ROLE OF ANTIHISTAMINIC DRUGS IN THE PREVENTION OF ADRENALINE INDUCED PULMONARY OEDEMA IN RABBITS

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(Received December 16, 1956)

Pulmonary oedema can be produced experimentally in laboratory animals by certain chemicals and irritating gases. Adrenaline is one of the substances, which when injected intravenously into rabbits, produces rapid and fulminating pulmonary oedema (Auer and Gates, 1917). The mechanism of production however is not yet clear. It is already known that Phenergan prevents adrenaline induced pulmonary oedema in rabbits (Halpern. 1949) but Stone and Loew, (1949) did not confirm the findings of Halpern. In order to clarify this confusion it was decided to repeat the experiments of Halpern and also to study the effects of antistine and synopen not previously studied.

MATERIALS AND METHODS

Rabbits have been used in this study, their weight and sex were noted. The animal was anaesthetised with open ether anaesthesia. After 20 mts. induction of anaesthesia, adrenaline 0.25 mg/kg. of the body weight of the animal was injected intravenously into the marginal ear vein of the rabbit. Anaesthesia was continued for further 20 minutes or till the animal died whichever was earlier. After the injection of adrenaline if the animal was living, it was killed by blow on its head. The heart, the lung with portion of the trachea were taken out in one sweep from which the lungs were separated, and placed upon absorbent paper to remove the fluid trickling from the surface of the lungs. The weight of the lungs was determined and lungs body weight ratio was calculated (weight of lungs in gm. body weight in kg.)

Stock solution of adrenaline was prepared in triple distilled water to which 2 cc. of pure hydrochloric acid was added and the solution was kept in frigidaire to prevent deterioration. Dilute solution of adrenaline was prepared every day before use by diluting 10 times the stock solution.

TABLE 1

Showing the normal lung/body weight Ratio

S. L. No. of Rablits	Wt. of Rabbits in Kg.	Wt of lungs in Gms.	Ratio of lung in Gm/body Wt. in Kg.	Death occuring within 10 mt. of inj. of normal saline	Death occurring within 20 mts. of inj. of normal saline	Autopsy
1	1.8	8.3	4.6	0	0	No oedema
2	1.8	7.3	4.05	0	0	No oedema
3	1.7	7.7	4.52	0	0	No oedema
4	1.7	7.2	4.23	0	0	No oedema
5	1.9	7.8	4.1	0	0	No oedema
Mean	1.77	7.66	4.3	None	None	None

RESULTS

Several series of experiments were carried out. At the first instance control experiments were performed under deep ether anaesthesia and 1 ml. normal saline was injected into the marginal ear vein after twenty minutes from the start of anaesthesia and anaesthesia was continued for another 20 minutes. At the end of this period the rabbit was killed, the lungs were taken out and lung body weight ratio was determined, (Table 1).

In the second series pulmonary oedema was produced by injecting adrenaline I. V., the animal was killed, and lung body weight ratio determined (Table) 2)

TABLE 2

Showing the effects of adrenaline on lung body weight ratio

Wt. of Rabbit in kg.	Wt. of lungs in gm.	Ratio of lung in gm /body wt. in kg	Death occuring within 10 mts. of injection	Death occurring within 20 mts. of inj.	Autopsy
1.6	11.8	7.4	—	—	Oedema
1.5	11.7	7.8	—	yes	Gross oedema
1.55	14	9.3	yes	—	Severe oedema
1.7	13.6	8.	—	yes	Gross oedema
1.7	13.4	7.9	—	—	Gross oedema
1.6	12.9	8.08	one	two	Oedema
Mean					

Rabbits were premedicated with the antihistamine compound, anthisan (mepyramine maleate) in doses of 20 mg. kg. body weight intraperitoneally. The anaesthesia was started twenty minutes after the intraperitoneal injection of the drug and the entire procedure detailed above was carried out and lung/body weight ratio determined. (Table 3)

TABLE 3

Showing the effects of anthisan adrenaline induced oedema

Wt. of Rabbits in kg.	Anthisan I.P. in mg.	adrena-line I.V. in mg.	Wt. of lung in gm.	Lung/ body wt. ratio	Death in 10 mt.	Death in 20 mt.	Autopsy
1.25	50	0.5	8.8	5.17	—	—	No lung oedema
1.7	50	0.5	7.9	4.16	—	—	No lung oedema
1.7	50	0.5	10.8	6 4	—	—	Slight oedema
1.9	50	0.5	12.1	6.3	—	—	Slight oedema
2.7	60	0.75	13.8	5.1	—	—	No oedema
1.85	—	—	10.6	5.42	Nil	Nil	Slight oedema in two
Mean							

Similarly the other antihistamine compounds like antistine (antazoline), synopen and phenergan (promethazine) were used to find out their effectiveness, (Table 4, 5 and 6). The results were examined statistically by performing "t" test between the lung/body weight ratio of different groups of experimental results and they were found significant (Table 7).

TABLE 4

Showing the effects of antistine against adrenaline

Wt. of Rabbits in kg.	Antistine in mg I. P.	Adr. in mg. I. V.	Wt. of lung in gm.	Lungs body wt. ratio.	Death in 10 mts.	Death in 20 mts.	Autopsy.
1.23	25	0.8	7	5.6	..	..	slight oedema.
2.5	50	1	11.4	4.5	..	Killed after 20 mts.	No oedema
1.25	35	0.5	7	5.6	..	..	Slight oedema
1.9	50	0.5	9.5	5.0	..	..	No oedema
1.0	50	0.5	10	5.2	..	..	Slight oedema
1.75 Mean	..	..	8.9	5.12	..	..	Slight oedema in three.

TABLE 5

Showing the effects of synopen against adrenaline induced oedema.

Wt. of Rabbits in kg.	Synop. in mg.	Adr. in mg.	Wt. of lung in gm.	Lungs body wt. ratio.	Death in 10 mts.	Death in 20 mts.	Autopsy.
2	50	0.5	13.6	6.8	yes	..	Slight oedema
1.7	50	0.4	10.8	6.4	..	..	Slight oedema
1.3	40	0.3	5.6	4.3	..		No oedema
1.7	50	0.5	7.9	4.6	yes	..	No oedema
2.5	75	0.75	11.4	4.5	..	..	No oedema
1.8 Mean			9.8	5.3	2 Two	yes One	Slight oedema in two.

TABLE 6

Showing the effects of phenergan against adrenaline induced oedema

Wt. of rabbits in kg.	Phen. in mg.	Adr. in mg.	Wt. of lung.	Lungs body Wt. Ratio	Death in 10 mts.	Death in 20 mts.	Autopsy.
1.3	40	0.3	6	4.6	—	—	No oedema.
2	50	0.5	8.4	4.2	—	—	No oedema.
1.7	50	0.5	7.9	4.6	—	—	No oedema.
2.7	75	0.75	11.6	4.3	—	—	No oedema.
1.47 Mean			8.5	4.4	—	—	Oedema absent in all.

TABLE 7

Showing the significance of "t" test between experimental results

Group of expt.	Mean lung/ body wt. ratio with standard error.	Comparison between series.		Probability value.
		I & II	11.1	Significant.
		II & III	5.047	Significant.
		II & IV	7.50	Significant.
		II & V	4.49	Significant.
		II & VI	10.88	Significant.

DISCUSSION

The results obtained in the present series confirm, at the first instance, the long known observation that adrenaline causes acute fulminating pulmonary oedema in rabbits leading in almost all cases to a rapid and fatal termination. The data obtained from the present series show that the lung/ body weight ratio was 4. 3 in the control series, and it was almost double, namely, 8. 08 in the second series.

The present work clearly shows that the antihistamine compounds, anthisan, antistine, synopen and phenergan have difinite protective effects in adrenaline induced pulmonary oedema in rabbits. These experiments besides corroborating the findings of Halpern (1949) with regards to phenergan and anthisan have established the value of antistine and synopen. It appears that phenergan is the most potent of the antihistamine compounds and antistine the least so far this action is concerned, which is comparable to the findings of Bain (1949).

The present results and that of Halpern (1949) are contrary to the findings of stone and Loew (1949) who employing the same animals, namely, rabbits for their experiments found that anthisan and phenergan, failed to prevent pulmonary oedema although they observed reduction in mortality of the animals by phenergan. A closer analysis of their results reveals the following points of difference from the present work :

Stone and Loew used large doses of adrenaline to produce the pulmonary oedema, namely 0. 375 mg./kg. (calculated as the base) in comparison with the dose used in the present series. Premedication with antihistamine drug was done in a different manner by Stone and Loew. They injected phenergan intravenously (10 minutes before adrenaline). Stone and Loew used 1. 5 mg./kg. of antihistaminic agent which is very small in proportion to adrenaline that he used. According to Staub's observation (1939) if injection of adrenaline liberates histamine in the tissues then the amount of antihistaminic agents used by (Stone and Lowe) fails far short of the amount of histamine liberated and could not therefore effectively combat it. Secondly the subcutaneous injection of the antihistamine 30 mts. prior to intravenous adrenaline might not have ensured the availability of the protective drug when pulmonary oedema began to commence. Intraperitoneal route of premedication, as in the present series, in all probability ensured a more rapid and uniform absorption and utilisation.

SUMMARY

I. The effects of anthisan, antistine, synopen and phenergan against adrenaline induced pulmonary oedema in rabbits have been studied.

II. All the four antihistaminics studied in this series have been found to inhibit or prevent the occurrence of pulmonary oedema in rabbits. The results have been found to be statistically significant. Phenergan has been found to be the most potent of the antihistaminics studied, and antistine least.

III. The data of the present experiments are in accord with Halpern's (1948) findings that phenergan prevents the onset of adrenaline induced pulmonary oedema.

IV. The reasons as to why the results have been different from those of Stone and Loew (1949) have been discussed.

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