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Title: THE USE OF H_1 and H_2 HISTAMINE BLOCKERS WITH MORPHINE: A DOUBLE BLIND STUDY

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Introduction. The fall in SVR and increase in CO often seen with IV morphine has been attributed to histamine release based largely on indirect evidence. This study was undertaken to accurately measure plasma histamine levels following the administration of morphine and to determine the cardiovascular effects of the administration of histamine blockers prior to the morphine.

Methods. 40 patients scheduled for elective coronary artery surgery were studied. In 4 groups; Group 1 received morphine 1 mg/kg; Group 2 received cimetidine (H_2 histamine blocker) 4 mgm/kg and morphine; Group 3 received diphendyramine (H_1 histamine blocker) 1mg/kg and morphine; Group 4 received both drugs prior to the morphine. Histamine blockers and placebo were prepared in 40 randomized, numbered, unlabeled vials. Measurements of the heart rate, mean BP, CO and plasma histamine levels were determined at: I,control; II, after the coded medications, III, with 1/3 of the morphine administered, IV, immediately after the morphine; V, VI, 5 and 10 min after the morphine. Metubine 0.3 mg/kg was administered concomitant with the morphine for airway management.

Results

TABLE 1

		I	II	III	IV	V	VI
BP mmHg	1	85±3	88±4	79±5	61±4[1]	73±8	74±5
	4	91±4	105±5[1]	97±4	79±4[1]	75±2[1]	76±2[3]
HR Beats/min	1	57±2	57±2	58±2	59±3	64±4	59±4
	4	56±5	72±5[1]	67±5	57±4	56±3	53±3
CO L/min	1	5.2 ±0.2	5.4 ±0.3	5.8 ±0.3[2]	6.1 ±0.4[2]	5.8 ±0.5	5.5 ±0.4
	4	4.9 ±0.2	5.4 ±0.3[2]	5.3 ±0.2[2]	4.8 ±0.3	4.5 ±0.3	4.3 ±0.3
SVR Arbitrary Units	1	14.8 ±0.7	15.5 ±1.2	12.2 ±0.5[1]	9.0 ±0.7[1]	11.5 ±1.0[2]	12.7 ±1.0
	4	17.4 ±1.0	18.4 ±1.0	16.8 ±1.0	14.6 ±1.0[2]	15.6 ±1.0	16.6 ±1.0
Plasma Histamine Units	1	696 ±124	629 ± 61	1736 ±713	6573 ±2531[2]	2924 ±887[2]	2216 ±885
	4	881 ±162	915 ±168	2083 ±794	8044 ±3701[2]	2887 ±1252	1402 ±521

[1]-$p<0.001$; [2]-$p<0.05$; [3]-$p<0.01$. (Mean±SEM)

Administration of morphine alone (Group 1) significantly decreased BP and SVR and increased CO and histamine. Prior administration of cimetidine and diphenhydramine (Group 4) increased HR,CO and BP prior to morphine. Following morphine the fall in BP and SVR was significantly attenuated in this group (BP-61±4 vs 79±4 mmHg-$p<0.001$; SVR-9.0±0.7 vs 14.6±4.0 arb. units $p<0.001$) as was the change in CO (6.1±0.4 vs 4.8±0.3 L/min, $p<0.01$). Both groups showed a comparable rise in plasma histamine (6573±2561 vs 8044±3701 pg/ml-NS).

Administration of diphenhydramine alone produced an increase in HR(52±3 to 62±2 beats/min, $p<0.01$) which had returned to control 5 min after the morphine (56±3 beats/min) and only slightly attenuated the fall in BP and SVR with morphine (BP-88±6 to 69±4 mmHg, $p<0.001$; SVR-17.8±2 to 12.3±1 arb. units, $p<0.001$). The increase in CO was not significant (4.7±0.2 to 5.1±0.3 L/min). Cimetidine alone produced no change in HR (60±3 to 61±3 but significant decreases in BP (81±3 to 64±3 mmHg,$p<0.001$) and SVR (18.4±4 to 14±1.5, $p<0.05$) occurred following the morphine. There was a decrease in CO (4.8±0.5 vs 4.4±0.5, $p<0.05$).

Discussion. These data demonstrate that the hemodynamic changes following morphine administration can be attributed to the rise in plasma histamine. The prior administration of H_1-and H_2 histamine blockers can significantly attenuate this response. It is possible, but unproven, that higher doses of the antihistamines could eliminate the histamine effects entirely. It is worth noting that 8 of 10 patients receiving morphine alone required the use of a pressor agent to treat hypotension, while none was required in the Group 4 patients.

The data also demonstrate that administration of an H_1 blocker alone (Group 3) is inadequate to prevent decreases in BP, SVR and increases in CO and suggest that the attenuation of these responses is due to the increase in HR. The H_2 blocker alone provided least protection apparently because of the lack of effect on HR. In these patients (Group 2) the fall in BP was accompanied by a decrease in CO. Pressor agents were required in 7 of 10 patients.

The dosage of dimethyltubocurarine (0.3 mgm/kg) was chosen because of its minimal cardiovascular effects and reported lack of histamine release (1,2). It is therefore unlikely that it played a significant role in the histamine release or hypotension noted in this study.

We conclude that the prior administration of H_1 and H_2 histamine blockers can significantly attenuate the adverse hemodynamic effects of IV morphine due to histamine release.

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2) Savarese, JJ, Ali, HH, Antonio, RP: The clinical pharmacology of metocurine. Anesthesiology 47:277-284, 1977.