be stressed, however, that the anesthetic effect is also determined essentially by the duration of contact between the anesthetic and the nerve, i.e., by the processes of absorption and permeability. In our experiments the effect of these factors was not taken into consideration, because steps were taken to prevent the rapid absorption of novocain into the surrounding tissues.

When infiltration anesthesia was tested in the irradiated animals, at all periods a marked decrease in the effect of the anesthetics was observed. Whereas before irradiation the duration of anesthesia varied from 25 to 60 min and amounted on the average to 35 min, 31 min, and 27 min respectively after application of novocain, bencaine, and mesocaine, only 30-40 min after irradiation in most experiments it did not exceed 15 min, falling on the average to 12, 15, and 12 min respectively. In some experiments anesthesia could not be obtained. The anesthetic effect was still further weakened 24 hr after irradiation. In half the animals it was not observed at all, and in the rest only very shallow and brief anesthesia was found. The mean duration of anesthesia at this period was shortened to 8-9 min. At later periods (on the 3rd, 5th, 7th, and 9th days), the effect of novocain and bencaine was slightly intensified, but was still much weaker than in the controls. The effect of mesocaine continued to diminish, presumably on account of, firstly, the effect of irradiation and, secondly, some decrease in the sensitivity to mesocaine on repeated injection. We observed this latter effect in experiments on nonirradiated guinea pigs (Table 2).

In addition to the weakening of the local anesthetic effect in the irradiated animals, a resorptive action of the anesthetics was observed when they were given in doses not producing changes in the state of the nonirradiated animals. This action was manifested as signs of excitation of the central nervous system. For instance, after administration of novocain and bencaine in doses of 30-40 μg to irradiated animals, they became restless and displayed motor excitation, increased reflex excitability, and so on. In response to a pinprick which, before injection of the anesthetic, gave rise to an ordinary skin-muscle reflex, they presented a violent generalized reaction. The same doses of the drugs had no effect on the behavior of the control guinea pigs. An increased tolerance to local anesthetics in animals irradiated with roentgen rays was also observed in experiments on mice exposed to a dose of 700 r. These showed that LD_{50} for novocain when injected subcutaneously was 0.55 mg/g for nonirradiated mice and 0.43 mg/g for irradiated mice

Variations in the pharmacological effect of a drug are largely determined by the physiological state of the organs and systems on which it acts. The question of the functional and morphological changes in the nervous elements of the cornea of irradiated animals has received scant attention in the literature. Very slight morphological changes in the nerve fibers and nerve endings in the cornea after local irradiation of the animal's eye in doses of 1800 and 3600 r have been described by T. V. Krestinskaya [5] in the only reference to this subject. We know, however, that disturbances in the physiological state of the sensory nerve endings in other regions have been found immediately after irradiation and over the next 2-4 days, frequently intermittent in character [2, 6, and others]. We may therefore assume that the changes which we observed in terminal anesthesia due to decicaine were associated with transient

TABLE 2. Duration of Infiltration Anesthesia before and after Irradiation of Guinea Pigs with Roentgen Rays (350 r)

Drug	Concentration of drug (%)	Duration of anesthesia (in minutes)						
		before irradiation	time after irradiation					
			30-40 min	days				
				1st	3rd	5th	7th	9th
Novocain	1	35	12	9	15	19	13	16
		100	34	26	43	54	37	46
Bencaine	1	31	15	8	13	13	10	13
		100	48	26	42	42	32	42
Mesocaine	0,25	27	12	9	—	3	0—1	—
		100	44	33		11	0—3	

Note: The duration of anesthesia is given in the denominator as a percentage of the original value.

changes in the functional state of the sensory nervous elements of the cornea, arising as a result of irradiation. The disturbance of the conditions of distribution of the anesthetic on account of increased permeability, changes in intraocular pressure, and so on, may also have been of some importance.

The fact that the sensory nerve fibers of the irradiated animals were more vulnerable to the action of the local anesthetic was also attributable, evidently, to certain changes in the condition of these fibers resulting from irradiation. It must be pointed out, however, that until recently functional changes in nerve fibers have been described only after whole-body irradiation of animals with lethal or super-lethal doses or after local irradiation in very high doses. We may conclude from our findings that these changes also develop after the administration of comparatively small (for cold-blooded animals) doses of radiation, such as 5000 r.

So far as the weakening of the local anesthetic action during infiltration of the tissues is concerned, this must evidently be attributed to the rapid lowering of the concentration of anesthetic at the site of injection and its penetration into the blood stream, as indicated by the onset of signs of its general toxic action on the animal. The probable reason for this was the increase in tissue permeability taking place during the first hours after irradiation [4 and others]. The anesthetics may, in turn, aggravate the disturbances of permeability. That this was possible was demonstrated by A. M. Ivanitskii [3], who observed an increase in the tissue permeability of irradiated animals under the influence of novocain. Besides leading to increased penetration of anesthetics into the blood stream, this increased permeability also increases their toxicity.

We were thus unable to produce a sufficiently high concentration of anesthetic at the site of injection into the irradiated animals, and thereby to avoid its toxic action. Hence, the basic condition for obtaining deep and prolonged infiltration anesthesia was disturbed.

The problem of surgical anesthesia for radiation injuries requires a special study.

SUMMARY

Experiments were conducted on animals subjected to X-irradiation. A study was made of the features peculiar to the effect of local anesthetizing agents in various types of anesthesia. As revealed, the effect of decicaine on the cornea of the eye (terminal anesthesia) became intensified during the first hours after the irradiation of the animals (rabbits – 1000 r) and reduced by the end of the first 24 hr. The initial value of the effect was restored by the third day. The extent of novocain block of the sensitive conductors (conduction anesthesia) is greater in irradiated animals (frog – 5000 r) than that in nonirradiated ones. The analgesic effect of anesthetics (novocain, bencaine, mesocaine) weakened during infiltration anesthesia administered to the irradiated animals (guinea pigs – 350 r).

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