PHARMACOLOGY

THE EFFECT OF VARIOUS ANESTHETICS ON THE DEVELOPMENT OF TOXIC PULMONARY EDEMA CAUSED BY AMMONIUM CHLORIDE

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Information about the pathogenesis of toxic pulmonary edema, produced by various substances (nitrites, phosgene, adrenalin, ammonium chloride, silver nitrate and others), is scant. The majority of investigators believed that the reason for the development of toxic edema was purely local injury to the vessels, changing the permeability of their walls with subsequent passage of liquid into the alveolar spaces.

The significance of neural mechanisms in the development of pulmonary edema has been shown in the works of national [1-3] and foreign [4-7] authors. In particular, the possibility of preventing the toxic pulmonary edema caused by adrenalin and ammonium chloride has been shown in the experiments of I. A. Serebrovsky. It remained unclear whether only ether has such an effect and whether this action of ether anesthesia is dependent on the inhibition of certain portions of the nervous system or on some side effects.

In order to clarify these questions, we carried out experiments on a model of toxic pulmonary edema while using anesthetics differing in their pharmacological and chemical characteristics.

The experiments were carried out on white rats. The first series of experiments was carried out on 32 animals. When 0.75 ml per 100 g weight of a 6% solution of ammonium chloride was administered intraperitoneally, as a rule by the 6-7th minute after the injection the rats developed an attack of acute tetaniform spasms. At the end of the attack, which usually lasted about 1-1 1/2 minutes, in all cases the animals were in a markedly depressed state, breathing infrequently, lacking corneal and pain reflexes. Later, breathing became less frequent, rales began. In a number of cases, the secretion of froth from the upper respiratory tract was observed. At the 30-40th minute the animals died.

At autopsy, the typical picture of pulmonary edema was observed even with macroscopic observation. A considerable amount of frothy liquid was found in the bronchial spaces. The lungs were solid, poorly aerated; on squeezing, depressions remained on their surface which did not disappear for a long time. In section, the pulmonary tissue was reddish-yellow in color, with hemorrhagic areas; a large amount of frothy reddish liquid ran off from the surface of the cut. The ratio of the weight of the lungs to the body weight of the animal was usually over 1%, reaching 2-2.2% in some cases, i. e. it was considerably greater than normal (0.7-1%).

Microscopic investigation showed that the alveolar spaces were filled with a proteinaceous liquid, in places with an admixture of erythrocytes. In some areas the erythrocytes filled the alveoli completely. In a number of cases a sharply demarcated perivascular and peribronchial edema of the connective tissue was found. The vessels were found to be plethoric. In the other organs (liver, kidneys, brain, spleen) plethora of the vessels was observed; in the liver and brain, in addition, slight perivascular edema was found.

In the second series of experiments, ammonium chloride was administered in the same doses during anesthesia produced by the subcutaneous injection of a 12% solution of urethane, using 1 ml per 100 g of weight. Fifteen animals were beheaded after 1-7 hours; 4 the next day. In 17 cases out of 19, pulmonary edema was not found in the course of either macroscopic or microscopic analysis. The weight coefficients of the lungs varied between 0.6-0.82. Only in two cases were separate hemorrhages and the appearance of edematous liquid in the alveoli observed; the coefficient reached 0.95-0.98.

In the third series of experiments, carried out on 20 animals, ammonium chloride was administered during ether anesthesia. Anesthesia was maintained for 1-2 hours, after which the rats were beheaded. In 17 cases pulmonary edema did not develop; the weight coefficients remained within normal limits. The ammonium chloride had a toxic effect on 3 rats and they died in 1-1 1/2 hours (from pulmonary edema); the weight coefficients were 1.1-1.45.

In the fourth series of experiments, carried out on 12 animals anesthetized with chloroform, the administration of ammonium chloride produced pulmonary edema in only one rat.

In the fifth series, 18 animals were anesthetized by the subcutaneous administration of a 5% solution of hexenal, using 0.3 ml per 100 g of the rat's weight. When anesthesia was achieved, ammonium chloride was injected. In 1 1/2 hours the animals were killed. Pulmonary edema did not develop in 14 rats.

In the sixth series, anesthesia was produced by the injection of 0.5-0.75 ml per 100 g of the rat's weight of a 5% solution of chloral hydrate. Out of 15 experiments, pulmonary edema was observed to develop in only 3 (the weight coefficients were 1.1-2.1; in the remaining cases they remained within normal limits).

In the next series of experiments, set up with 54 animals, the effect of anesthesia produced by the subcutaneous injection of a 1% solution fo chloralose using 0.5, 0.7 and 1-1.5 ml per 100 g weight with subsequent administration of ammonium chloride was studied.

In 10 experiments with a dose of 0.5 ml, which produced superficial anesthesia, pulmonary edema developed in all the animals. Administration of chloralose in a dose of 0.7 ml per 100 g weight prevented development of edema in 7 cases out of 25. When fatal doses of chloralose were administered (1-1.5 ml per 100 g weight) the animals died 1-1 1/2 hours after the experiment began, while in 9 cases out of 19 pulmonary edema did not develop.

The results of our experiments are shown in the illustration.

Microscopic investigation also indicates the absence of pulmonary edema in the cases when the weight coefficients were within normal limits.

In the supplementary group of control experiments, in which the animals were killed by the injection or inhalation of a lethal dose of anesthetic (hexenal, urethane, ether, chloroform, chloralose), pulmonary edema was only found in individual cases of death caused by inhalation of ether and chloroform; in all the rest of the experiments, neither macro- nor microscopic pulmonary edema was found. The weight coefficients corresponded to normal.

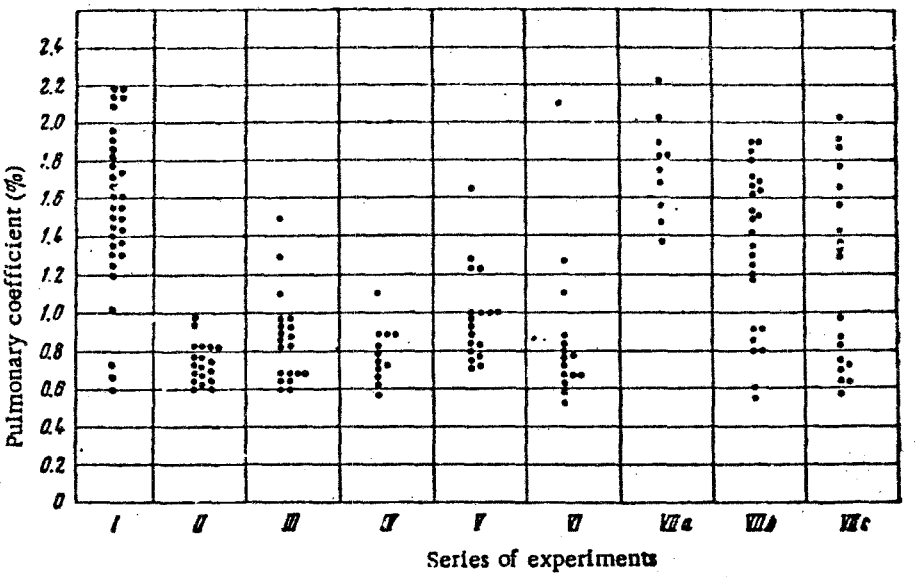
Summarizing the data we obtained, it can be observed that in the majority of cases preliminary anesthetization of the animal prevented the development of the toxic pulmonary edema caused by the administration of ammonium chloride. However, in a number of cases (experiments with chloral hydrate, ether, hexenal) pulmonary edema still developed after the administration of ammonium chloride, a fact basically connected, apparently, with the insufficient depth of the anesthesia.

The experiments using chloralose as an anesthetic should be put in a special group. The results of this series varied. But here also certain rules can be found; with light anesthesia, pulmonary edema developed in all the experiments, with medium anesthesia it was absent in 7 cases out of 25 and in deep anesthesia it was absent in 9 out of 19.

At the time our experiments were finished, Ya. A. Lazaris communicated* the data obtained in his laboratory on the possibility of preventing toxic pulmonary edema produced by ammonium chloride, by means of

*Enlarged quorum of the executive committee of the All-Union Society of Pathophysiologists (Moscow, 1953).

various anesthetics with the exception of chloralose. The author expressed the opinion that the indicated effect is dependent on the interruption during anesthesia of pathological reflex arcs which arise during the action of ammonium chloride. The author considers the brain stem area to be the level of these reflexes by which he explains the failure of chloralose, "a typical cortical" anesthetic by Pick's classification, as a preventative.



Effect of various anesthetic substances on the development of toxic pulmonary edema produced by ammonium chloride. I) Control group; II) urethane anesthesia; III) ether anesthesia; IV) chloroform anesthesia; V) hexenal anesthesia; VI) chloral hydrate anesthesia; VII) chloralose anesthesia; a) dose of 0.4 ml of a 1% solution per 100 g of weight; b) 0.7 ml; c) 1-1.5 ml.

In spite of the coincidences in the basic results of our experiments with the data of Ya. A. Lazaris and M. A. Serebrovskaya, we do not consider it possible to agree fully with the opinion of the indicated authors.

The results of the experiments with chloral hydrate which are characterized, in common with chloralose, by primarily cortical action do not fall within the framework of their concept. In experiments with various anesthetics (including hexenal and chloralose) a certain relationship can be observed between depth of anesthesia and its prevention of pulmonary edema, without regard to its pharmacological characteristics. Ya. A. Lazaris and I. A. Serebrovskaya did not take into account also the possible pathogenic significance of the direct action of ammonium chloride on the central nervous system and the sharp rise in its excitability.

The results of the experiments which were carried out permit denial of the importance of direct injury of the vessel walls by ammonium chloride in the pathogenesis of pulmonary edema. The prevention of pulmonary edema by the action of anesthetics also, apparently, is not determined by their direct effect on the permeability of the vessel membranes.

The speculation regarding the levels of the "pathological reflexes", based on Pick's representations regarding the localization of the action of anesthetics, cannot be admitted to be sufficiently well founded. The pathogenesis of toxic pulmonary edema (especially of its neurogenic components) requires further deeper study.

LITERATURE CITED

[1] G. S. Kan, Materials for Study of the Role of the Nervous System in the Pathogenesis of Acute Pulmonary Edema, * Dissertation (1951).

[2] I. A. Serebrovskaya, Byull. Eksptl. Biol. i Med. 1952, No. 5, pp. 45-49.

*Published in Russian.

[3] A. D. Speransky in the book, Lobar Pneumonias (Experimental and Clinical)*, (Moscow, 1942), pp. 3-17.

[4] G. Campbell, and M. Visscher, Am. J. Physiol. 157, 1, pp. 130-134 (1949).

[5] G. Cameron, and S. De, J. Pathol. Bacteriol. 61, 3, 375-387 (1949).

[6] H. Koenig, and R. Koenig, Am. J. Physiol. 158, 1, 1-15 (1949).

[7] E. Mackay, Proc. Soc. Expt. Biol. Med. 74, 4, 695-697 (1950).

*Published in Russian.