Haemodynamic changes and circulating histamine concentrations following protamine administration to patients and dogs

Robert K. Stoelting MD, David P. Henry MD,
Kenneth M. Verburg MD,
Richard L. McCammon MD, Robert D. King MD,
John W. Brown MD

Haemodynamic changes and the circulating concentrations of histamine associated with the intravenous infusion of protamine were measured in six adult patients undergoing elective aortocoronary bypass graft surgery and twelve halothane-anaesthetized dogs. Administration of protamine ($4.7 \text{ mg} \cdot \text{kg}^{-1}$) over five minutes to patients at the conclusion of cardiopulmonary bypass did not produce haemodynamic changes or alterations in the arterial or mixed venous concentrations of histamine. Likewise, the administration of protamine ($4.5 \text{ mg} \cdot \text{kg}^{-1}$) over five minutes to six dogs produced no haemodynamic changes or alterations in the arterial concentrations of histamine. Conversely, administration of protamine ($4.5 \text{ mg} \cdot \text{kg}^{-1}$) as a rapid intravenous injection to six other dogs produced a decrease (about 30 per cent below control) in systolic, diastolic and mean arterial pressure ($p < 0.05$) at 2.5 minutes following the injection. These decreases in blood pressure were paralleled by increases

in the arterial concentration of histamine from $295 \pm 71 \text{ pg} \cdot \text{ml}^{-1}$ (mean $\pm$ SD) before protamine to $860 \pm 646 \text{ pg} \cdot \text{ml}^{-1}$ ($p < 0.05$) 2.5 minutes after protamine. Haemodynamic changes and the arterial concentration of histamine were not different from control five minutes after protamine administration.

It is concluded that administration of protamine over five minutes to patients or dogs does not evoke significant haemodynamic changes or alterations in circulating concentrations of histamine. Conversely, rapid injection of protamine to dogs evokes transient decreases in blood pressure that are paralleled by increases in the arterial concentrations of histamine.

Key words

BLOOD, COAGULATION: protamine, cardiovascular effects of protamine, histamine.

From Indiana University School of Medicine and the Lilly Laboratory for Clinical Research, Indianapolis, Indiana.

Address correspondence to: Dr. Robert K. Stoelting, Department of Anesthesia, Fesler Hall Room 204, 1120 South Drive, Indiana University School of Medicine, Indianapolis, Indiana 46223.

Haemodynamic changes evoked by the intravenous administration of protamine to reverse heparin anticoagulation may be species dependent. For example, studies in dogs describe hypotension, decreased systemic vascular resistance and bradycardia following the intravenous administration of protamine.¹⁻³ In contrast, data obtained from patients suggests a more benign circulatory effect of protamine.⁴⁻⁶ When haemodynamic changes do accompany the administration of protamine, the transient decrease in blood pressure and the suggestion that the rate of protamine infusion is important implies a protamine-induced histamine release. Indeed, protamine is a basic drug that could release histamine and other vasoactive molecules from mast cells and basophils. Recently, the basic drugs d-tubocurarine and morphine have been reported to produce haemodynamic changes that parallel in-

creases in the circulatory concentrations of histamine.⁷ Finally, others have proposed a direct negative inotropic effect of protamine.⁸

The present study was conducted in patients and dogs with the goal of detecting any species difference in the haemodynamic changes associated with the intravenous administration of protamine. In addition, the plasma concentrations of histamine were measured to define the possible role of this vasoactive substance when haemodynamic changes accompany infusion of protamine.

Methods

Patient studies

Six adult patients (61 ± 3 years, 75 ± 8 kg, mean $\pm$ SD) scheduled for elective aortocoronary bypass graft surgery were studied. The protocol was approved by the institutional Review Committee for the study of human subjects and informed consent was obtained. All patients were receiving propranolol preoperatively with the last dose administered with the preoperative medication on the morning of surgery. Preoperative medication was with intramuscular morphine and scopolamine and oral diazepam. Following placement of catheters in a peripheral vein and the radial artery, anaesthesia was induced with diazepam $0.5 \text{ mg} \cdot \text{kg}^{-1}$ administered intravenously over five minutes. Skeletal muscle paralysis was produced with metocurine ($0.15 \text{ mg} \cdot \text{kg}^{-1}$) plus pancuronium ($0.08 \text{ mg} \cdot \text{kg}^{-1}$). Following intubation of the trachea, a thermidilution pulmonary artery catheter was positioned in the pulmonary artery via the right internal jugular vein. Maintenance of anaesthesia was with morphine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ administered intravenously plus intermittent isoflurane to treat elevations in blood pressure more than 20 per cent above awake levels. All patients received methylprednisolone (1 gram) and cefamandole (1 to 2 grams) intravenously shortly after the induction of anaesthesia.

Cardiopulmonary bypass was initiated 55 ± 15 minutes after the induction of anaesthesia and lasted 114 ± 26 minutes. Hemodilution and hypothermia was utilized and the activated clotting time maintained at greater than 400 seconds with heparin. At the conclusion of cardiopulmonary bypass, the patient's intravascular fluid volume was adjusted by the infusion of pump perfusate via the aortic cannula. When systemic and pulmonary artery

pressures were judged optimal and had been stable for at least three minutes, the aortic and venous cannulae were removed. Control haemodynamic measurements and arterial and venous blood for measurement of histamine concentrations, blood gases and pH, and were obtained. Blood for plasma histamine measurements was drawn simultaneously from the radial artery and distal port of the pulmonary artery catheter and immediately placed in pre-cooled test tubes containing EDTA. The plasma was separated within 30 minutes of collection using a centrifuge and the samples frozen for subsequent analysis.

The dose of protamine ($352 \pm 103 \text{ mg}$, $4.7 \text{ mg} \cdot \text{kg}^{-1}$) (Eli Lilly) was calculated from the activated clotting time titration curve for each patient and subsequently administered as a continuous intravenous infusion over five minutes via a peripheral forearm vein. All measurements were repeated at the conclusion of and five minutes after the protamine infusion. No anaesthetic or vasoactive drugs were being administered and surgical manipulation of the heart was deferred during the period of data collection.

Circulating histamine concentrations were determined using a new radioenzymatic assay.^{9,10} The assay has a sensitivity of $2.2 \text{ pg} \cdot \text{ml}^{-1}$ and a coefficient of variation of less than ten per cent. The sensitivity of the assay is due to the use of (1) a methyl donor (^3H -S-adenosylmethionine) with a specific activity of $76.1 \text{ Ci} \cdot \text{mmol}^{-1}$; and (2) purified histamine N-methyltransferase. The enzyme is purified from rat kidney by centrifugation, pH 5.0 treatment, ammonium sulfate precipitation, ion exchange chromatography and molecular exclusion chromatography.^{9,10} Specificity of the assay was insured by performing the methyl transfer reaction at 0 to 4 Celsius.¹¹

Standard formulae were used to calculate systemic vascular resistance, pulmonary vascular resistance and stroke volume. Data were analyzed using a two-way analysis of variance and Dunnet's test. A *p* value less than 0.05 was considered statistically significant.

Dog studies

Twelve mongrel dogs ($9 \pm 1 \text{ kg}$) received intravenous thiopentone (10 to $15 \text{ mg} \cdot \text{kg}^{-1}$) followed by intubation of the trachea. Maintenance of anaesthesia was with 1 to 1.5 per cent inspired halothane

TABLE I Measurements (mean $\pm$ SD) in patients receiving protamine over 5 minutes

	Control	End protamine infusion	5 minutes after protamine
Systolic blood pressure (mmHg)	120 $\pm$ 15	120 $\pm$ 14	120 $\pm$ 16
Diastolic blood pressure (mmHg)	65 $\pm$ 15	65 $\pm$ 13	65 $\pm$ 15
Mean arterial pressure (mmHg)	86 $\pm$ 15	85 $\pm$ 11	87 $\pm$ 17
Heart rate (beats/min)	77 $\pm$ 15	72 $\pm$ 13	71 $\pm$ 10
Systolic pulmonary artery pressure (mmHg)	26 $\pm$ 7	25 $\pm$ 7	24 $\pm$ 7
Diastolic pulmonary artery pressure (mmHg)	13 $\pm$ 3	11 $\pm$ 3	12 $\pm$ 3
Mean pulmonary artery pressure (mmHg)	19 $\pm$ 5	16 $\pm$ 4	17 $\pm$ 5
Pulmonary artery occlusion pressure (mmHg)	12 $\pm$ 2	12 $\pm$ 2	11 $\pm$ 3
Mean right atrial pressure (mmHg)	9 $\pm$ 3	8 $\pm$ 2	7 $\pm$ 3
Cardiac output (l/min)	5.8 $\pm$ 1.1	5.6 $\pm$ 0.5	5.4 $\pm$ 0.6
Stroke volume (ml/beat)	78 $\pm$ 16	79 $\pm$ 12	78 $\pm$ 17
Systemic vascular resistance (units)	14 $\pm$ 3	14 $\pm$ 2	15 $\pm$ 4
Pulmonary vascular resistance (units)	1.2 $\pm$ 0.6	0.8 $\pm$ 0.3	1.1 $\pm$ 0.4
Arterial histamine (pg·ml ⁻¹)	156 $\pm$ 63	242 $\pm$ 317	214 $\pm$ 125
Mixed venous histamine (pg·ml ⁻¹)	186 $\pm$ 165	445 $\pm$ 616	256 $\pm$ 137
PaO ₂ (mmHg)	356 $\pm$ 50	362 $\pm$ 54	356 $\pm$ 70
PvO ₂ (mmHg)	47 $\pm$ 5	46 $\pm$ 9	44 $\pm$ 4
PaCO ₂	35 $\pm$ 3	33 $\pm$ 4	33 $\pm$ 3
pHa	7.44 $\pm$ 0.004	7.46 $\pm$ 0.05	7.48 $\pm$ 0.05
Haematocrit (per cent)	31 $\pm$ 1		
Oesophageal/Temperature (Celsius)	34.9 $\pm$ 0.5		

plus 60 per cent nitrous oxide in oxygen. Ventilation of the lungs was adjusted to maintain the PaCO₂ between 30 to 40 mmHg. Esophageal temperature was monitored and a heating pad utilized to maintain temperature between 36.5 and 37.5°C. A catheter was placed in the femoral artery for continuous recording of blood pressure and calculation of heart rate. Propranolol 0.1 mg·kg⁻¹ was administered intravenously shortly after the induction of anaesthesia. Heparin was not administered to the dogs. After at least one hour of anaesthesia, control haemodynamic measurements (systolic, diastolic and mean arterial pressure and heart rate) and arterial blood for determination of histamine concentration and blood gases were

obtained. Six dogs then received intravenous protamine 4.5 mg·kg⁻¹ administered over five minutes and six other dogs received the same dose of protamine as a rapid intravenous injection. Haemodynamic measurements and arterial blood for plasma histamine determinations were obtained at various times up to ten minutes after the injection of protamine. Blood samples for histamine determination were handled as described for the patients.

Results

The intravenous administration of protamine over five minutes to six patients did not produce hemodynamic changes (Table I). Likewise, circulating histamine concentrations did not change signifi-

TABLE II Measurements (mean $\pm$ SD) in dogs receiving protamine over 5 minutes

	Control	Protamine infusion		After protamine	
		2.5 min	5 min	5 min	10 min
Systolic blood pressure (mmHg)	105 $\pm$ 9	104 $\pm$ 10	95 $\pm$ 15	103 $\pm$ 9	104 $\pm$ 9
Diastolic blood pressure (mmHg)	64 $\pm$ 9	64 $\pm$ 9	58 $\pm$ 14	61 $\pm$ 7	59 $\pm$ 7
Mean arterial pressure (mmHg)	78 $\pm$ 8	77 $\pm$ 8	71 $\pm$ 9	74 $\pm$ 9	72 $\pm$ 9
Heart rate (beats/min)	112 $\pm$ 7	111 $\pm$ 7	111 $\pm$ 6	113 $\pm$ 10	110 $\pm$ 11
Arterial histamine (pg·ml ⁻¹)	334 $\pm$ 217		453 $\pm$ 266	445 $\pm$ 194	305 $\pm$ 208
Protamine (mg)	43 $\pm$ 8				

TABLE III Measurements (mean $\pm$ SD) in dogs before and for 10 minutes after rapid injection of protamine

	Control	After protamine			
		1 min	2.5 min	5 min	10 min
Systolic blood pressure (mmHg)	105 $\pm$ 16	102 $\pm$ 18	78 $\pm$ 25*	95 $\pm$ 9	99 $\pm$ 14
Diastolic blood pressure (mmHg)	68 $\pm$ 14	65 $\pm$ 16	47 $\pm$ 18*	59 $\pm$ 7	62 $\pm$ 11
Mean arterial pressure (mmHg)	80 $\pm$ 13	77 $\pm$ 15	58 $\pm$ 20*	71 $\pm$ 7	74 $\pm$ 12
Heart rate (beats/min)	107 $\pm$ 16	107 $\pm$ 14	99 $\pm$ 22	101 $\pm$ 17	104 $\pm$ 14
Arterial histamine (pg·ml ⁻¹)	291 $\pm$ 71	351 $\pm$ 129	860 $\pm$ 465*	431 $\pm$ 241	315 $\pm$ 69
Protamine (mg)	38 $\pm$ 5				

* $p < 0.05$.

ificantly ($p > 0.05$) although there was a trend for levels to be increased at the conclusion of the protamine infusion. The mixed venous concentrations of histamine were greater than the arterial levels, but this difference was not significant ($p > 0.05$).

Administration of protamine to dogs produced haemodynamic changes that were dependent on the rate of infusion. For example, administration of protamine over five minutes did not significantly ($p < 0.05$) reduce blood pressure, alter heart rate or change the arterial concentration of histamine (Table II). Conversely, the rapid intravenous administration of protamine transiently lowered blood pressure in association with nearly a three-fold increase in the arterial concentration of histamine (Table III, Figure).

Discussion

These data obtained in patients fail to demonstrate haemodynamic changes or alterations in circulating concentrations of histamine when protamine was administered over five minutes to reverse heparin anticoagulation at the conclusion of cardiopulmonary bypass. It is important to emphasize that all our patients were haemodynamically stable and were presumed to be normovolemic. A similar rate of administration of protamine to halothane-anesthetized dogs, also, did not alter blood pressure, heart rate or the arterial concentration of histamine. Conversely, the same dose of protamine administered as a rapid intravenous injection to dogs produced transient reductions in systolic, diastolic and mean blood pressure ($p < 0.05$) that paralleled equally transient increases in the arterial concentrations of histamine ($p < 0.05$). It is well known that rapid injection of a basic drug and the resulting high

plasma concentration is more likely than a slow infusion to provoke degranulation of mast cells and basophils manifesting as release of histamine.¹²

It has been postulated that the dog is more likely than man to experience protamine-induced haemodynamic changes presumably due to histamine

FIGURE The mean arterial pressure (solid circles) (mean $\pm$ SD) decreased (* $p < 0.05$) 2.5 minutes following the rapid injection of protamine (4.5 mg·kg⁻¹) to six halothane-anesthetized dogs. This decrease in mean arterial pressure was accompanied by a corresponding increase (* $p < 0.05$) in the arterial concentration of histamine (open circles).

release.⁴ Our data do not directly support this speculation since administration of similar doses of protamine over five minutes to dogs and patients were not associated with significant changes in blood pressure. There was, however, a tendency for circulating histamine concentrations to increase during the five minutes of protamine infusion in both patients and dogs. Rapid intravenous injection of protamine to patients was not tested in this study so comparison of circulating histamine concentrations with dogs receiving protamine rapidly is not possible. Perhaps, rapid injection of protamine to patients would evoke histamine release to a similar extent as observed in dogs. Nevertheless, in another report, administration of protamine over 30 seconds or 60 seconds to patients at the conclusion of cardiopulmonary bypass produced only minor and transient decreases in blood pressure and systemic vascular resistance.⁶

Previous studies have suggested protamine may have direct cardiac depressant effects.^{3,8} In our patients, however, there was no evidence of cardiac depression as reflected by unchanged right atrial pressure, pulmonary artery occlusion pressure and cardiac output.

Protamine has been reported to result in pulmonary vascular vasoconstriction with corresponding increases in pulmonary vascular resistance.¹³ This observation, however, is not supported by data from our patients in whom pulmonary vascular pressures and calculated pulmonary vascular resistances did not change.

Heart rate did not change in response to protamine infusion. This contrasts with previous animal reports describing bradycardia.² Conversely, an increased heart rate in association with protamine infusion could reflect histamine-induced epinephrine release.¹⁴ We speculate that background beta-adrenergic blockade in our patients and dogs contributed to the lack of change in heart rate. Alternatively, drugs used for anaesthesia (morphine, halothane) or intrinsic cardiac disease in patients may have blocked heart rate changes. Propranolol was utilized in our dogs to more closely mimic the clinical picture in which protamine is administered to patients. Previous animal data, however, have demonstrated that propranolol does not alter the haemodynamic effects evoked by protamine.³

We elected not to heparinize the dogs prior to administering protamine. This decision was based

on the assumption that interaction of protamine with heparin was in no way responsible for any haemodynamic effects. In retrospect, this may be questioned, as it has been suggested that the protamine-heparin complex may be important for eliciting haemodynamic changes attributed to protamine.¹⁵ Nevertheless, the absence of haemodynamic changes in heparinized patients receiving protamine and the presence of blood pressure changes that paralleled increases in the circulating concentration of histamine when protamine was administered to unheparinized dogs fails to support the speculated haemodynamic importance of the protamine-heparin complex.

Our patients all received methylprednisolone shortly after the induction of anaesthesia. Although the intervals varied somewhat, it was usually about three hours after methylprednisolone when protamine was administered. Conceivably, methylprednisolone which is alleged to prevent activation of complement in the lung could have attenuated the haemodynamic effects evoked by protamine.⁶ Indeed, generation of complement-derived anaphylatoxins has been attributed to protamine as well as exposure of blood to components of the cardiopulmonary bypass machine.¹⁶ Similarly, methylprednisolone may have stabilized mast cell and basophil membranes and inhibited release of histamine. This, however, is unlikely, since 12 to 24 hours is required for glucocorticoids to inhibit histamine release.¹⁷ Our desire not to alter the usual clinical management of our study patients was the reason for not studying a group not receiving methylprednisolone. Dogs, however, were not given methylprednisolone and the absence of haemodynamic changes in those animals receiving protamine over five minutes supports our hypothesis that the presence or absence of methylprednisolone does not influence the haemodynamic responses to protamine.

Morphine, as administered to our patients, is more likely than fentanyl to evoke a transient release of histamine.⁸ This raises a theoretical question of histamine depletion by morphine which might attenuate or prevent subsequent protamine-induced release of this vasoactive substance and associated circulatory effects. It is not possible to discount this possibility in our study, but the time interval between morphine administration and injection of protamine (at least three hours) plus the

unlikely ability of any drug to significantly deplete total body histamine stores leads us to conclude that morphine did not influence our results via this theoretical mechanism. Furthermore, none of our patients manifested circulatory changes during the initial administration of morphine that were associated with cutaneous flushing suggestive of histamine release.

In contrast to patients, maintenance of anaesthesia in the dogs did not include morphine. The decision to administer halothane to the dogs was based on our desire to produce a stable depth of anaesthesia so as to minimize the potential impact of a changing or inadequate depth of anaesthesia on the magnitude of protamine-induced circulatory changes. We felt this goal was more likely to be attained with a volatile anaesthetic rather than a narcotic.

Measurement of arterial and mixed venous concentrations of histamine revealed a consistent, although not statistically significant, difference with the venous concentration being greater than the arterial. This observation suggests histamine may be removed from the circulation as it traverses the lungs. Furthermore, a higher mixed venous concentration of histamine supports release of this vasoactive substance from splanchnic tissues and the skin. Conversely, others have demonstrated protamine-induced circulatory effects in patients when protamine was injected directly into the aorta but not intravenously.¹⁸

In summary, our data demonstrate that administration of protamine over five minutes to patients following cardiopulmonary bypass does not evoke haemodynamic changes or physiologically important alterations in the circulating concentrations of histamine. Likewise, protamine administered over five minutes to dogs was haemodynamically benign. Conversely, rapid injection of protamine to dogs caused transient decreases in blood pressure that paralleled equally transient increases in the arterial concentrations of histamine (Table III, Figure).

References

- 1 Hurt R, Perkins HA, Osborn JJ, Gerbode F. The neutralization of heparin by protamine in extracorporeal circulation. *J Thorac Surg* 1956; 32: 612-9.
- 2 Gourin A, Streisand RL, Greineder JK, Stuckey JH. Protamine sulfate administration and the cardiovascular system. *J Thorac Cardiovasc Surg* 1971; 62: 193-204.
- 3 Fadali MA, Papacostas CA, Duke JJ, Ledbetter M, Oskakken M. Cardiovascular depressant effect of protamine sulphate: experimental study and clinical implications. *Thorax* 1976; 31: 320-3.
- 4 Conahan TJ, Andrews RW, MacVaugh H. Cardiovascular effects of protamine sulfate in man. *Anesth Analg* 1981; 60: 33-6.
- 5 Sethna DH, Moffitt E, Gray RJ, *et al.* Effects of protamine sulfate on myocardial oxygen supply and demand in patients following cardiopulmonary bypass. *Anesth Analg* 1982; 61: 247-51.
- 6 Shapira N, Schaff HV, Piehler JM, White RD, Sill JC, Pluth JR. Cardiovascular effects of protamine sulfate in man. *J Thorac Cardiovasc Surg* 1982; 84: 505-14.
- 7 Roscow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anaesthesia. *Anesthesiology* 1982; 56: 93-6.
- 8 Iwatsuki N, Matsukawa S, Iwatsuki K. A weak negative inotropic effect of protamine sulfate upon the isolated canine heart muscle. *Anesth Analg* 1980; 59: 100-2.
- 9 Verburg KM, Bowsher RR, Henry DP. A new radioenzymatic assay for histamine using purified histamine N-methyltransferase. *Life Sci* 1983; 32: 2855-67.
- 10 Bowsher RR, Verburg KM, Henry DP. Histamine N-methyltransferase: quantification, tissue distribution, purification, and immunologic properties. *J Biol Chem* (in press).
- 11 Verburg KM, Bowsher RR, Henry DP. Kinetic analysis of histamine N-methyltransferase: effect on the histamine radioenzymatic assay. *Fed Proc* 1983; 42: 907.
- 12 Beaven MA. Anaphylactoid reactions to anesthetic drugs. *Anesthesiology* 1981; 55: 3-5.
- 13 Lowenstein E, Johnston WE, Lappas DG, *et al.* Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. *Anesthesiology* 1983; 59: 470-3.
- 14 Moss J, Fahmy NR, Sunder N, Beaven MA. Hormonal and hemodynamic profile of an anaphylactic reaction in man. *Circulation* 1981; 63: 210-3.
- 15 Egertson WS, Robinson CLN. The anti-heparin, anticoagulant and hypotensive properties of hexadimethrine and protamine. *Lancet* 1961; 2: 635-7.
- 16 Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation

during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N Engl J Med* 1981; 304: 497-503.

- 17 Schleimer RP, Lichtenstein LM, Gillespie E. Inhibition of basophil histamine release by anti-inflammatory steroids. *Nature* 1981; 292: 454-5.
- 18 Milne B, Rogers K, Cervenka F, Salerno T. The haemodynamic effects of intraaortic versus intravenous administration of protamine for reversal of heparin in man. *Can Anaesth Soc J* 1983; 30: 347-51.

Résumé

On a mesuré les répercussions sur l'hémodynamique et les concentrations plasmatiques d'histamine occasionnées par l'infusion de protamine chez six patients adultes opérés pour pontage aorto-coronarien et chez douze chiens anesthésiés à l'halothane.

Chez les patients à l'arrêt de la circulation extra-corporelle, l'infusion de protamine ($4.7 \text{ mg} \cdot \text{kg}^{-1}$) n'a eu aucun effet sur l'hémodynamique ou les concentrations artérielles et veineuses d'histamine. De la même façon, l'infusion d'une dose de $4.5 \text{ mg} \cdot \text{kg}^{-1}$ de protamine sur une période de cinq minutes chez six chiens n'a eu aucun effet. Cependant lorsque la dose a été administrée en injection intraveineuse rapide à six autres chiens, on a observé une réduction de l'ordre de 30 pour cent de la pression artérielle systolique et diastolique et moyenne ($p < 0.05$) 2.5 minutes après l'injection. Ces modifications de pression artérielle s'accompagnaient de façon parallèle d'une augmentation de la concentration artérielle d'histamine, concentration qui passait de $295 \pm 71 \text{ pg} \cdot \text{ml}^{-1}$ ($M \pm DS$) à $860 \pm 465 \text{ pg} \cdot \text{ml}^{-1}$ ($p < 0.05$) 2.5 minutes après l'injection. Ces mesures d'hémodynamie et d'histamine avaient retrouvé les valeurs de contrôle cinq minutes après l'administration de protamine.

On en conclut que l'injection de protamine sur un période de cinq minutes aux patients comme aux chiens ne suscite pas de modifications hémodynamiques notables ou de changements de concentration de l'histamine plasmatique. Cependant, l'injection rapide de protamine chez des chiens provoque une diminution fugace de la pression artérielle, diminution qui s'accompagne de concentration à la hausse d'histamine dans le sang artériel.