JPRS: 4633

22 May 1961

CZECHOSLOVAK STUDIES OF EFFECT OF NEUROPLEGIA ON RADIATION CASES AND OF THE DANGERS OF AEROSOL INHALATION

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1636 CONNECTICUT AVE., N.W.
WASHINGTON 25, D. C.

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JPRS: 4633

CSO: 1706-S

CZECHOSLOVAK STUDIES OF EFFECT OF NEUROPLEGIA ON RADIATION CASES AND OF THE DANGERS OF AEROSOL INHALATION

[Following are translations of articles on the above subject, selected from a Czech source. Further source information accompanies each article.]

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THE INFLUENCE OF NEUROPLEGIA ON THE COURSE OF RADIATION SICKNESS AND BURNS

[Following is the translation of an article by L. Klabusay et al. in Casopis Lekaru Ceskych (Czech Physicians Magazine), Vol C, No 9, Prague, 3 March 1961, pages 262-264.]

The working committee of the Burn Therapy Section in Ostrava has been working for several years on burn problems. Good results were achieved by timely application of neuroplegia, especially of the modified mixture M_2 (hydergine, pathesin, sandosten-calcium). The clinical treatments were most successful with small doses of the M_2 mixture.

In certain instances, burns and irradiation may occur at the same time. Our good experience with the modified mixture M_2 encouraged us to experiment further and find out whether in case of both burns and irradiation the neuroplegia would have an healing effect also.

TABLE 1

Group of animals	Died in 7 days	Died in 28 days	Survived %	Condition of the burned area	Significance
Burned animals	9	2	45	13.2 ± 0.6	-
Irradiated animals	0	16	20	-	-
Irradiated and burned animals	7	13	0	13.4 ± 0.74	unimportant
Burned animals treated with the M_2 mixture	3	0	85	9.8 ± 1.1	$p = 0.05$
Burned and irradiated animals treated with the M_2 mixture	8	12	0	14.9 ± 0.91	unimportant
Irradiated animals treated with the M_2 mixture	0	18	10	-	-

The Experiment

For our experiment we used male rats of the Wistar type, weighing 120 to 150 grams. These rats were fed with Larsen food. We divided them into six groups of 20 rats each in the following manner:

1. Burned without treatment. 2. Irradiated without treatment. 3. Burned and irradiated without treatment. 4. Burned and treated with the M_2 mixture. 5. Irradiated and treated with M_2. 6. Burned, irradiated and treated with the M_2 mixture.

Animals were burned, in accordance with previous experiments, with gas flames. Rats were exposed to the flame for 20 seconds and burns covered an area of 5x6 cm on the depilated skin of the back. In case of both burns and irradiation, the animals were exposed first to irradiation and 60 minutes afterwards to flames.

The therapeutical Roentgen apparatus of the SUPER-SANAX type was used for irradiation under the following conditions in each case: 180 kV, 15 mA, filter 3 Al, OK 100 cm r/min. 16.6.

TABLE 2

Groups of animals	Content of ascorbic acid in adrenal capsules, gama/mg	Lipids in adrenal capsules	Weight of adrenal capsules, mg/100 g.
Burned animals	2.8 ± 0.17	decreased	28.2 ± 3.4
Irradiated animals	2.4 ± 0.23	decreased	30.7 ± 2.6
Irradiated and burned animals	2.2 ± 0.21	decreased	31.2 ± 2.1
Burned animals treated with the M_2 mixture	3.62 ± 0.16	normal	26.4 ± 2.8
Burned and irradiated animals treated with the M2 mixture	2.7 ± 0.12	decreased	32.3 ± 3.3
Irradiated animals treated with the M_2 mixture	1.9 ± 0.28	decreased	26.4 ± 3.2

Statistically important is the content of ascorbic acid in adrenalin capsules only in case of burned animals treated with M_2 mixture (3.62 gama/mg). Other comparisons are insignificant.

The first day, the modified mixture M_2 was served to the animals one hour before burns were effected and 12 hours afterwards. During the

four following days, the mixture was used twice a day and subsequently injected into a muscle once a day. In this manner, injections were continued to the end of the experiment. Each serving of the modified mixture M_2 was prepared in the following manner: hydergine - 0.2 ml per kg, 5 per cent pathesin - 2 ml per kg, sandosten-calcium - 3 ml per kg. The mixture was prepared by dilution in physiological solution. The amount applied was 1 ml per animal.

In cases where treatment of burns was not undertaken, the skin of burned animals was deadened and on the whole alternated. We classified the effected areas by measuring the longest two diameters (maximum 6x5:2 = 15). We also classified the length of survival in two groups, 7 and 28 days, and the extent of the burned area after 10 days. The content of ascorbic acid and lipids in adrenal capsules was examined five days after burns. For that experiment, other rats were used, eight rats in each group. The animals were put to death and the adrenal capsules were weighed. In one adrenal capsule the content of ascorbic acid was determined by the Roe and Kuether method. The other adrenal capsule was subjected to histological examination for the content of lipids. Results are shown in Table 2.

Analysis and Discussion

Table 1 shows that survival is greatest in the group of burned animals treated with the M_2 mixture. When these animals were irradiated afterwards, none of them lived over 28 days. The same applies to the group of burned and irradiated animals that were not subjected to treatment. In the group of irradiated rats not treated with the M_2 mixture, the survival was slightly higher, 20 per cent, as compared with 10 per cent of the group subjected to treatment. Similarly, the healing effect of the M_2 mixture was apparent only in those cases where the animals were not concurrently irradiated. The content of the ascorbic acid in the adrenal capsules was greatly decreased in all irradiated animals. In the group of irradiated animals treated with the M_2 mixture, this decrease was most remarkable. On the other hand, we proved that the M_2 mixture checked the decrease of ascorbic acid in the adrenal capsules in the group of burned but not irradiated rats.

The experiment has provided evidence that the M_2 mixture has a beneficial effect on burns and the entire healing process only in case of burned animals. It is most probable that the M_2 mixture is also beneficial to the adversely effected catabolic phase (content of ascorbic acid) following the burning period. Mixture M_2 shows no healing or protective effect on animals which were concurrently irradiated. Similar results were reached by Stepanek and Praslicka with hibernization of irradiated animals.

It is evident that the modified mixture M_2 has an adverse effect on the course of burn disease if the animals are concurrently irradiated. We do not know as yet what is the cause of this adverse effect in combined cases of irradiation and burns.

Summary

The effect of small doses of a modified mixture M_2 on the course of irradiation sickness and burns was investigated. It is evident that the M_2 mixture during concurrent irradiation of the animals loses its therapeutic effect on burns and even has an adverse effect on the course of the disease.

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ACCIDENTS AND DANGERS ASSOCIATED WITH AEROSOL INHALATION TREATMENT

[Following is the translation of an article by Dr I. Pavlik in Casopis Leakaru Ceskych (Czech Physicians Magazine), Vol C, No 9, Prague, 3 March 1961, pages 275-277.]

Inhalation of medicaments is considered to be the most harmless form of treatment. It is maintained that the toxicity is lowered when drugs are applied through inhalation, as for instance in the case of adrenalin (Friebel, Graeser and Rowe). In spite of this we meet with adverse and even dangerous consequences of the inhalation treatment. All of these cases are more or less characteristic of this method.

Deep inhaling alone, overdone by some patients in the belief that the healing process is accelerated, may lead through hyperventilation to akalotic symptoms, caused by decrease of potassium and calcium in the serum and by decrease of blood pressure (Schaub and Co.) The inhaling person experiences dizziness and weakness. The sensitive, vaso-labile patient, may experience short fainting spells. The period after inhalation is sometimes accompanied by headaches of vaso-motor nature, caused either by previous hypocapnia or sometimes by mechanical, osmotic and thermic irritatior of the mucous membrane of the nasal cavity or the paranasal cavities.

When the nose cavity is rinsed, or when the patient inhales with the Schnitzer equipment, an infection may be carried with the stream of the liquid into the mouth of the eustachian tube and cause catarrh or even inflammation of the middle ear. This inflammation can easily happen especially in cases of acute rhinitis with abundant secretion, rich in virulent infectious agents. In such cases I advise against inhalation.

In the spacious and moist atmosphere of the inhalatorium, a mildew infection may be incurred, especially in cases of insufficiently ventilated and disinfected halls. With men, the freshly shaven skin can be effected by mildew and cause a mycotic eruption. It is advisable, therefore, not to shave with razor blades before taking the treatment. Electric shavers leave the skin more firm and less prone to infection. Eruptions so incurred can be easily healed by tar paste with salicyl.

A rare, yet occurring accident is the dislocation of the mandible when inhaling with a mouthpiece. This accident may happen not only in cases of habitual dislocation but also as a first case. In such instances

it is necessary, of course, to abstain from the inhaler and to fix the dislocated mandible through the usual treatment (liquid and mashed food, careful talking) to prevent recurrent dislocation.

More dangerous is the inflammation of the larynx which may occur after the inhalation. This is usually the case with patients having a small measure of pre-existing edema or hightened tissue irritation because of a sluggish local process. In cases of throat tuberculosis or carcinoma, edema of the larynx may develop only a few hours after inhalation of pure mineral water. Edema of the larynx could cause such a breathing obstacle that tracheotomy has to be executed. In most cases, however, the narrowing of the larynx grows worse gradually and usually climaxes in dyspnea during the night, requiring immediate help.

In a few cases, inhalation causes mycotic embolization into the brain. It is well known that the septic deposit process in lungs is sometimes complicated by the metastatic abscess in the brain (10 - 15% of the cases, according to Aschoff Herxheimer). Inhalation can be the stimulant in these cases and spread the infection. There is no doubt that heightened blood circulation and deep breathing accelerate such a process.

We shall describe an interesting case of a male patient, J. K., No. 118/51, 31 year old, an auto driver. This patient was sent to us after a month of treatment in a hospital for a nonspecified empyema of the left chest. Our diagnosis pointed to bronchiectasis of the lower left lobe with a retraction of the left hemitorax. For brevity we shall mention only facts directly connected with the brain complication. The fourth day after inhalation the patient complained about numbness that started in the right foot and spread through the right side of the body to the head. This feeling lasted a few minutes and the patient was shaky when walking. Subsequently, this phenomenon occurred twice a day, sometimes when he was walking, sometimes while he was resting. Three days later this numbness was accompanied by constriction of muscles in the right upper part of the trunk, lasting for about two minutes. The next morning, after breakfast, while defecating, he was again struck by the muscle constriction in the right part of the trunk. His right leg and right arm were paralyzed and he could not walk.

The neurological examination states: the skull not painful when tapped, nerves I, II, VIII subjective without difficulties, temporal veins solid and winding. Slight exophtalmus, bulbs freely movable in all directions, absence of nystagmus. Pupils isocoric, react well to both stimuli. In the area of the second and third branch of nerve V, slight hyperesthesis to the right. Function not affected. Cheek nerve inervates correctly. Labial reflexes increased. Tongue coated, lies in central line, soft palate freely movable. Neck: nape not painful, stems and protrusions of nerves also not painful. Blood pressure 110/80, pulse 60/min. Stomach soft, arephlexis to the right, is missing on the left. Stomach musculature shows in the right half periodical rhythmic cramps which shake the patient's whole body. Right cremastic

reflex missing. Upper extremities: R. bicipit slightly lower on the right, to the right Mingazzini drop. Lower extremities: L 2-S 2 symmetrically outfitted, alive. Hypotonisis to the right. On the right positive irritative and destructive pyramidal appearances. Walk: spastical to the right. Standing: 1-III light titubation. Right side hemiparesis with epilepsis of the Jackson type to the right. Suspicion of a metastatical brain abcess from a bronchial deposit was expressed. Sedimentation of red blood cells during the entire stay in the sanatorium was increased, around 30 mm/hr, temperature normal with occassional subfebrilia, urine b = 0, s = 0, white blood cells not found. Background of both eyes normal. Blood sugar 115 mg%, residual N = 58 mg%, NaCl = 481 mg%. ECG is physiological (preponderance of the left ventricle). Picture of the skull shows no provable pathological changes. The number of leucocytes is 14,600.

The patient was transferred to the neurological section of the KUNZ in Gottwaldov. From there he was sent to the neurological clinic in Brno. This clinic confirmed a brain abscess, and the patient was cured with penicilin.

Therapy through antibiotics presents a new source of drug allergy. Aerozol therapy with penicilin was introduced by Abramson in 1940. Penicilin was introduced by Abramson in 1940. Penicilin is blamed for forty death cases and many severe anaphylactic reaction (Coleman and Siegel) [See Note].

([Note] In 1957 Peters listed the unbelievable number of 1,000 death cases in the US alone. According to the WHO survey in 17 countries, the mortality rate in penicilin treatment is 1 per 70,000.)

It is assumed, for instance, that streptomycin is a hapen attached to alpha and beta globulins of sera and in this manner transformed into an antigen. (Mosonyi et al.) Similar process of allergization may be true with other antibiotics. It is necessary to point out that the first dose of an an antibiotic may cause irritation on different levels. The patient may be sensitized by a hardly noticable mildew infection of the skin, as for instances the interdigital epidermophytosis of the foot (Reichlin et al.) Not only antibiotics, but other microorganic products may cause allergy. The use of trypsin is not without danger either. The allergic reaction occuring while one inhales antibiotics may be manifested only by unpleasant dryness of the mucous membrane of the mouth which may develop into stomatitis, and can cause cheilitis and glossitis, obstructed expectoration and breathing. Inhalation is sometimes a cause of asthma paroxysm. Serious anaphylactic reactions have never been noticed with therapeutic inhalation. While not tolerating regular antibiotics, the patient may be treated by those which are not absorbed by the mucous membrane when inhaling and which do not cause sensibilization as does tyrotricin aerozol (Wolfer) or bacitricin. The patient may become oversensitive to any element, even to adrenalin and its derivatives. It is necessary to distinguish between allergic sensibility and inverse reaction to overdoses.

Little attention is given to the whole effect of inhalers. A mist of antibiotics is dispersed through exhaling into a wide surrounding of the inhalatorium. This mist settles on walls, floors, furniture, and comes into contact with a monumental number of microbes which the antibiotic is unable to destroy. On the contrary, resistant microbes develop in an unforseeable proportion. We have to consider also the fact that more than half of the applied antibiotics is wasted without any benefit to the patient, and that others may encounter resistant microbes. Therapeutic inhalation of antibiotics requires careful consideration and abstention from inhalation if a direct local application may be used. We consider it an absurdity to apply a million units of penicilin through inhalation four times a day in cases of lung abscesses if it is sufficient to apply 100,000 units directly into the cavity (besides the rest of the treatment). In the case of a lung deposit, aerozol reaches all other places, but not the area it is aimed for. Such collosal doses are used because the effected part does not ventilate as effectively as the rest of the lungs, and the absorbed antibiotics are also less effective. In this area, a vaso-constriction may occur, affecting the whole lung and causing development of resistant microbes. In vitro we find them to be good receptors, as for instance tuberculosis mycobacteria on streptomycin. Clinically, this reaction is of small importance. It is evident, however, that such resistance can develop into a real resistance.

With today's technique of inhalation we cannot speak about inhalation of strong and effective medicaments, as, for instance, cardiac tonics, insulin, etc. Because of the great amount of dispersion, it is impossible to accurately estimate the dose. We are compelled, therefore, to choose another way of application, as, for instance, rectal application, if peroral application or injection is impossible.

We tried to prove that even such a harmless therapy as the inhalation of medicaments of low toxicity can be accompanied by unpleasant accidents, more or less characteristic of this method. We have to point out the dangers because of the expanding use of this treatment. We have to demand from our production such apparatuses as will satisfy our need, decrease waste of medicaments and remove the danger of cumulative development of microbiotics resistant to antibiotics.

Summary

Inhalation treatment is a relatively safe method unless highly differentiated drugs are used. Nevertheless, accidents are possible. Hyperventilation alone causes difficulties. The stream of the fluid can carry the infection to the middle ear, the skin may be irritated and infected in the moist and spacious inhalatorium. In inhalations by means of an apparatus, dislocation of the mandible occurred. Inhalation also caused severe edema of the larynx. The development of a metastatic brain abscess was also observed in direct connection with the inhalation treatment. Allergic reactions to antibiotics and other substances are frequent. There is considerable danger of the development

of resistant microbes as a result of the dispersal of non-utilized aerozol of antibiotics. It is therefore necessary to produce inhalation apparatuses which will prevent the waste of antibiotics and do away with the dangers mentioned.

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