Toxicity of Betazole Hydrochloride for the Pertussis-Sensitized Mouse.* (31226)

SAUL MALKIEL AND BETTY J. HARGIS
Research Laboratory, The Memorial Hospital, Worcester, Mass.

Betazole hydrochloride (Histalog™) has been described as being as potent a stimulant to gastric secretion as histamine but without the characteristic side effects or toxicity of the latter(1,2). Pharmacological effects in the experimental animal include a) stimulation of gastric secretion in the dog(2), b) maintenance of blood pressure in the anesthetized dog(2) and cat(3), and c) the absence of a spasmogenic effect on the isolated guinea pig ileum(3). Moreover, this drug has been particularly useful in patients with allergic manifestations such as asthma, urticaria, etc., thus further emphasizing the diminished histamine-like action.

The present report presents additional data purporting to indicate that betazole is essentially without histamine activity. This conclusion is based on the observation that the toxicity of betazole for the white mouse is not enhanced by pertussis-vaccination. Under these experimental conditions, the lethal effect of histamine is enhanced 30- to 50-fold in this inherently histamine-insensitive animal(4). An apparent chronic toxicity to betazole is demonstrated concomitantly.

Materials and methods. White, female Carworth Farm mice (CFW) of about 26 g weight were used essentially in groups of ten. The animals were maintained on Purina Laboratory Chow and drinking water allowed *ad lib. Bordetella pertussis* phase I cells, 6×10^9, in 0.5 ml volume were injected intraperitoneally (i.p.). This was followed on the fourth subsequent day by an i.p. inoculation of various doses of either histamine phosphate or Histalog™† usually dissolved in no more than 0.6 ml volume of saline solution. Groups of unvaccinated mice serving as controls were treated comparably. The mortality rate was recorded after an additional 24 hours and, also, at 72, 96, and 240 hours for the control series.

Results and discussion. From the data in Table I the LD_{50} of histamine phosphate is 0.027 mg/g body weight for the pertussis-sensitized and 0.807 mg/g for the control, unvaccinated mouse as calculated by the method of Finney(5). The difference between these values is highly statistically significant, $p = <0.001$. The corresponding values for betazole, 0.72 mg/g and 0.86 mg/g, respectively, are not statistically significant. There is a highly significant difference between the values for histamine and betazole for the pertussis-sensitized ($p = <0.001$) but not for the control mice.

The mortality rate of normal mice resulting from an i.p. injection of betazole was recorded at 24 hours. At 0.4 mg/g dose the death rate was 10%, at 0.8 mg/g, 30%, and at 1.0 mg/g, 90%. However, even at the lower dose levels the death rate approached 90% at 96 hours following the single inoculation. In contrast, mice which fail to succumb within 24 hours after histamine challenge recover completely(6). Thus a chronic toxicity to betazole is demonstrated at the LD_{50} and lower dose levels.

The essentially identical LD_{50} of betazole obtained for the pertussis-treated and control mice is consistent with the hypothesis that this drug is devoid of any histamine-like action. This agrees with results of studies(2,3) obtained in other animals. The above observation demonstrating the toxicity of betazole further substantiates this concept. It should be stressed that in clinical practice 0.5 mg/1000 g of Histalog™ is comparable to the usually employed dose of histamine phosphate, 0.0275 mg/1000 g, for fractional gastric analysis. There is no toxic effect at this level which is approximately 1/1000th of the toxic dose of betazole for the mouse.

Summary. The LD_{50} of betazole for the per-

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TABLE I. Mortality of Pertussis-Treated Mice Following Challenge with Histamine and Betazole.

	Control mice		Pertussis-treated	
	Histamine	Betazole	Histamine	Betazole
LD_{50}	.807 mg/g*	.86 mg/g	.027 mg/g*†	.72 mg/g†

* The difference between these values is highly statistically significant, $p = <.001$.
† The difference between these values is highly statistically significant, $p = <.001$.
Challenge dose given on 4th day subsequent to pertussis-sensitization and deaths recorded after 24 hr.

tussis-sensitized mouse is about 80× that for histamine. Death following challenge is probably the result of a toxic effect other than a histamine-like shock. Betazole is considered to possess a negligible histamine-like action.

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Initial Dietary Influences on Antibody Absorption in Newborn Puppies.* (31227)

MYLON E. FILKINS† AND D. DALE GILLETTE (Introduced by M. J. Swenson)
Department of Physiology and Pharmacology, College of Veterinary Medicine, Iowa State University, Ames

The newborn animal can absorb ingested antibody for only a short period after birth. The factors which regulate this period of intestinal absorption of intact protein molecules are not well understood, although the subject of considerable research in several species(1, 2,3,4). Earlier work had indicated the possibility that the initiation of ingestion and digestion of food, particularly proteins, was linked to this limited absorption of antibodies (5,6). The present study was undertaken to investigate the influence of dietary protein on antibody absorption in newborn puppies.

The appearance of specific antibody in the blood after the antibody was fed is assurance of intestinal absorption, but contrarily the absence of the specific antibody in the blood after being fed poses the problem of whether or not this antibody was destroyed or altered after it passed intact through the intestinal epithelium. The progress of fluorescently labeled antibodies was followed in order to eliminate doubts of this kind.

Methods. Antibody absorption of puppies allowed to nurse was compared to that of puppies fed a sucrose-control diet, a balanced but synthetic diet, and to puppies not fed at all. Some puppies were naturally whelped and suckled. Surgically obtained, colostrum-free puppies were kept in groups of 2 or 3 in a room maintained between 24 and 29°C. All puppies were weighed and at various times after birth a randomly selected puppy was fed a single dose of the antibody at a rate of 3 ml/100 g. Blood samples were taken 12 to 15 hours later and analyzed.

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