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Study of histamine release induced by acute administration of antitumor agents in dogs

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Summary. The effects of eight antitumoral drugs known to cause anaphylactoid side effects in clinical use were studied in dogs. Blood pressure, heart rate, and blood and plasma histamine levels were monitored. L-asparaginase, methotrexate, 5-fluorouracil, bleomycin, and cisplatin had no effect on these parameters. Doxorubicin, Vehem (teniposide), and Vepeside (etoposide) induced hypotension, tachycardia, and a rise in histamine levels. In the cases of Vehem and Vepeside, the excipient (respectively, cremophor EL and tween 80) induced the same effects. These agents, like elliptinium, which had been previously studied, induce nonspecific histamine release – unlike the other drugs studied. The mechanism of clinically observed anaphylactoid side effects is discussed in the light of these findings.

Introduction

Several antitumoral drugs can cause anaphylactoid side effects in man, the symptoms of which are akin to those of type I hypersensitivity reactions [28, 30]. Weiss [30] has classified twenty-four implicated drugs in three groups according to the frequency of occurrence of accidents: appreciable risk (e.g., L-asparaginase, teniposide or Vehem, cisplatin), infrequent (e.g., doxorubicin, elliptinium, bleomycin, methotrexate), and very low (e.g., 5-fluorouracil estoposide or Vepeside). Turpin et al. [28] agree with this order, except cisplatin and Vepeside, which they found less and more frequently implicated, respectively. The mechanisms of these reactions are usually not known, and little experimental work has been done to elucidate them. Previous work on the systemic effects of elliptinium has revealed the ability of this drug to induce nonspecific histamine release in the dog [9], the guinea pig, and in human cells (basophils and lung tissue) [8]. We report here the results of the extension of this type of study to other antitumoral agents chosen according to two criteria: their ability to induce anaphylactoid reactions in man, and the fact that they belong to different classes of antitumoral agents. These agents were given to dogs and, as advocated by Lorenz [21], histamine-like effects were sought (e.g., hypotension, tachycardia), providing indirect evidence of histamine release, and direct assay of histamine in blood and plasma was performed. The results are discussed in the light of clinical observations.

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Material and methods

Animals

Thirty mongrel dogs of either sex, weighing 15 ± 3 kg, housed in individual cages in a large colony room, and starved overnight before the experiment, were used.

Procedure

Study of cardiovascular effects. Animals were anesthetized with chloralose (80 mg/kg, i.v.) after prior injection of sodium pentobarbital (6 mg/kg, i.v.). They were breathing spontaneously throughout the experiment. Arterial blood pressure was measured with a Statham P23 GB transducer connected to a catheter introduced into the right or the left tibial artery; heart rate was recorded by lead II EKG. The two parameters were recorded simultaneously and continuously on a Beckman type RM Dynograph. Mean arterial blood pressure was calculated as diastolic plus one third of the pulse pressure.

Determination of histamine levels. Eight venous blood samples (5 ml) were drawn from the inferior vena cava (via a catheter introduced through the saphen) 5 and 2 min before and 1, 3, 6, 10, 30, and 60 min after injections, and were collected in heparinized tubes. A first aliquot (1 ml) diluted with Tyrode's solution (2.6 ml) and 4 *N* perchloric acid (0.4 ml) was used for blood histamine assay. A second aliquot (4 ml), used for plasma histamine assay, was centrifuged at 1,800 *g* and 4° C for 10 min; the supernatant fluid (1.5 ml) was extracted and diluted with Tyrode's solution (1.2 ml) and 4 *N* perchloric acid (0.3 ml). The two mixtures were agitated in a Vortex apparatus and were allowed to settle for at least 2 h; they were then centrifuged at 3,000 *g* for 15 min. The supernatant fluids were extracted and kept for histamine assay.

Histamine was assayed by an automated, continuous flow fluorimetric technique [20] derived from the method of Shore et al. [27]. This technique allows 60 samples of 350 µl to be assayed. The treshold of sensitivity was 200 pg histamine base per ml. The response was linear, from 500 pg/ml to 5 ng/ml, with a coefficient of variation $\leqslant \pm 5\%$ for 0.5–2 ng/ml and that of $\pm 0.5\%$–2% for higher concentrations.

Drug treatment

Drugs used are listed in Table 1. The method is made more sensitive by the use of doses generally higher than the maximal therapeutic doses used in man and by rapid i.v. injections (30 s) (drug-induced histamine release increases with the rapidity of injection) [11]. However, the reactions of the animals were tested by preliminary doses before the final one was chosen. Several doses were often given successively. The trade preparations used were dissolved or diluted in saline and injected i.v. in a 5-ml volume.

The presence of the histamine-releasing agents cremophor EL [23] and tween 80 [12] in Vehem and Vepeside dosage forms, respectively, made it necessary to study their effects under the same experimental conditions to separate the respective activities of the antitumoral drug and its excipient. They were thus given pure at doses corresponding to doses of Vehem and Vepeside containing 0.3 mg/kg of teniposide and 0.075 mg/kg of etoposide respectively. Five dogs were given cremophor EL (15 mg/kg, i.v.) and five others were given tween 80 (0.3 mg/kg, i.v.).

Each of the thirty dogs used in this work took part in two experiments, 1 week apart, and received a different treatment each time. Dogs were in a normal clinical state prior to their second treatment, and the control values of the cardiovascular parameters were similar in the two experiments.

Statistical analysis

Statistical analysis was performed using raw data. The results, expressed as mean ± SEM, were analyzed by a two-way ANOVA followed by a multiple comparison test, the Bonferroni test [29]. The degree of significance, as opposed to predrug values, was 5%.

Table 1. Drug treatments

Drug used	Maximal doses in single administration in man	Doses administered (mg/kg, i.v., 30 s)	Number of experiments[a]
L-Asparaginase (Kidrolase, Specia)	1000 IU/kg i.v. infusion	45 and 180 IU/kg	5
Methotrexate (Methotrexate, Specia)	0.2 mg/kg i.v. injection	0.75 and 3 1.5	4 4
5-fluorouracil (Fluorouracile, Roche)	15 mg/kg i.v. injection or infusion	7.5 and 30	4
Doxorubicin (Adriblastine, Roger Bellon)	75 mg/m^2 i.v. injection	0.375 and 1.5	4
Bleomycin (Bleomycine, Roger Bellon)	15 mg i.v. injection	0.075 and 0.3 and 1.5 3	4 1
Teniposide (Vehem, Sandoz)	60 mg/m^2 i.v. infusion	0.075 and 0.3	5
Etoposide (Vepeside, Sandoz)	60 mg/m^2 i.v. infusion	0.075	5
Cisplatin (Cisplatyl, Roger Bellon)	100 mg/m^2 i.v. injection	0.75 3	4 2

[a] Each of the thirty animals used took part in two experiments, 1 week apart. Preliminary experiments performed to test the reactions of animals are not included. Trade names are indicated in parantheses

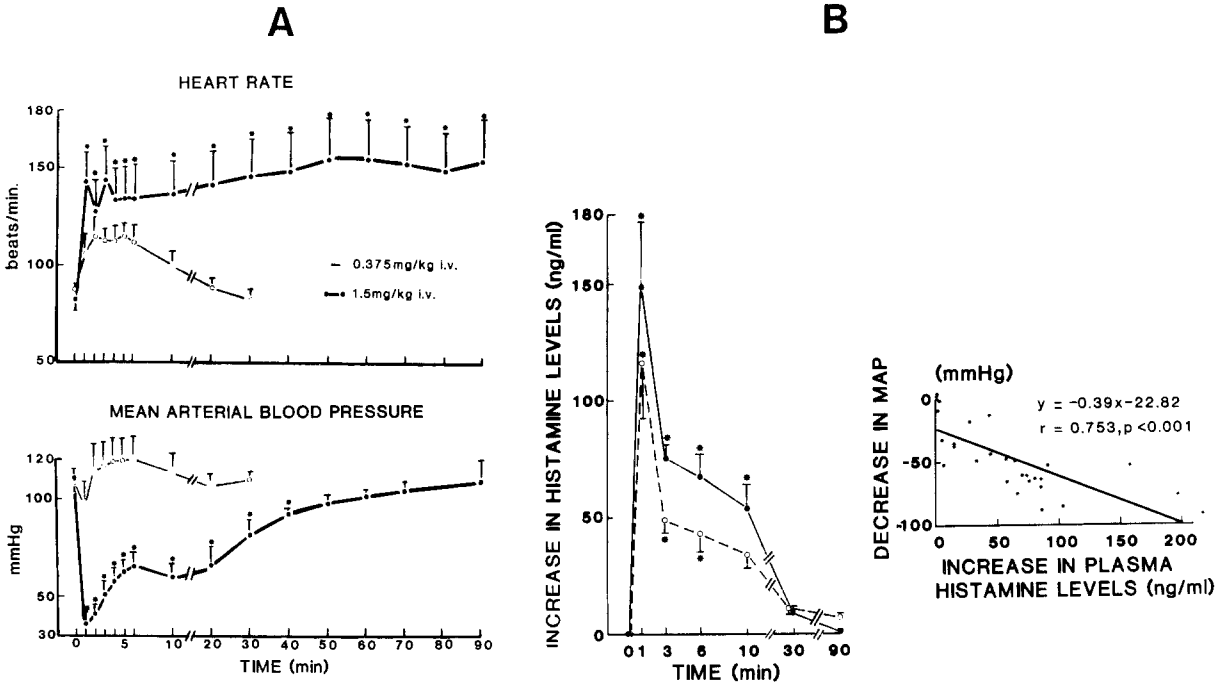

Fig. 1. Cardiovascular (A) and histamine-releasing (B) properties of doxorubicin. Two doses were administered successively i.v. Plasma (———) and blood (– – – –) histamine levels were determined after the dose of 1.5 mg/kg. The bars represent SEM (n = 4); *, $P < 0.05$ vs predrug values

Results

No change in arterial blood pressure, heart rate, or histamine levels was observed after injections of L-asparaginase, methotrexate, 5-fluorouracil, bleomycin, and cisplatin.

Doxorubicin (0.375 mg/kg) induced only weak hypotension and short-lived tachycardia. The dose of 1.5 mg/kg markedly decreased mean blood pressure at 1 min after injection and for 40 min thereafter. The heart rate was increased at 1 min after injection and remained at the same level throughout the whole experiment (90 min) (Fig. 1 A).

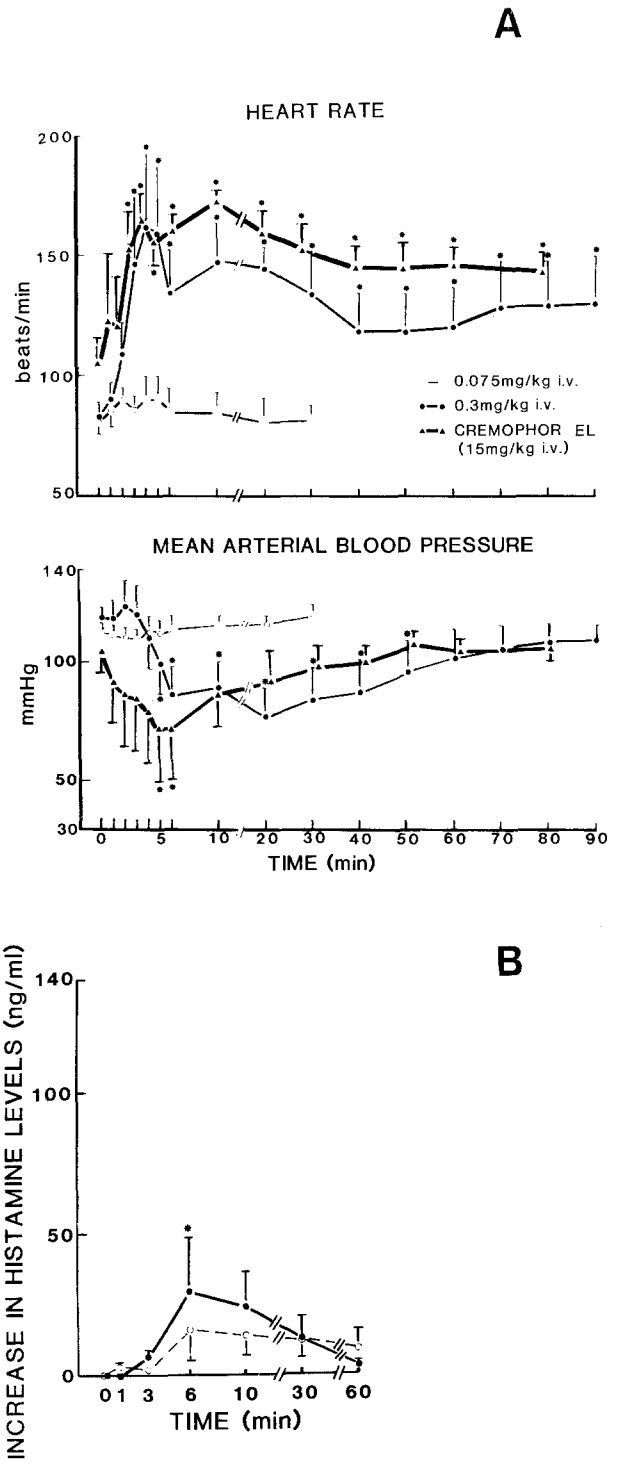

Fig. 2. A. Cardiovascular effects of Vehem (0.075 and 0.3 mg/kg teniposide administered successively i.v.) and cremophor EL given at a dose equivalent to 0.3 mg/kg of teniposide in Vehem dosage form. **B.** Time course of plasma (———) and blood (– – – –) histamine levels after Vehem (0.3 mg/kg teniposide). The bars represent SEM. $n = 5$ in each group; *, $P < 0.05$ vs predrug values.

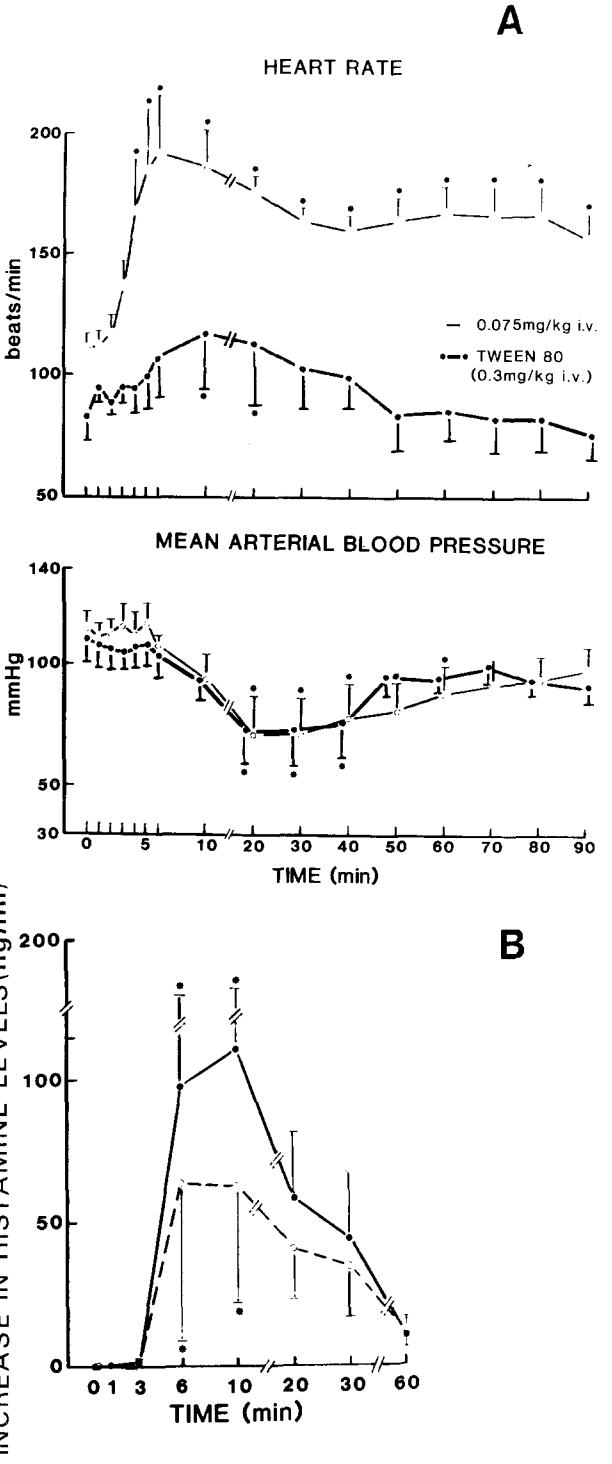

Fig. 3. A. Cardiovascular effects of Vepeside (0.075 mg/kg, i.v., etoposide) and tween 80 given at a dose equivalent to 0.075 mg/kg etoposide in Vepeside dosage form. **B.** Time course of plasma (———) and blood (– – – –) histamine levels after Vepeside (0.075 mg/kg etoposide). The bars represent SEM. $n = 5$ in each group; *, $P < 0.05$ vs predrug values

This dose induced a significant increase in plasma and blood histamine levels, maximal at 1 min, which was maintained for 10 and 6 min, respectively (Fig. 1 B). A significant correlation ($r = 0.753$; $P < 0.001$) was found between the decrease in mean arterial pressure (MAP) and the increase in plasma histamine levels.

Vehem, inactive at 0.075 mg/kg teniposide, induced delayed hypotension and tachycardia at 0.3 mg/kg. The fall, only significant as of 5 min after injection, became maximal at 20 min and lasted 50 min. Tachycardia, maximal at 4 min, was maintained throughout the whole experiment. The intensity and kinetics of hypotension and tachycardia, induced by cremophor EL, were similar to those of Vehem (Fig. 2 A). Vehem (0.3 mg/kg teniposide) induced a delayed increase in plasma histamine levels (at 6 min), which lasted, though not significantly, until 30 min (Fig. 2 B). No significant correlation was evident between variations in MAP and plasma histamine levels. Blood histamine levels showed the same time course without significant variations. Previously described histamine release induced by cremophor EL [23] was confirmed here in two dogs (+142 ng/ml) (decrease in MAP: −74 mm Hg) and +18 ng/ml (decrease in MAP: −13 mm Hg).

Vepeside (0.075 mg/kg etoposide) also induced delayed hypotension and tachycardia. A decrease in blood pressure became significant only at 20 min and persisted until 60 min. Maximal tachycardia appeared at 6 min and remained statistically significant throughout the whole experiment. The decrease in MAP induced by tween 80 was similar to that induced by Vepeside. Tween 80 induced a delayed and less marked tachycardia, only significant at 10 and 20 min (Fig. 3 A). Vepeside (0.075 mg/kg etoposide) significantly increased plasma and blood histamine levels at 6 and 10 min after the injection, despite wide-ranging individual values. The levels were markedly increased, though nonsignificantly, at 20 and 30 min (Fig. 3 B). Variations in MAP and plasma histamine levels were not significantly correlated.

Discussion

Of the eight agents studied, only doxorubicin, Vehem (teniposide), and Vepeside (etoposide) showed histamine-releasing properties under the experimental conditions used. Plasma and blood levels of histamine were significantly increased, reflecting release not only from basophils but also from tissue mastocytes.

Results obtained with doxorubicin confirm those obtained previously in the dog [4, 16]. Vehem and Vepeside given at low doses induced marked but delayed variations in cardiovascular parameters and in plasma and blood histamine. The delay suggests a mechanism of histamine release different from that of doxorubicin. The histamine-releasing cremophor EL and tween 80, which caused the same blood pressure changes as the drug in its dosage form, might be involved. However, the absence of any significant correlation between the fall in blood pressure and rise in plasma histamine suggests that the hypotension is not unequivocally due to the release of histamine. The tachycardia induced by Vehem and Vepeside is, as with doxorubicin, more persistent than the hypotension, which points to mechanisms other than simple reflex response to the fall in blood pressure. The tachycardia due to cremophor EL is comparable to that due to Vehem, but that due to tween 80 is much weaker than that due to Vepeside, suggesting that etoposide may possess a specific cardioaccelerator activity. The profile of these three dosage forms corresponds to that described for elliptinium, which produces the same variations, though of weaker intensity, in the dog [11]. This nonspecific histamine release might contribute to the anaphylactoid side effects observed in man with these agents. Indeed, these four agents often induced reaction after the first administration, soon after the start of the injection, and without progression to a more intense and generalized reaction with repeated doses (see [2, 30] for doxorubicin, [15, 23] for Vehem, [28, 32] for Vepeside, [17, 26] for elliptinium). However, for Vehem and Vepeside the excipient could be at least partly responsible.

On the other hand, for the other antitumoral agents tested, the absence of histamine-releasing activity in our sensitive conditions seems to rule out nonspecific histamine release as a mechanism for the observed anaphylactoid accidents, and suggests an immunological mechanism. Symptomatology and biological modifications reported for anaphylactoid reactions due to these drugs agree with this interpretation. This is particularly true for L-asparaginase, methotrexate, and 5-fluorouracil: (1) they induced biological modifications, i.e., the appearance of IgE, IgG [10, 19] or IgA, IgM [33] antibodies against L-asparaginase, of methotrexate-protein-IgG complexes [5]; (2) the pattern of occurrence of anaphylactoid reactions is typical – they occurred after several courses, recurring when treatment was resumed and developing within a few minutes after the infusion was started [6, 13, 14]. These latter characteristics were also observed with bleomycin [1], but the release of an endogenous pyrogen by this drug [7] makes the mechanism of side effects in man still unclear. The reports about cisplatin suggest an immunological mechanism for induced anaphylactoid reactions: (1) they occurred only in patients who had received prior cisplatin therapy [3, 18]; (2) IgE antibodies had been observed in patients with cisplatin hypersensitivity reactions [18, 25]. However, Wiesenfeld et al. [31] have failed to demonstrate any IgE-mediated reaction in a cisplatin-sensitive patient, and Parrot et al. [24] have obtained results in experimental studies with sodium chloroplatinate that suggested a nonspecific release of histamine. Thus, cisplatin induced immunologically mediated anaphylactoid reactions, but a nonspecific histamine release cannot be excluded.

A better knowledge of the mechanism involved in the induction of anaphylactoid effects is necessary to provide prevention measures, whether avoidance of further courses of treatment with the same drug if an immunological mechanism seems likely, or a slower administration rate or premedication with "anti-allergic" drugs if a nonspecific histamine release is expected.

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