Title: A QUANTAL ANALYSIS OF THE DOSE-RESPONSE OF MIVACURIUM FOR PLASMA HISTAMINE INCREASE, FACIAL ERYTHEMA AND ARTERIAL PRESSURE DECREASE.

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Introduction

Facial erythema and decrease in arterial pressure are usually associated with increase of plasma histamine following rapid injection of large doses of benzylisoquinolinium type neuromuscular blocking drugs.[1] This so-called "histamine-release" phenomenon has never been formally treated as a dose-response in humans. To enable this analysis, specifically for the new short-acting nondepolarizer mivacurium[1], we have quantalized the data to produce dose-response curves for (1) clinically pertinent levels of plasma histamine increase, i.e., 100% or more above baseline; (2) readily apparent facial erythema; and (3) decrease in mean arterial pressure of 20% or more below baseline.

Methods

The study was approved by the Hospital Subcommittee on Human Studies. Informed consent was obtained from 53 ASA I-II patients, ages 32.6±9.7 years and weights 75.3±11.7 kg. Diazepam (0.1-0.2 mg/kg) and morphine (0.1-0.15 mg/kg) premedication was given one hour before arrival in the O.R.

Direct arterial pressure via radial catheter, EKG, tachograph-counted heart rate, and indirectly elicited thumb twitch at 0.15 Hz were recorded continuously. Anesthesia was induced with thiopental (4-8 mg/kg) and fentanyl (4-8 ug/kg) i.v., and maintained with N_2O/O_2 (4L/2L) and additional thiopental and/or fentanyl as needed to minimize changes in baseline arterial pressure and heart rate. Tracheal intubation was accomplished without a relaxant. End-tidal CO_2 was kept between 35 and 45 mm Hg by controlled ventilation. Esophageal temperature was kept between 34.5 and 37.5°C and O_2 saturation was kept above 97% as measured by pulse oximetry.

After a 10-min stable baseline period, mivacurium was injected as a rapid (15 sec) or slow (60 sec) bolus into a rapidly-running i.v. stream. All measurements were completed in the absence of patient stimulation.

Arterial samples were obtained for plasma histamine determination at t=-2,+2, and +5 min following mivacurium injection. A radioenzymatic method was used for histamine assay.[2]

Incidence of the following in each mivacurium dosage group was noted:

(1) Individuals showing obvious facial erythema
(2) Individuals responding with 20% or more decrease in mean arterial pressure
(3) Individuals demonstrating plasma histamine increase of 100% or more above baseline.

Incidences were converted to percentages and plotted on log-probit scales. Dose-response curves were calculated and ED50 derived in each case. The safety ratios (ED50 for the above responses/ED95 for neuromuscular blockade) were calculated.

Results

Data are listed in Tables 1 and 2. The dose-response curves do not differ significantly. Facial flushing and decreases in arterial pressure were transient (0.2-4.5 min). Peak plasma levels of histamine were observed at +2 min. All levels were within normal limits at +5 min. An obvious rightward shift of the dose-response curves by a factor of at least 2 occurs during slow injection, since incidence of all phenomena was 0 following 0.25 mg/kg given over 60 seconds.

Table 1

Dose mg/kg	Plasma Histamine (pg/ml±SE) Baseline	+ 2 min	Duration(min) MAP < 80% of baseline(range)
0.1	548±120	362±71	none
0.15	613±210	990±357	none
0.20	756±245	1470±548	0.3-2.2
0.25	881±240	1163±315	0.5-1.0
0.30	312±86	2266±730*	0.2-4.5
0.25 (slow)	364±102	452±94**	none

* p<0.001 vs baseline
** p<0.001 vs 10-15 sec bolus

Table 2

Dose mg/kg	Incidence: Plasma Histamine Increase>100%	Facial Erythema	MAP Decrease >20%
0.1	0/8	0/9	0/9
0.15	3/9	1/9	0/9
0.20	3/8	2/9	4/9
0.25	3/7	5/8	4/8
0.30	6/9	7/9	7/9
0.25(slow)	0/9	0/9	0/9
ED50(mg/kg) (95% conf.limits)	0.241 (0.181-0.322)	0.255 (0.206-0.316)	0.242 (0.197-0.297)
ED50/ED95 for neuromuscular blockade	3.0	3.2	3.0

Discussion and Conclusions

The data show that a dose-response curve for incidence of a moderate increase in plasma histamine (100% above baseline) closely approximates data from clinical correlates such as facial flushing and fall in arterial pressure which may be produced without the availability of a histamine assay. The ED50 values represent dosage of mivacurium where half the population will develop a perceptible side-effect following rapid injection. The transient nature of the side-effect suggests, however, that its clinical significance is minor in healthy patients. Determination of the ED50 for these phenomena allows the calculation of well-defined safety ratios, e.g. ED50/ED95 for neuromuscular blockade, which facilitate comparisons among various relaxants. The safety ratio of 3.0-3.2 for mivacurium is slightly greater than that of atracurium and about three times that of d-tubocurarine. The data show that the safety ratio may be increased by slower injection or infusion.

References

1. Savarese JJ et al. Anesthesiology (1988, in press).
2. Moss J et al. Anesthesiology 55:19-25, 1981.