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Prophylactic Administration of Histamine 1 and/or Histamine 2 Receptor Blockers in the Prevention of Heparin- and Protamine-Related Haemodynamic Effects

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SUMMARY

The efficacy of prophylactic administration of H1 and H2 receptor blockers to prevent adverse haemodynamic responses to heparin and protamine was studied. The control group (n=10) received no histamine receptor blocker, group H1 (n=10) received oral terfenadine 60 mg, group H2 (n=10) received oral ranitidine 300 mg, and group H1+H2 (n=10) received both terfenadine and ranitidine on the night before the operation and on call to the operating room. Heparin sulphate 300 U/kg was injected directly into the right atrium, and protamine hydrochloride was administered at the conclusion of bypass over at least three minutes through a peripheral route. Following the injection of heparin, plasma histamine-like activity (H-LA) was increased significantly in all four groups. While systolic, diastolic, mean arterial and central venous pressures were decreased significantly in the control group, no significant changes were observed in the H1 and H2 groups. Protamine infusion did not lead to an increase in H-LA. Prophylactic administration of histamine receptor blockers (H1 or H2) attenuated the heparin-induced adverse haemodynamic response but did not change the protamine-related haemodynamic effects. Factors other than histamine may play a major role in protamine induced cardiovascular changes.

Key Words: BLOOD: coagulation, heparin, protamine; SURGERY: cardiovascular; HISTAMINE: antagonists, terfenadine, ranitidine

During cardiac surgery with extracorporeal circulation, high doses of heparin and protamine are administered and changes in haemodynamics have been described previously[1-3]. Although a possible reason for these reactions is a short-lasting elevation in plasma histamine (H) concentration, the mechanisms of these reactions remain unclear[2]. Prophylactic administration of H1 and/or H2 receptor blockers in the prevention of heparin and protamine related haemodynamic effects is still controversial[3].

The purpose of the study was to investigate the efficacy of prophylactic administration of H1 and H2 receptor blockers in preventing the adverse haemodynamic responses and to determine the plasma histamine-like activity (H-LA) following the injection of heparin and protamine during open heart surgery.

METHOD

Following Ethics Committee approval and written informed patient consent, a study was carried out on 40 open heart surgery patients, with good ventricular function as defined by an ejection fraction >50% and left ventricular end diastolic pressure <12 mmHg. Patients receiving inotropic or chronotropic support or IV vasodilator therapy from the start of the rewarming phase of cardiopulmonary bypass (CPB), those taking insulin preparations containing protamine, those with sudden haemodynamic changes resulting from surgery (bleeding or manipulation)

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and those with a history of prior vasectomy or protamine administration were excluded from the study. The routine medication was continued up to and including the morning of operation in all patients. All patients received diazepam 10 mg orally on the evening before operation and one hour before induction as premedication.

Forty patients were randomized by computer generated numbers into four groups of 10 each. The patients in the control group received no histamine receptor blocker. The patients in group H1 received an H1 receptor blocker (terfenadine 60 mg p.o.), group H2 patients received an H2 receptor blocker (ranitidine 300 mg p.o.) and the patients in group H1 + H2 received both H1 and H2 receptor blockers (terfenadine and ranitidine) on the night before and on call to the operating room. The investigators were blinded to the patient groups.

Anaesthesia was induced with diazepam, propofol, fentanyl and vecuronium bromide and maintained with isoflurane, nitrous oxide in oxygen and vecuronium as required. After a median sternotomy, heparin sulphate 300 U/kg was administered directly into the right atrium, and after separation from CPB, protamine hydrochloride was administered over at least three minutes through a peripheral intravenous route (according to Activated Clotting Time (ACT), Protamine Dose Assay Worksheet, Hemochron 801) in all patients. All injections and surgical manipulations of the heart were delayed until all measurements had been completed following the administration of heparin and protamine.

Plasma H-LA, systolic (SAP), diastolic (DAP), mean (MAP) arterial pressures, central venous pressure (CVP) and heart rate (HR) were measured before heparin injection (h0) and 1 minute (h1) and 3 minutes (h2) after the completion of the injection of heparin. The measurements were repeated before protamine injection (p0) and 1 minute (p1), 3 minutes (p2) and 5 minutes (p3) after the injection of protamine was completed. Blood specimens for H-LA were centrifuged at +4°C and 3000G within one minute of obtaining the sample, and 1 ml of 1.0N HCl was added into the 1 ml plasma for deproteinization, and stored at –40°C until it was analysed. Guinea pig ileal smooth muscle was used for bioassay of plasma H-LA, a method for screening labile unknowns[4]. Although it can not be used to quantitate biologically inactive metabolites, it is reasonably sensitive and can detect < 1 ng of pure active compound.

The within-group changes from the awake values were tested with the Student's t test. The differences in haemodynamic variables and plasma histamine levels between the four groups were compared with two-way and univariate-multivariate repeated measures analysis of variance. A *P* value less than 0.05 was considered as significant.

RESULTS

Demographic characteristics of the patients in the four groups were similar (Table 1).

H-LA was increased significantly following heparin administration (Figure 1), while there was no significant change following protamine injection in the four groups (Figure 2).

After the injection of heparin, SAP, DAP, MAP and CVP were decreased significantly in the control

TABLE 1

Demographic characteristics of the patients expressed as mean (SE)

	Control	H1	H2	H1 + H2
Sex (M/F)	8/2	6/4	7/3	8/2
Age (years)	46.3 (5.4)	43.8 (5.8)	42.6 (3.9)	47.1 (3.7)
Weight (kg)	65.2 (5.0)	66.7 (5.9)	68.4 (2.6)	66.1 (3.7)
Number (CABG/VR)	6/4	5/5	5/5	5/5

CABG: Coronary artery bypass gratfting; VR: Valvular replacement.

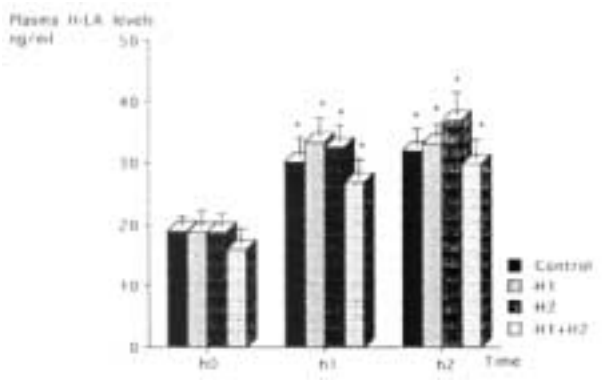

FIGURE 1: Changes in plasma H-LA levels, before heparin (h0), 1 min (h1) and 3 mins (h2) after heparin. **P* < 0.05 compared the h0.

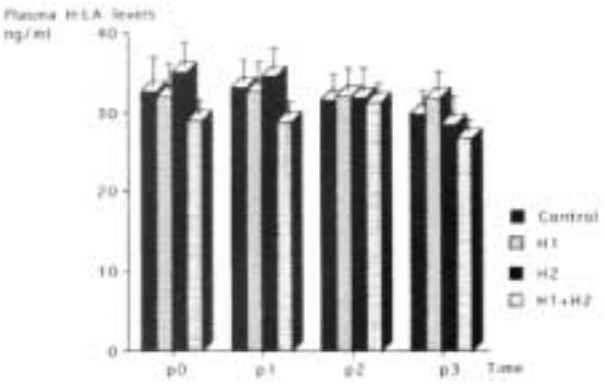

FIGURE 2: Changes in plasma H-LA levels, before (p0), 1 min (p1), 3 min (p2) and 5 min (p3) after protamine.

group, SAP and MAP were decreased and HR was increased significantly in group H1 + H2. Despite the significant increase in H-LA, there were no significant changes in the haemodynamic variables in groups H1 and H2 (Table 2).

TABLE 2

*The haemodynamic measurements in all groups expressed as mean (SE) before (h0), 1 min after (h1), 3 min after heparin (h2); *P < 0.05 compared with h0*

	h0	h1	h2
SAP (mmHg)			
Control	95.8 (5.5)	89.2 (6.6)	82.4 (7.5)* ($P = 0.04$)
H1	103.3 (7.4)	98.7 (6.4)	97.2 (7.2)
H2	104.4 (4.9)	105.1 (3.3)	102.5 (3.8)
H1 + H2	116 (3.5)	110.4 (2.3)	107.6 (2.4)* ($P = 0.033$)
MAP (mmHg)			
Control	64.4 (2.4)	61.9 (3.0)	59.4 (2.7)* ($P = 0.016$)
H1	72.7 (5.1)	71.3 (4.8)	69.1 (5.3)
H2	80.9 (4.4)	78.3 (4.0)	78.2 (4.3)
H1 + H2	76.5 (4.6)	71.9 (4.3)	71.6 (4.7)* ($P = 0.048$)
DAP (mmHg)			
Control	50.5 (3.7)	48.7 (3.9)	45.4 (3.2)* ($P = 0.048$)
H1	56.8 (4.8)	55.9 (4.7)	54.6 (4.7)
H2	64.1 (5.8)	63.1 (5.4)	61.3 (5.0)
H1 + H2	57.9 (5.2)	55.3 (4.5)	55.3 (5.6)
HR (beats/min)			
Control	72.2 (4.0)	71.5 (4.0)	71.0 (4.9)
H1	77.4 (5.6)	77.6 (5.5)	83.6 (6.7)
H2	82.7 (9.7)	81.9 (8.6)	83.6 (8.4)
H1 + H2	79.1 (5.5)	81.6 (7.4)	85.3 (7.3)* ($P = 0.029$)
CVP (mmHg)			
Control	4.8 (3.5)	4.1 (3.3)* ($P = 0.001$)	4.1 (3.5)* ($P = 0.007$)
H1	4.5 (4.1)	4.5 (4.1)	4.4 (4.2)
H2	6.0 (5.9)	5.9 (5.6)	6.0 (5.6)
H1 + H2	4.5 (3.6)	4.5 (3.7)	4.3 (3.8)

Following protamine administration CVP decreased significantly in all groups except the H1 + H2 group. Systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) showed significant decrease in the H1 and H1 + H2 groups, while only SAP decreased significantly in the control group (Table 3).

SAP and MAP values demonstrated significant differences among the four groups following heparin injection ($P = 0.001$, $P = 0.01$ respectively, univariate-multivariate repeated measures analysis of variance). Haemodynamic values following the injection of protamine did not differ between the groups.

DISCUSSION

Several studies describing the haemodynamic responses to the injection of heparin and protamine during cardiac surgery have been previously reported[1-3]. The most significant effects which have been observed after heparin administration are a decrease in MAP and systemic vascular resistance as well as an increase in cardiac index[1]. Adt et al[5] assumed histamine to be the major mediator of heparin-induced changes in haemodynamics, and they did not find a difference between the cardiovascular reaction and plasma histamine levels following heparin injection with or without preservative. Casthely et al[3] observed that patients pretreated with a H2 receptor antagonist developed more pronounced hypotension than a group treated with H1 blockade. In our study, after heparin administration H-LA increased significantly in all four groups and prophylactic administration of H1 or H2 receptor blockers attenuated the heparin-induced adverse haemodynamic response. On the other hand, the combined use of H1 and H2 receptor blockers did not prevent the decrease in SAP and MAP.

TABLE 3

*The haemodynamic measurements in all groups expressed as mean (SE) (mean ± SE): before (p0), 1 min after (p1), 3 min after (p2), 5 min after protamine; *P < 0.05 compared with p0*

	p0	p1	p2	p3
SAP (mmHg)				
Control	113.9 (8.0)	102.0 (8.5)* ($P = 0.003$)	101.6 (9.0)* ($P = 0.008$)	100.5 (7.6)* ($P = 0.002$)
H1	116.1 (4.9)	108.8 (3.9)	106.9 (4.3)* ($P = 0.02$)	108.7 (4.5)
H2	105.6 (3.5)	101.7 (4.8)	103.6 (4.6)	103.0 (4.3)
H1 + H2	118.2 (6.7)	112.1 (5.8)* ($P = 0.033$)	112.1 (5.8)* ($P = 0.033$)	113.3 (6.3)
MAP (mmHg)				
Control	76.4 (5.3)	72.5 (5.5)	72.5 (5.5)	73.3 (3.6)
H1	80.2 (4.9)	72.3 (3.6)* ($P = 0.003$)	70.0 (3.5)* ($P = 0.005$)	73.0 (3.7)* ($P = 0.031$)
H2	75.4 (2.8)	74.3 (3.6)	73.7 (3.3)	72.7 (2.9)
H1 + H2	81.4 (4.9)	76.5 (4.5)	79.3 (4.4)	76.5 (4.0)* ($P = 0.002$)
DAP (mmHg)				
Control	57.6 (4.2)	57.2 (4.5)	56.8 (4.8)	57.5 (3.2)
H1	59.6 (4.6)	54.4 (3.8)* ($P = 0.016$)	54.9 (4.0)* ($P = 0.009$)	54.5 (4.2)* ($P = 0.018$)
H2	59.0 (3.7)	55.3 (2.7)	54.7 (3.2)	58.7 (3.6)
H1 + H2	63.0 (4.3)	62.2 (3.5)	61.9 (4.3)	58.7 (4.4)* ($P = 0.025$)
HR (beats/min)				
Control	78.1 (5.4)	79.1 (6.0)	77.2 (3.7)	75.1 (3.4)
H1	81.6 (6.2)	78.5 (4.0)	78.3 (4.1)	76.6 (4.0)
H2	78.5 (7.7)	77.2 (5.4)	75.6 (5.3)	77.1 (5.6)
H1 + H2	75.6 (3.6)	79.6 (3.8)	78.7 (5.0)	76.9 (4.6)
CVP (mmHg)				
Control	4.1 (4.2)	3.1 (4.0)	2.9 (3.8)* ($P = 0.014$)	2.3 (3.9)* ($P = 0.003$)
H1	5.8 (4.8)	5.3 (4.3)	5.0 (4.5)	4.2 (3.7)* ($P = 0.011$)
H2	5.1 (3.7)	4.8 (3.3)	4.4 (3.1)* ($P + 0.04$)	4.1 (2.8)* ($P = 0.02$)
H1 + H2	6.0 (3.7)	6.2 (4.2)	5.9 (4.0)	5.2 (4.5)

Prospective human studies on the cardiovascular effects of protamine vary in their methods with respect to dose of protamine, rate of injection, route of administration, physical status of the patients, anaesthetic conditions, the cardiovascular responses measured, the times at which these responses were measured and number of patients studied[2,6-19]. The route and rate of administration may be important in the adverse haemodynamic responses. It has been shown that the greatest haemodynamic changes and elevation of plasma histamine levels occurred when protamine was administered rapidly via the central route and the least when administered slowly via the peripheral vein[8,9,11-13]. It was postulated that the heparin-protamine complex formed when protamine is injected into the right atrium passes directly to the lung, resulting in histamine release. When protamine is injected into a peripheral vein, the complex becomes diluted and histamine release may be prevented[12].

The role of prophylactic administration of H1 and/or H2 receptor blockers in the prevention of protamine-related haemodynamic effects are not clear. Kambam et al[13] observed that pretreatment with H1 and H2 receptor blockers did not attenuate the cardiovascular depression caused by rapid administration of protamine. Parsons et al[14] concluded that the normal response to protamine might be modified, but not abolished by H1 and H2 receptor blockade. Habazettl et al[6] showed that simultaneous H1 and H2 blockade had no effect on haemodynamic changes, thromboxane release or leukocyte counts in heparin-protamine reactions. In our study we observed that the least haemodynamic changes occurred in the H2 group following the injection of protamine. The reason for this might be an indirect effect of H2 receptor blockade, since H2 receptor blockers have been shown to decrease the beta-endorphin response to stress by 50% whereas the ACTH response was almost totally blocked[15]. In addition, histamine itself is known to have positive inotropic and chronotropic effects in the human heart through H2 receptor stimulation in atrial and ventricular myocardium[16] and it has been suggested that in the absence of H2 receptor stimulation by histamine, there was no cardiac response to protamine[14,16]. Kamban et al[17] presented two case reports of an anaphylactoid syndrome occurring following the administration of protamine, and they reversed the adverse haemodynamic variables with a single dose of IV cimetidine.

Recent studies indicate that the haemodynamic changes seen after the protamine injection are only partially mediated through histamine action: bradykinin, serotonin and thromboxane may also be mediators of the haemodynamic changes[2,8]. In our study, although we did not observe a significant increase in H-LA, there were some haemodynamic changes in all groups following the administration of protamine.

In conclusion prophylactic administration of histamine receptor blockers (H1 or H2) attenuated the heparin-induced adverse haemodynamic response, despite elevation of plasma H-LA levels. There was no significant change in plasma H-LA levels following the protamine administration in the four groups and prophylactic administration of histamine receptor blockers did not change the protamine-related haemodynamic effects. Factors other than histamine may play a major role in protamine-induced cardiovascular changes. Further studies are needed to define the predisposing factors which leads to this reaction.

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