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# Effects of Benadryl on Anaphylactic and Histamine Shock in Rabbits and Guinea Pigs.

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Recent work[1,2] suggests that the mechanism of anaphylactic shock is best explained with the inclusion of a stage at which histamine is released. On the assumption that the release of histamine is the factor leading to shock and death, therapeusis of anaphylactic and allergic states has turned to β-dimethylaminoethyl benzhydryl ether hydrochloride ("Benadryl") and related drugs.[3,4] Success in this has been offered as further proof of the thesis that histamine intoxication is the chief untoward effect of anaphylaxis. Protection against anaphylaxis by benadryl was reported in experiments on passive sensitization of guinea pigs and intravenous administration of the antigen.

The experiments here reported resulted from a search for the antianaphylactic effects of benadryl. In the 2 species studied, one might expect that if the principal symptoms of shock and the cause of death attendant on anaphylactic shock were ascribable to the release of histamine, the amelioration of anaphylactic shock by benadryl would parallel its effects on histamine shock. That such is not the case is shown by the experiments which follow; the implications of these findings will be discussed.

*Experiment I.* To test the effects of benadryl on histamine shock in rabbits, 25 animals were employed, 12 of which received premedication with benadryl. The animals fell into 3 groups, each containing rabbits of similar size and history and each being divided into experimental and control groups. Benadryl was administered in divided doses totaling 10 mg per kg or in single doses of 4 mg per kg. Striking protection at all the dose levels is demonstrated in Table I.

*Experiment II.* To test the effects of benadryl on anaphylactic shock in rabbits, 23 animals were sensitized to egg white. This was accomplished by injecting egg white on alternate days in the following dosages: 1 cc, i.v.; 0.5 cc, i.v.; and 1 cc, i.m. The rabbits were used between 3 and 5 weeks following the first dose. Group A consisted of 10 rabbits so sensitized, half of which were premedicated with 5 mg of benadryl per kg 25 minutes before injection of the antigen. The 5 rabbits not treated with benadryl were all severely shocked, and 4 of 5 died. Those premedicated were similarly shocked, and none of the 5 animals recovered. In group B, benadryl (5 mg per kg in 3 animals; 10 mg per kg in 3) was administered 24 hours previously, with a second dose 20 minutes before the antigen. No difference in the effects of a smaller dose of antigen (0.6 cc) was observed between experimental and control animals.

*Experiment III.* To test the effects of benadryl on anaphylactic shock in the actively sensitized guinea pig, each of 11 animals was sensitized by a single intraperitoneal injection of 5 cc 25% egg white in saline. Twenty days later 7 of these received 10 mg of benadryl per kg administered intraperitoneally. Thirty minutes later 5 of the premedicated animals and 4 controls were injected intraperitoneally with 0.75 cc of egg white. All animals showed severe shock; 3 of 4 control, and 3 of 5 treated, guinea pigs died. Two animals given only benadryl showed no ill effects.

*Discussion.* Experiment I indicates that benadryl is, under the conditions of the ex-

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1 Dragstedt, C. A., *J. Allergy*, 1945, **16**, 69.

2 Code, C. F., *Proc. Staff Meetings Mayo Clin.*, 1945, **20**, 439.

3 Loew, E. K., and Kaiser, M. E., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 235.

4 Friedlaender, S., Feinberg, S., and Feinberg, A. R., PROC. SOC. EXP. BIOL. AND MED., 1946, **62**, 65.

TABLE I.
Effects of Benadryl on Histamine Shock in Rabbits.

| Group | No. | Wt, kg | Premedication | Histamine dose | Effect* |
|---|---|---|---|---|---|
| A | 1 | 1.8 | None | 2.0 mg hist. phosph. | 4 |
| | 2 | 1.8 | " | " | 4 |
| | 3 | 1.8 | " | " | 4 |
| | 4 | 1.8 | " | " | 4 |
| | 5 | 1.8 | " | " | 3 |
| | 6 | 1.8 | Benadryl, i.p., 5 mg per kg 4 | " | 1 |
| | 7 | 1.8 | hr before hist., plus 5 mg | " | 0 |
| | 8 | 1.8 | per kg 15 min before hist. | " | 0 |
| | 9 | 1.8 | | Died before hist. was admin. | |
| B | 10 | 2.5 | None | 2.75 mg hist. phosph. | 2 |
| | 11 | 3.4 | " | 4.13 | 4 |
| | 12 | 3.0 | " | 3.44 | 3 |
| | 13 | 3.0 | " | 2.75 | 4 |
| | 14 | 3.0 | Benadryl, i.p., 4 mg per kg, | 3.50 | 3 |
| | 15 | 3.2 | 15 min. before hist. | " | 0 |
| | 16 | 3.0 | | " | 0 |
| | 17 | 3.6 | | " | 0 |
| C | 18 | 2.3 | None | 2.10 | 3 |
| | 19 | 2.3 | " | " | 4 |
| | 20 | 2.3 | " | " | 4 |
| | 21 | 2.3 | " | " | 3 |
| | 22 | 2.3 | Benadryl, i.p., 4 mg per kg, | 2.10 | 2 |
| | 23 | 2.5 | 15 min before hist. | " | 0 |
| | 24 | 2.3 | | " | 0 |
| | 25 | 2.3 | | " | 2 |

* Four grades of shock were as follows: 1, signs of collapse but animal able to move when stimulated; 2, resting in normal position but unable to move; 3, prostrate position or on side; 4, dead of shock.

periment, an effective antagonist of histamine. This means either that it opposes histamine in its effect on the shock organs or that it acts chemically to remove or neutralize histamine. The present experiments do not differentiate between these 2 possible modes of action and the reader is referred to the recent discussion of Code.[2] The lack of antianaphylactic effect of benadryl shown in Experiment II, even in doses which were highly effective against histamine, indicates either that the histamine released upon anaphylactic shock is not vulnerable to this antihistamine drug, or that some other factor is involved in the shock and death caused by the antigen. As the most recent demonstrations of the antianaphylactic nature of these drugs have been made on guinea pigs, Experiment III on that species was set up (Table III). The 5 experimental animals all showed severe shock, though treated with 10 mg per kg of benadryl. Our results seem at direct variance with those of Loew and Kaiser[3] and Friedlaender, Feinberg, and Feinberg,[4] for they conclude that benadryl offers marked protection to anaphylaxis in the guinea pig. However, it is important to note that their animals were passively sensitized and that they administered the antigen intravenously. While the shock states which they observed were primarily pulmonary in nature, in our animals, in which the antigen was administered by a different route, the shock developed more slowly and was characterized principally by prostration with few respiratory symptoms. Similar alteration of anaphylactic shock with routes of administration other than intravenous have been demonstrated by Williamson.[5]

*Summary.* 1. Benadryl offers effective pro-

[5] Williamson, R., *J. Hyg.*, 1936, **36**, 588.

TABLE II.
Effects of Benadryl on Anaphylactic Shock in Rabbits.

| Group | No. | Wt, kg | Sensitive | Premedication | Shock dose | Effect |
|---|---|---|---|---|---|---|
| A | 1 | 2.0 | Yes | None | 1.0 cc egg white | 4 |
| | 2 | 1.8 | " | " | " | 4 |
| | 3 | 1.8 | " | " | " | 4 |
| | 4 | 2.0 | " | " | " | 4 |
| | 5 | 1.8 | " | " | " | 3 |
| | 6 | 2.3 | " | Benadryl, i.p., 5 mg per kg 25 | " | 4 |
| | 7 | 1.8 | " | min before injection with | " | 4 |
| | 8 | 1.8 | " | antigen | " | 4 |
| | 9 | 2.0 | " | | " | 4 |
| | 10 | 2.3 | " | | " | 4 |
| B | 11 | 1.8 | " | Benadryl, i.p., 5 mg per kg 24 | 0.6 cc | 3 |
| | 12 | 1.8 | " | hr before shock, plus 5 mg | " | 2 |
| | 13 | 1.8 | " | per kg 20 min before antigen. | " | 3 |
| | 14 | 1.8 | " | Benadryl, i.p., 10 mg per kg 24 | " | 4 |
| | 15 | 1.8 | " | hr before shock, plus 5 mg | " | 3 |
| | 16 | 1.8 | " | per kg 20 min before antigen. | " | 4 |
| | 17 | 1.8 | " | None | " | 3 |
| | 18 | 1.8 | " | " | " | 4 |
| | 19 | 1.8 | " | " | 1.0 cc | 3 |
| | 20 | 1.8 | " | " | " | 3 |
| | 21 | 1.8 | " | " | " | 2 |
| | 22 | 1.8 | " | " | " | 4 |
| | 23 | 1.8 | " | " | " | 2 |

TABLE III.
Effects of Benadryl on Anaphylactic Shock in Actively Sensitized Guinea Pigs.

| No. | Wt, g | Premedication | Antigen | Results |
|---|---|---|---|---|
| 1 | 350-400 | None | 0.75 cc egg white, i.p. | Died in 20 min. |
| 2 | " | " | " | " " 30 " |
| 3 | " | " | " | " " 35 " |
| 4 | " | " | " | Survived prolonged severe shock |
| 5 | " | 10 mg per kg 30 min before antigen | " | Died in 30 min. |
| 6 | " | " | " | " " 35 " |
| 7 | " | " | " | " " 40 " |
| 8 | " | " | " | Survived prolonged severe shock |
| 9 | " | " | " | " " " " |
| 10 | " | " | None | No ill effects |
| 11 | " | " | " | " " " |

tection against histamine shock in rabbits. 2. Benadryl did not protect against anaphylactic shock in rabbits sensitized to egg white. 3. Benadryl did not protect guinea pigs actively sensitized to egg white against anaphylaxis induced by intraperitoneal administration of the antigen under the dosage conditions employed.