Prophylactic administration of histamine$_1$ and histamine$_2$ receptor blockers in the prevention of protamine-related haemodynamic effects

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We studied the effects of the prophylactic administration of histamine$_1$ and histamine$_2$ receptor blockers on haemodynamic changes, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MBP), central venous pressure (CVP), and heart rate (HR ,beats·min^{-1}) before and after the administration of protamine in two groups of patients having coronary artery bypass graft surgery. Group I patients received no histamine blockers, whereas patients in Group II were treated prophylactically with both H_1 (diphenhydramine) and H_2 (cimetidine) receptor blockers. The mean SBP, DBP, MBP, CVP, and HR before (and after) administration of protamine in group I patients were 114 ± 16 (90 ± 16) mmHg, 64 ± 11 (51 ± 8) mmHg, 81 ± 11 (65 ± 10) mmHg, 10 ± 3 (11 ± 7) mmHg, and 92 ± 10 (87 ± 13) before (and after) protamine administration. Group II patients had mean SBP, DBP, MBP, CVP, and HR of 113 ± 19 (113 ± 17) mmHg, 61 ± 12 (62 ± 11) mmHg, 79 ± 15 (80 ± 13) mmHg, 9 ± 3 (9 ± 2) mmHg, and 88 ± 6 (86 ± 4) before (and after) protamine administration. Our data show that only in Group I patients who did not receive histamine receptor blockers, were there significant haemodynamic changes following protamine administration ($P < 0.05$). We conclude that the prophylactic administration of histamine receptor blockers prevents some of the adverse haemodynamic effects associated with protamine administration.

Avec le concours de candidats à une revascularisation coronarienne, nous avons mesuré l'effet de l'utilisation de bloqueurs des récepteurs histaminiques H_1 et H_2 avant l'injection de protamine, sur la réponse hémodynamique à cette dernière. Les patients du Groupe I ne recevaient aucun pré-traitement mais nous injections prophylactiquement de la dyphenhydramine (anti-H_1) et de la cimétidine (anti-H_2) à ceux du Groupe II. Les moyennes des pressions artérielles systoliques, diastoliques, des tensions veineuses centrales et du pouls avant (et après) l'injection de protamine étaient respectivement dans le Groupe I de: 114 ± 16 (90 ± 16), 64 ± 11 (51 ± 8), 81 ± 11 (65 ± 10), 10 ± 3 (11 ± 7) mmHg et de 92 ± 10 (87 ± 13) battements·min^{-1}. Dans le Groupe II, ces mêmes moyennes étaient de: 113 ± 19 (113 ± 17), 61 ± 12 (61 ± 11), 79 ± 15 (80 ± 13), 9 ± 3 (9 ± 2) mmHg et de 88 ± 6 (86 ± 4) battements min^{-1}. La protamine n'a entraîné de changements hémodynamiques significatifs ($P < 0,05$) que chez les patients du Groupe I, ceux qui n'avaient pas reçu de pré-traitement. Il semble donc que l'injection prophylactique de bloqueurs des récepteurs histaminiques puisse prévenir certains des effets hémodynamiques de l'injection de protamine.

Key words
ALLERGY: protamine;
BLOOD: coagulation, protamine;
HISTAMINE: antagonists, cimetidine, diphenhydramine.

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Protamine, a highly alkaline compound, is used routinely to reverse the anticoagulation effect induced by heparin. Protamine administration is associated with adverse haemodynamic responses including acute anaphylaxis.[1–3] Prophylactic treatment with histamine$_1$ (H_1) and hista-

TABLE Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), central venous pressure (CVP), and heart rate (HR) before and after protamine administration in patients (n = 15) who did not receive histamine receptor blockers (Group I) and in patients (n = 15) who received histamine receptor blockers (Group II). Results are expressed as mean ± SD.

	Group I patients			*Group II patients*		
	Before	*After*	*P*	*Before*	*After*	*P*
SBP, mmHg	114 ± 14	90 ± 16	*,†	113 ± 19	113 ± 17	NS, *
DBP, mmHg	64 ± 11	51 ± 8	*,†	61 ± 12	62 ± 11	NS, *
MBP, mmHg	81 ± 11	65 ± 10	*,†	79 ± 15	80 ± 13	NS, *
CVP, mmHg	10 ± 3	11 ± 7	NS	9 ± 3	9 ± 2	NS
HR·min^{-1}	92 ± 10	87 ± 13	NS	88 ± 6	86 ± 4	NS

*$P < 0.05$, multifactor analysis of covariance and Turkey's multiple range test for significance between two groups.
†$P < 0.05$, Student's paired t test, NS = not significant.

mine$_2$ (H_2) receptor blockers has been shown to be beneficial in preventing histamine-related side-effects in patients receiving x-ray contrast dye, morphine, and certain neuromuscular blocking drugs.[4–6] Although pretreatment with H_1 and H_2 receptor blockers does not inhibit histamine release, it seems to attenuate the untoward acute haemodynamic responses by competing with histamine at the receptor site. The purpose of the present study was to investigate the efficacy of H_1 and H_2 receptor blockers in the prevention of protamine-related adverse haemodynamic responses.

Methods

Thirty ASA physical status III patients (aged 46–71 yr, both sexes) undergoing coronary artery bypass graft surgery were included in the study. Patients with a history of diabetes mellitus receiving protamine containing insulin and patients who had received protamine in the past were excluded from the study. With the approval of our Institution Review Board for the Protection of Human Subjects, informed consent was obtained from all the patients. Patients were randomly divided into two groups of 15 each. Group I patients acted as a control group and did not receive H_1 and H_2 receptor blocking agents. Group II patients received both H_1 receptor blocker (diphenhydramine, 0.2 mg·kg^{-1}, IV, during rewarming time) and H_2 receptor blocker (cimetidine, 300 mg, PO, at bedtime, the night before and 300 mg, PO, on call to the operating room, on the day of surgery). All patients received heparin sulfate (10 mg·ml^{-1}, Upjohn), 4 mg·kg^{-1}, IV, before the extracorporeal circulation (ECC) was commenced. Protamine sulfate (preservative-free solution, 10 mg·ml^{-1}, Elkins-Sinn, Inc.), 8 mg·kg^{-1}, IV, was administered over five to eight minutes in all patients except one in the control group after the ECC was discontinued. Protamine was given in all patients via a peripheral intravenous line. Haemodynamic responses including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MBP), and central venous pressure (CVP) were recorded just before protamine administration, and continuously for ten minutes after protamine administration was commenced. A decrease in SBP and MBP of more than 20 per cent or a change in HR of more than 20 per cent or a change in CVP of more than 20 per cent were considered significant. Only the maximum changes in haemodynamic variances were compared with those obtained before protamine administration. Student's paired t test was used to compare the haemodynamic effects in both groups before and after protamine administration. Differences between Groups I and II were analyzed by multifactor analysis of covariance and Tukey's Honestly Significant Difference testing. A P value less than 0.05 was considered significant.

Results

Results are shown in the Table. The mean ± SD of the ages and ejection fractions of Groups I and II were 62.6 ± 9 yr, 53 ± 4 per cent, and 60.2 ± 11 yr and 52 ± 5 per cent, respectively ($P > 0.05$). None of the Group II patients who received H_1 and H_2 receptor blockers showed any significant changes in pressures or HR following the protamine administration. Significant decreases in SBP, DBP and MBP were seen in Group I patients who did not receive histamine receptor blockers ($P < 0.05$, paired t test). In five of the 15 patients in Group I there was more than 20 per cent reductions in SBP, DBP, and MBP following the protamine administration. Two of these five patients required intense resuscitation measures including histamine receptor blockers, fluids, and vasopressors. One of these two patients developed an anaphylactoid reaction following IV administration of 200 mg protamine, and a second reaction following a repeat IV administration of 50 mg of protamine. Spontaneous recovery from heparin-induced anticoagulation was allowed in this patient.

Discussion

The results of our present study showed that in 33 per cent of patients who did not receive histamine blockers there were more than 20 per cent reductions in SBP, DBP, and MBP following protamine administration. Our results also showed that in patients with prophylactic administration of both H_1 and H_2 receptor blockers, there were no significant changes in haemodynamic variables following protamine administration.

Histamine is released from mast cells and is the chief mediator of allergic reactions. Two distinct histamine receptors, H_1 and H_2, mediate histamine effects. An allergic reaction that is mediated by IgE antibody is known as an "anaphylactic reaction" or type 1 sensitivity reaction.[7] When IgE antibody is not responsible for the reaction, it is called an "anaphylactoid reaction."[8] One cannot distinguish between anaphylactic and anaphylactoid reactions on the basis of the clinical picture. Some of the chemical mediators liberated in response to an allergic reaction include histamine, kinins, and prostaglandins. The liberated mediators produce a variety of symptom complexes. An elevation of plasma histamine levels has been documented especially following the administration of protamine via the central route.[9] Protamine is a protein derived from fish sperm and is immunogenic. Adverse haemodynamic effects varying from mild hypotension to severe anaphylactic reactions have been reported following the administration of protamine.[10] Mild hypotension seen after protamine administration is probably from decreased peripheral vascular resistance secondary to histamine release and is usually associated with rapid administration.[11] Rapid administration is defined as administration of a heparin neutralizing dose within three minutes.[10] True anaphylactic reactions are rare, and are usually not related to the rapidity of administration of protamine. Other suggested mechanisms for hypotension following protamine administration include splanchnic pooling of blood (decreased preload), negative inotropy, and calcium chelation.[12] Patients with a history of either diabetes mellitus receiving protamine containing insulin[13] or prior exposure to protamine or allergy to fish[14] are particularly prone to these adverse reactions. Other adverse haemodynamic effects associated with protamine include a rare syndrome of pulmonary vasoconstriction,[15] hypoxemia,[16] pulmonary oedema[17] and platelet dysfunction.[18] The role of histamine blockers in the later type of reactions where histamine is not involved has not been investigated.

In conclusion, our data suggest that the prophylactic administration of H_1 and H_2 receptor blockers prevents some of the unwanted haemodynamic effects associated with protamine administration in patients undergoing coronary artery bypass surgery.

References

1 *Moorthy SS, Pond W, Rowland RG.* Severe circulatory shock following protamine. Anesth Analg 1980; 59: 77–8.

2 *Conahan TJ III, Andrews RW, MacVaugh H.* Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981; 60: 33–6.

3 *Shapira N, Schaff H, Piehler JM, et al.* Cardiovascular effects of protamine sulfate in man. J Thorac Cardiovasc Surg 1982; 86: 505–14.

4 *Lieberman P, Siegle RL, Taylor WW.* Anaphylactoid reactions to iodinated contrast material. J Allergy Clin Immunol 1978; 62: 174–80.

5 *Philbin DM, Moss J, Akins CW et al.* The use of H_1 and H_2 histamine antagonists with morphine anesthesia: a double-blind study. Anesthesiology 1981; 55: 292–6.

6 *Scott RPF, Savarese JJ, Basta SJ.* Atracurium: clinical strategies for preventing histamine release and attenuating the hemodynamic response. Br J Anaesth 1985; 57: 550–3.

7 *Kelly JF, Patterson R.* Anaphylaxis: course, mechanisms, and treatment. JAMA 1974; 227: 1431–6.

8 *Watkins J.* Anaphylactoid reactions to IV substances. Br J Anaesth 1979; 51: 51–60 .

9 *Pierre A, Goodman K, Fyman P et al.* Hemodynamic changes after the administration of protamine. Anesth Analg 1986; 65: 78–80.

10 *Horrow JC.* Protamine: a review of its toxicity. Anesth Analg 1985; 64: 348–61.

11 *Frater RWM, Oka Y, Hong Y, Tsubo T, Loubser PG, Masone R.* Protamine-induced circulatory changes. J Thorac Cardiovasc Surg 1984; 87: 687–92.

12 *Goldman BS, Joison J, Austen WG.* Cardiovascular effects of protamine sulfate. Ann Thor Surg 1969; 7: 459–71.

13 *Levy J, Zaidan J, Faraj B.* Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. Anesth Analg 1986; 65: 739–42.

14 *Knape J, Schuller J, deHaan P et al.* An anaphylactic reaction to protamine in a patient allergic to fish. Anesthesiology 1981; 55: 324–5.

15 *Lowenstein E, Johnston WE, Lappas DG et al.* Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983; 59: 470–316.

16 *Kim YD, Michalik R, Lees DE et al.* Protamine induced arterial hypoxemia: the relationship to hypoxic pulmonary vasoconstriction. Can Anaesth Soc J 1985; 32: 5–11.

17 *Olinger GN, Becker RM, Bonchek LI.* Noncardiac pulmonary edema and peripheral vascular collapse following cardiopulmonary bypass: rare protamine reaction? Ann Thor Surg 1980; 29: 20–5.

18 *Radegran K, McAshlan C.* Circulatory and ventilatory effects of induced platelet aggregation and their inhibition by acetylsalicylic acid. Acta Anaesthesiol Scand 1972; 16: 76–84.