Title: CUTANEOUS SIGNS OF HISTAMINE RELEASE FOLLOWING BUTORPHANOL OR MORPHINE

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Introduction. Intradermal or intravenous administration of morphine causes itching, urticaria, and redness, effects thought to be due to the release of histamine from tissue mast cells. It has never been clear that these changes bear any relationship to plasma histamine levels or to the production of clinically significant hemodynamic changes. It has been recently demonstrated that high doses of morphine (1 mg/kg IV) produce substantial elevations in plasma histamine with concomitant decreases in systemic vascular resistance (SVR).[1] Butorphanol produces no change or a small decrease in SVR[2] and appears not to elevate plasma histamine in dogs.[3] Skin changes were not measured in any of these studies. The purpose of the present study was to assess various cutaneous signs of histamine release following IV morphine or butorphanol and to compare them with simultaneous measurements of plasma histamine.

Methods. Sixty patients (ages 19-55, ASA I-II) gave institutionally approved informed consent. Premedication was pentobarbital 1-2 mg/kg IM. An IV infusion of lactated Ringer's was started in a hand or wrist vein, and an 18-gauge cannula was inserted in the opposite antecubital vein for blood sampling. The cannula was filled with heparin flush and allowed to remain in place for several minutes before samples were taken. Patients were randomly assigned to receive one of 6 treatments (n = 10/group): morphine 0.125, 0.25 or 0.5 mg/kg; butorphanol 0.025, 0.05 or 0.1 mg/kg. Morphine (10 mg/cc) and butorphanol (2 mg/cc) were prepared in coded vials. After a control blood sample for plasma histamine, narcotic was infused at a rate of 2 cc/min through a rapidly running IV line. At 2 and 5 min after drug administration, blood samples were taken, BP and HR were recorded, and evidence of local histamine release was scored as follows: 1 point each for presence of itch, redness or heat on a) IV arm, b) face, c) legs or torso; 1 point for presence of urticaria. These measurements were all made prior to the induction of anesthesia. Measurement of plasma histamine has been described previously.[4] Differences between doses and drugs were determined by two-way analysis of variance.

Results. There were no significant differences between groups for any demographic variable. There were no consistent changes in BP or HR for either drug at any dose. Mean histamine scores and plasma histamine measured at 2 minutes are listed in Table 1. Low, medium and high doses of butorphanal (B) and morphine (M) are labeled B1, B2, B3, M1, M2 and M3, respectively. There were no significant dose-response relationships for the cutaneous signs of histamine release. There were highly significant differences between drugs for redness and itching on the IV arm (M > B, $p < 0.0006$), torso (M > B, $p < 0.0014$), and total score (M > B, $p < 0.0003$).

There was no significant difference in facial itching or redness; the incidence of urticaria was too low for meaningful analysis. Plasma histamine was not elevated significantly in any group.

Discussion. Histamine release becomes a clinically significant problem when it is of sufficient magnitude to produce hemodynamic changes. Previous studies indicate that this will occur when plasma histamine is elevated.[1] The present study was designed to evaluate cutaneous changes as predictors of plasma histamine increase. The results show clearly that morphine produces more itching and redness than butorphanol; however, no dose-response relationships could be demonstrated for these effects despite a wide range of doses. Cutaneous changes were not correlated with plasma histamine levels since the latter did not change significantly. It is reasonable to assume that substantial release of histamine must occur in tissues before detectable amounts enter the bloodstream. Our results indicate that a) large amounts of histamine are not likely to be released by doses of morphine or butorphanol used in conventional balanced anesthesia; and b) prominent itching and flushing may occur without changes in plasma histamine.

Table 1:

Histamine scores and plasma histamine changes.

	B1	B2	B3	M1	M2	M3
Histamine Score*						
IV Arm	0.2 ±0.13	0.4 ±0.16	0.1 ±0.10	0.7 ±0.15	0.6 ±0.16	0.7 ±0.15
Face	0.3 ±0.15	0.9 ±0.10	0.6 ±0.16	0.6 ±0.16	0.8 ±0.13	0.7 ±0.15
Torso	0.2 ±0.13	0.2 ±0.13	0.1 ±0.10	0.6 ±0.16	0.6 ±0.16	0.5 ±0.17
Urticaria	0.1 ±0.10	0.1 ±0.10	0.0 ±0.0	0.2 ±0.13	0.0 ±0.1	0.2 ±0.13
Total	0.8 ±0.32	1.6 ±0.31	0.8 ±0.25	2.1 ±0.41	2.0 ±0.26	2.1 ±0.35
Plasma Histamine†	2.3 ±17.0	10.4 ±13.4	28.0 ±25.5	-18.1 ±11.0	-15.0 ±12.0	-4.4 ±15.6

* ± S.E.M.; † % change from control; n = 10/group

References

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