THE ACCUMULATION OF SULFATHIAZOLE IN INFLAMMATORY FOCI OF THE SKIN IN ANIMALS WHILE ASLEEP AND AWAKE

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In recent years drug-induced sleep has been widely used in the treatment of many diseases.

It is known that inhibition of the cerebral cortex of long or short duration may have a favorable effect on the development and course of certain pathological reactions [4-6, 9 and others]. It has also been shown that during sleep changes occur in the course of many physiological processes in man and animals. N. I. Leporskii observed a marked fall (tenfold) in the gastric secretion in healthy persons during sleep [8]. In rabbits, during sleep induced by medinal, the pulse is slowed, the respirations are less frequent and the body temperature falls [10]. It has further been shown that in rabbits during drug-induced sleep the concentration of penicillin in the blood and organs is higher than when awake, and the excretion of the drug in the urine of animals takes place more slowly [2, 3, 10, 13].

Investigations of the blood and urine of dermatological patients treated with sulfonamides have shown that at night, during sleep, the concentration of sulfonamides in the blood is considerably higher than during the daytime and the excretion of the drug in the urine of patients takes place more slowly during sleep. V. A. Kozlov observed delay in the excretion of ink particles from the peritoneal cavity of anesthetized animals [7]. S. Sh. Sakanyan observed increased absorptive powers of the reticuloendothelial system towards congo red in the majority of a series of animals under morphine-chloroform-ether anesthesia. He also showed that painful stimulation lowers the absorptive powers of the reticuloendothelial cells [14, 15]. Painful stimulation is known to be accompanied by severe constrictions of capillaries [1], which may be reflected in the deposition of dyes and drugs in the tissues.

In the present work we studied the influence of drug-induced sleep on the accumulation of sulfathiazole in foci of inflammation in the skin. For this purpose we carried out 3 series of experiments on 26 adult rabbits.

EXPERIMENTAL METHOD AND RESULTS

First series of experiments: accumulation of sulfathiazole in foci of inflammation in the skin due to the action of a 10% mixture of chloroform in alcohol in rabbits while asleep and awake. Application of a 10% mixture of chloroform in alcohol (9 parts chloroform by volume and 1 part of 96° ethyl alcohol) causes a sensation of burning and pain and later forms an inflammatory lesion of the skin, terminating by necrosis of the superficial or deep parts of the skin, depending on the exposure [11, 12]. Knowing these properties, we employed this mixture and investigated its effect on the development of inflammation and on the deposition of a drug in the skin of animals during sleep. Observations were made on 9 rabbits: 6 rabbits were given intravenous injections of hexobarbitone (5% solution) in a dose of 100 mg per 1 kg body weight and 3 rabbits were controls, i.e. did not receive the drug.

Sleep developed in the animals a moment after injection of the drug. As soon as they were asleep, these animals together with the controls were injected intravenously with 4 ml each of a 3% solution of sodium

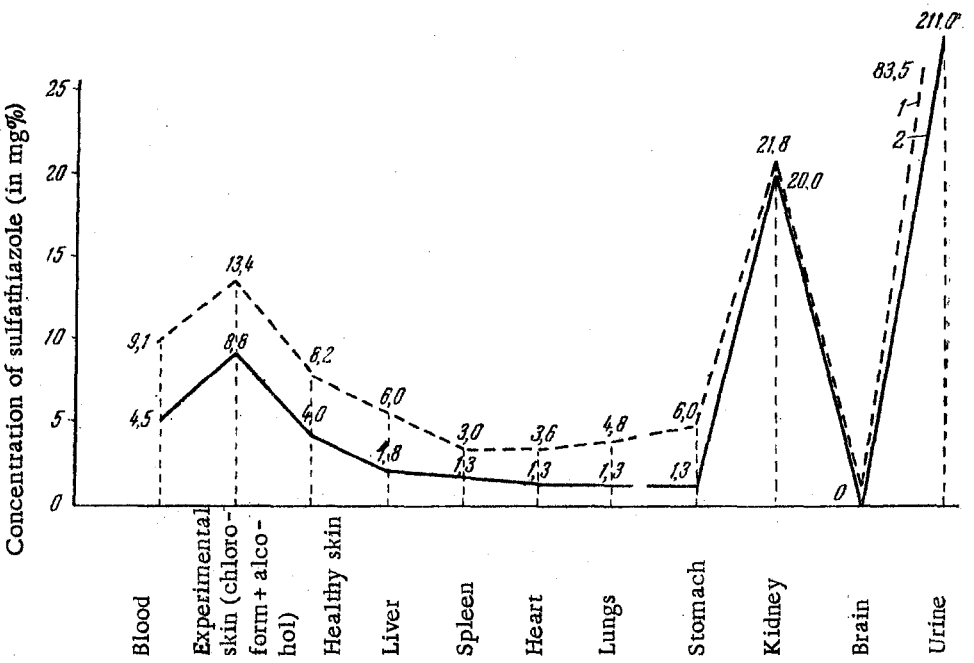

Fig. 1. Content of sulfathiazole (in mg%) in the blood, organs and urine of rabbits while asleep and awake, 1 hour after injection of the drug and application of a 10% mixture of chloroform in alcohol to the skin.
1) Sleeping animals; 2) waking animals.

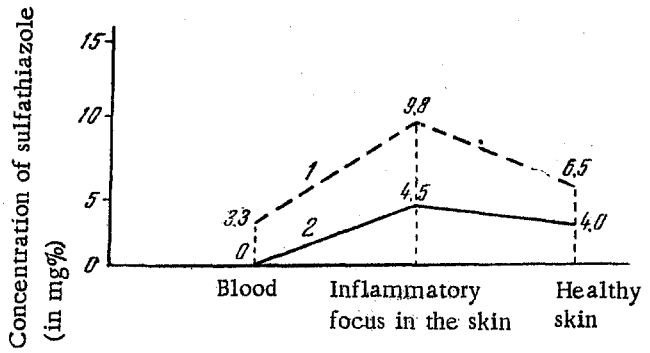

Fig. 2. Mean concentration of sulfathiazole (in mg%) in the blood, the inflammatory focus in the skin and the healthy skin of rabbits while asleep and awake.
1) Sleeping animals; 2) waking animals.

sulfathiazole per 1 kg body weight, and at the same time to the shaven skin of the lateral surface of the trunk was applied for 2 minutes a gauze swab soaked in a 10% mixture of chloroform in alcohol. All the control rabbits and some of the rabbits in a state of sleep reacted to the chloroform-alcohol mixture (they shuddered and twiched at the side).

At the site of application of the mixture the control rabbits developed clear erythema and edema of the skin; in the sleeping rabbits the erythema was less clear and the edema less marked. One hour after injection of sulfathiazole, 2 ml of blood was taken from the auricular vein and the animals were killed by injection of air into the vein. The organs of the animals were examined for their sulfathiazole content by A. M. Timofeeva's method.

During the investigation it was found that the sulfathiazole concentration in the skin at the site of action of the chloroform-alcohol mixture (in the experimental rabbit) and also in all the organs and blood of the animals in a state of hexobarbitone-induced sleep, was 2 or 3 times higher than that in the control animals (Fig. 1). The concentration of the drug in the urine of the animals during sleep was 2½ times lower than when awake.

The percentage of combined sulfathiazole in the urine of the sleeping animals was just over half (24%) that in the controls (45%). The increased concentration of the drug in the tissues of the sleeping animals, and the lower percentage of combined sulfathiazole indicate that in these animals during sleep the processes of combination of the drug are depressed and excretion of the drug from the body is slowed.

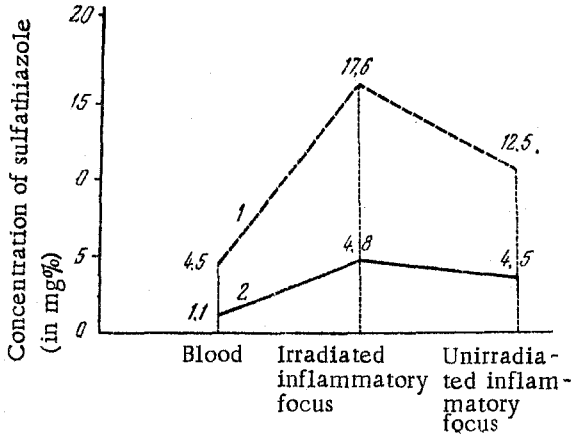

Fig. 3. Content of sulfathiazole in the inflammatory foci of rabbits irradiated by a Sollux lamp while asleep and awake. 1) Animals irradiated while asleep; 2) animals irradiated while awake.

Second series of experiments: accumulation of sulfathiazole in foci of suppurative inflammation of the skin in rabbits while asleep and awake. There were 10 rabbits in this experiment. All the animals were inoculated subcutaneously with 10^8 organisms from a 48-hour agar culture of a hemolytic Staphylococcus aureus. After 24 hours well marked foci of inflammation were seen at the site of injection of the culture of microorganisms, with the appearance of localized erythema and infiltration of the skin and a central pustule. The diameter of the foci of inflammation did not exceed 2-3 cm.

Six rabbits received intravenous injections of 5% hexobarbitone solution in a dose of 100 mg per 1 kg body weight. At the same time they were injected intravenously with a dose of 4 ml per 1 kg body weight of a 3% solution of sodium sulfathiazole. The remaining four (control) rabbits received sulfathiazole alone, without hexobarbitone. One hour after the injection of sulfathiazole an operation was performed on all the rabbits (the focus of inflammation and a piece of healthy skin were excised from the animals). Blood was taken from the auricular vein 2 hours after the injection of sulfathiazole. During the investigation we found the following concentrations of sulfathiazole (Fig. 2): in the control animals in the inflammatory focus — 4.5 mg%, in healthy skin — 4 mg% and in the blood — 0. In the animals receiving hexobarbitone (i.e. sleeping), the concentrations of the drug were significantly higher than in the controls: in the inflammatory focus — 9.8 mg%, in healthy skin — 6.5 mg% and in the blood — 3.3 mg%. The higher concentration of the drug in the tissues of the sleeping animals indicated that accumulation of sulfathiazole in the tissues is more strongly marked in animals during sleep.

Third series of experiments: accumulation of sulfathiazole in foci of inflammation of the skin in animals under the influence of irradiation by a Sollux lamp while asleep and awake. There were 7 rabbits in the experiment, and in each of them 2 suppurative inflammatory foci were induced in the skin by intradermal injection of 10^8 microorganisms from a 24-hour agar culture of a hemolytic Staphylococcus aureus into the lateral surface of the trunk. 24 hours after inoculation, 4 rabbits were given intravenous injections of hexobarbitone (5% solution) in a dose of 100 mg per 1 kg body weight; the 3 remaining rabbits did not receive hexobarbitone and acted as controls. Immediately after falling asleep all the rabbits (sleeping and controls) were injected intravenously with a dose of 4 ml per 1 kg body weight of a 3% solution of sodium sulfathiazole, and at the same time one inflammatory focus was irradiated for 15 minutes by a Sollux lamp at a distance of 20 cm. As a result of irradiation the erythema of the skin at the foci of inflammation was intensified. All the control rabbits reacted with pain to the irradiation (they twitched at the side, trembled and tried to get away from the apparatus). Two hours after the injection of sulfathiazole, 2 ml of blood was taken from the auricular vein of the animals and the foci of inflammation in the skin were excised.

The following concentrations of sulfathiazole were established by the investigation (Fig. 3): in control animals — in the blood — 1.1 mg%, in the irradiated inflammatory focus — 4.8 mg%, unirradiated — 4.5 mg%; in the experimental rabbits (receiving hexobarbitone) — in the blood — 4.5 mg%, in the irradiated inflammatory focus — 17.6 mg%, unirradiated — 12.5 mg%, i.e. in the last series of animals the concentration of sulfathiazole in the tissues examined was almost 4 times as high as in the first series. The amount of free sulfathiazole in the sleeping animals reached 55 mg% in the blood, 74 mg% in the irradiated inflammatory focus and 88 mg% in the unirradiated focus; meanwhile the values for the control animals were: in the blood — 0, in the irradiated inflammatory focus — 48 mg% and in the unirradiated focus — 62 mg%. The higher level of free sulfathiazole in the blood of the sleeping rabbits indicates a slowing of the processes of combination of sulfathiazole in these animals.

From the experiments described the following conclusions may be drawn.

In animals receiving painful stimulation by a mixture of chloroform and alcohol while asleep, the concentration of sulfathiazole in the tissues is higher than in animals similarly stimulated while awake, and under these circumstances the sulfathiazole concentration in the inflammatory foci in the skin is higher in the sleeping than the waking animals.

The sulfathiazole concentration in the inflammatory foci in the skin is higher in animals irradiated with a Sollux lamp while asleep than in those irradiated while awake, and the sulfathiazole content of the urine in sleeping animals is $2\frac{1}{2}$ times lower than in waking animals, which may indicate a depression of the excretory function in animals in a state of sleep.

The lower percentage of combined sulfathiazole in the tissues of sleeping animals is evidence of retardation of the combination of sulfathiazole in these animals.

SUMMARY

The accumulation of sulphathiazol was studied in inflammatory foci of the skin of rabbits during sleep. The injury was inflicted with 10% mixture of chloroform and alcohol applied to the skin or by the intradermal injection of staphylococcus culture. Sleep was induced by the administration of hexabarbitone. The animals were sacrificed or operated in 1-2 hours after the administration of sulphathiazol. The concentration of sulphathiazol in the blood, inflammatory foci and internal organs was found to be greater during sleep than while being awake. The irradiation of the inflammatory foci by ultraviolet rays during sleep resulted in intentified accumulation of sulphathiazol in the inflammatory foci as compared to the accumulation in the animals irradiated while awake.

LITERATURE CITED

[1] Z. M. Butkovskaya and R. A. Fel'berbaum, Byull. Éksptl. Biol. i. Med. 7, 19-23 (1957).*

[2] I. N. Vedrova, The Role of the Nervous System in the Pathogenesis of Skin and Venereal Diseases, 211-224, Leningrad (1957).**

[3] I. N. Vinokurov, Zhur. Mikrobiol. Épidemiol. i Immunobiol. 2, 18-19 (1952).

[4] V. S. Galkin, Anesthesia, Izd. VMMA (Naval Medical Academy) (1944).**

[5] P. F. Zdrodovskii, Med. Rabotnik No. 90 (1953).

[6] P.F. Zdrodovskii, Reactivity in Infection and Immunity, Moscow (1950).**

[7] V. A. Kozlov, Mechanisms of Pathological Reactions No. 16-20, pp. 150-157 (1950).**

[8] N. I. Leporskii, Transactions of the Naval Medical Academy vol. 24, pp. 85-87, Leningrad (1950).*

[9] N. M. Ovchinnikov, Vestnik Venerol. i Dermatol. 3, 33-38 (1952).

[10] N. M. Ovchinnikov and R. L. Zelikova, Vestnik Venerol. i Dermatol. 3, 16-20 (1951).

[11] S. K. Rozental', Experimental and Clinical Investigations, vol. 4, pp. 39-49, Leningrad (1945).**

[12] S. K. Rozental', Experimental and Clinical Investigations, vol. 7, pp 168-186 (1949).**

[13] S. N. Sazhina and L. A. Shteinlukht, Experimental and Clinical Investigations, vol. 10, pp. 80-83 (1954).**

[14] S. Sh. Sakanyan, The Effect of Pain on the Absorptive Power of the Reticuloendothelial System, Dissertation, Erevan (1939).**

[15] S. Sh. Sakanyan, Klin. Med. 2, 67-73 (1951).

*Original Russian pagination. See C. B. Translation.

**In Russian.