Toxicity of Histamine and Dial with Urethane in Intact and Adrenalectomized Hamsters.* (22513)

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To select suitable doses of histamine, in a study of the effect of a chemical stress on peripheral circulation in the cheek pouch of the golden hamster (*Mesocricetus auratus*), data on toxicity of this substance in hamsters were accumulated. Since our observations of the circulation during stress with histamine necessitated the use of anesthesia, we have determined the toxicity of combinations of histamine and the anesthetic of choice, dial with urethane, selected because of sustained action from single doses. So far as we know, detailed information on the toxicity of histamine for hamsters has not been reported, and in view of the increasing use of this animal for experimental purposes an account of our work may be useful.

Methods. Tests were performed on 467 male hamsters, 8 to 10 weeks old, weighing 80 to 100 g. Of these, 271 were intact, 166 had been adrenalectomized 4 or 12 days previously, and 30 were sham-operated controls. The histamine used in most of the experiments was the chemically-pure base (Fisher). In previous work this form of histamine gave more uniform results, although more toxic than the acid phosphate (Burroughs-Wellcome) which has been commonly employed in adrenal studies. A few tests with the acid phosphate were done in 34 hamsters. Intraperitoneal injections of 5 to 10% histamine were used in adrenalectomized hamsters and a 20% solution was used for intact hamsters. Anesthesia was induced by dial with urethane (hereinafter referred to as DU), containing 0.1 g diallylbarbituric acid, 0.4 g urethane, 0.4 g monoethylurea per cc (Ciba Pharmaceutical Products, Inc.). Single doses of 0.1 cc per 100 g body weight injected intraperitoneally provided a constant level of anesthesia within one hour and lasting for more than 5 hours. Consequently, the dose of histamine was given one hour after the injection of DU. The body temperature of the animals was maintained during DU anesthesia by contact with glass coils containing circulating warm water. Pretreatment with cortisone consisted of 12 daily subcutaneous injections of a saline suspension of cortisone acetate (Cortone, Merck), 25 mg per cc, diluted when necessary with Aqueous Vehicle No. 1 (Merck). Toxicity tests were performed on the twelfth day. The total mortality in each series at the end of 4 hours after histamine was recorded as a measure of toxicity.

Results. The results of the tests on intact hamsters are summarized in Table I. The LD_{50} at 4 hours for chemically-pure histamine in unanesthetized male hamsters is approximately 75 mg per 100 g body weight. The combination of histamine with DU anesthesia is considerably more toxic (LD_{50} at 4 hours between 20 and 30 mg), although DU alone does not cause death. Pre-treatment with 12 daily doses of 0.3 mg of cortisone appreciably reduced the mortality resulting from 30 mg of histamine per 100 g in hamsters under DU anesthesia, and also provided some protection against 60 mg per 100 g. Pre-treatment with 5 mg of cortisone acetate per day for 12 days provided some protection against the larger doses of histamine in unanesthetized hamsters and against 30 mg per 100 g in the DU group. The smaller doses of cortisone may afford greater protection against histamine and DU intoxication than the larger doses, since 5 mg daily doses are toxic *per se* in the hamster(1).

Adrenalectomy increased the susceptibility of unanesthetized hamsters to histamine poisoning about 10 times (Table II). DU anesthesia alone was toxic to adrenalectomized hamsters, although it did not kill intact hamsters. Very small doses of histamine (0.25

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TABLE I. Toxicity of Histamine and Dial with Urethane in Hamsters with Intact Adrenals.

Procedure	Dose of histamine base (mg/100 g body wt) 0	20	30	40	55	60	65	75	80	90	95	100	Total No. of hamsters
No anesthesia					0* (10)	10 (20)	30 (10)	50 (10)	53 (15)	60 (20)	60 (10)	86 (15)	110
Dial with urethane anesthesia	0 (10)	33.3 (9)	90 (10)	80 (10)	100 (20)	100 (20)							79
Cortisone, 5 mg/day, for 12 days; no anesthesia						0 (10)		11 (9)				33.3 (9)	28
Cortisone, 5 mg/day, for 12 days; DU anesthesia	0 (10)		60 (10)			100 (10)							30
Cortisone, 0.3 mg/day, for 12 days; DU anesthesia	0 (9)		20 (10)			80 (10)							29
Histamine phosphate; no anesthesia												60 (5)	5

* Upper figure, % mortality within 4 hr; lower figure in parenthesis, No. of animals.

TABLE II. Toxicity of Histamine and Dial with Urethane in Adrenalectomized Hamsters.

Procedure	Dose of histamine base (mg/100 g body wt) 0	.25	.5	2	5	8	10	12	15	20	Total No. of hamsters
No anesthesia				0* (7)	18 (16)	66 (18)	86 (15)	60 (10)	100 (6)	100 (9)	81
DU "	78 (14)	100 (4)	100 (9)	100 (9)							36
Cortisone, 1 mg/12 days; DU anesthesia	0 (10)	0 (10)									20
Histamine phosphate; no anesthesia					0 (9)		20 (10)			50 (10)	29
Sham-operated controls; no anesthesia					0 (10)		0 (15)			0 (5)	30

* Upper figure, % mortality within 4 hr; lower figure in parenthesis, No. of animals.

mg per 100 g) combined with DU anesthesia were 100% lethal for adrenalectomized hamsters. Considerably larger doses (5, 10 and 20 mg per 100 g) did not kill any of the sham-operated controls. Histamine acid phosphate was likewise much more toxic to adrenalectomized hamsters. Pre-treatment with 12 daily doses of 1 mg of cortisone acetate provided complete protection within the 4-hour observation period, both against DU anesthesia alone and DU with 0.25 mg of histamine per 100 g.

The magnitude of susceptibility of the golden hamster to intoxication by intraperitoneal histamine is about the same as that of rats(2) or of mice(3). Consequently, the hamster may be considered as one of the more resistant species. Furthermore, the increase in susceptibility following adrenalectomy resembles that found in rats(4,3). The histamine tolerance test should, therefore, be useful in studying adrenal insufficiency in hamsters.

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