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Title: MAC REDUCTION OF ISOFLURANE BY FENTANYL.

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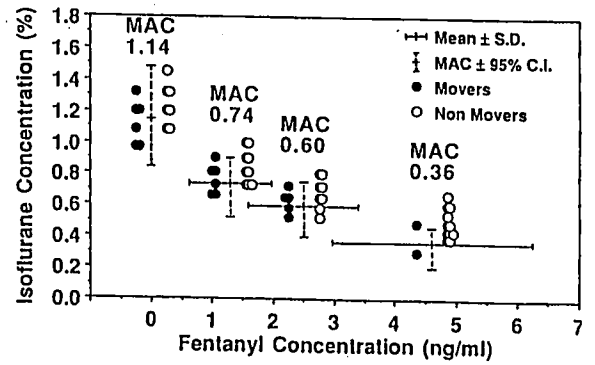
Introduction. Isoflurane and fentanyl are the most common combination of drugs used to maintain anesthesia. The MAC reduction of isoflurane by fentanyl (at steady plasma and biophase concentrations) has not previously been defined in man.

Methods. Following IRB approval, all patients signed a written informed consent. Inclusion criteria were ASA I or II patients between 20-60 on no medication known to influence MAC. Patients received in random order either no fentanyl or 3 predetermined concentrations of fentanyl. Fentanyl was administered via a pharmacokinetic model driven infusion device that is capable of delivering fentanyl to a desired plasma concentration[1]. At each of these plasma fentanyl concentrations patients were also randomly allocated to receive a predetermined steady state end tidal concentration of isoflurane. The fentanyl infusion and a gaseous induction with isoflurane in oxygen were started simultaneously. Following loss of consciousness succinylcholine (1 mg/kg) was given and endotracheal intubation was performed. Immediately thereafter the isoflurane was manipulated to maintain the measured (Puritan Bennett Anesthetic Agent monitor 222™) end-tidal concentration at the preselected value. Patients were mechanically ventilated to normocapnia and temperature was maintained during the study. Blood samples for fentanyl concentration were taken from a vein in the contralateral arm to the fentanyl infusion. These samples were taken at 10 min after the initiaion of the infusion, prior to and immediately following skin incision to insure that the desired fentanyl concentration had been maintained constant during the study. A minimum of 20 minutes was allowed between the start of the fentanyl infusion and skin incision. Patients were observed for purposeful movement for 60 seconds following skin incision. The reduction of MAC by each desired fentanyl concentration group was calculated using a maximum likelihood solution to a logistic regression model.

Results. Data from 58 patients are presented. The results are presented in the figure. The mean (±sd) fentanyl concentration in each group was 0, 1.5(±0.8), 2.35 (±0.7), 4.68 (±1.6) ng/ml.

Discussion. When defining drug interactions it is critical that both have obtained a steady biophase (effect compartment) concentration. For Isoflurane this was ensured by maintaining a constant end tidal concentration. For fentanyl a steady plasma concentration was maintained and we accounted for its ke0 by waiting 20 min.(3 times T1/2 keO) prior to assessing response to skin incision. The most dramatic MAC reduction of isoflurane was seen as the fentanyl concentration increased from 0 to 1.5 ng/ml. Further increases in fentanyl concentration continued to reduce the MAC of Isoflurane but to a lesser degree. Defining the MAC reduction of all the opiates will allow a clear comparison of their relative anesthetic potency and allow their more rational administration with inhalational anesthetics.

References. 1) Glass PSA, et al. Anesthesiology 73: 1082-90, 1990.



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Title: TIVA - PROPOFOL AND COMBINATIONS OF PROPOFOL WITH FENTANYL

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INTRODUCTION: There has been increasing interest in total intravenous anesthesia (TIVA) especially with the recent release of propofol (P). We wished to answer the following questions: a) can propofol be administered as a sole anesthetic? b) when combining fentanyl (F) with P, as the stimulus varies is it more appropriate to increase the concentration of F or P?

METHODS: Following IRB approval and written informed consent 62 patients between 18-55 years presenting for lower limb or lower abdominal surgery were entered into the study. Patients were randomly assigned to one of three groups: A (P as sole agent), B (P at a constant concentration and F concentration varied) and C (F at a constant concentration and P varied). Patients were premedicated with a benzodiazepine prior to induction. P and F were administered via CACI[1] (a pharmacokinetic model driven infusion device) to a desired whole blood (P) or plasma (F) concentration. Blood samples for P, F, catecholamine, and cortisol concentrations were taken at set time intervals. In A and C patients were induced with P. In B patients were induced with F. In B an infusion of P (to 2.5 µg/ml) and in C an infusion of F (to 1.5 ng/ml) was started 3 minutes prior to induction and terminated at the end of surgery. After incision P (A and C) or F (B) were titrated to provide adequate anesthesia which was determined by predefined hemodynamic, somatic and autonomic responses. If after 15 minutes a patient showed no sign of inadequate anesthesia then the P concentration in A and C was decreased by 0.5 µg/ml and the F concentration in B was decreased by 0.5 ng/ml. For inadequate anesthesia up to 3 increases in P (0.5,1,2 µg/ml- A,C) or F (0.5,1,2ng/ml-B) were allowed. Inadequate anesthesia after a third increase was considered a protocol failure. If naloxone was required at the end of surgery for inadequate ventilation (<8 breaths/minute or PCO_2 >50mmHg) this was also considered a protocol failure. At the end of the surgical procedure the infusions were stopped and the times to spontaneous ventilation, response to command, orientation and an Aldrete score of 10 were recorded. The number of protocol failures was compared using Fisher's exact test. ANOVA was used to compare between group differences. $p<0.05$ was considered significant.

RESULTS The propofol and fentanyl doses and concentrations, and the recovery parameters are presented in the table. There were 7 protocol failures in A, 8 in B, and 1 in C ($p<0.05$ C vs A or B). At the end of surgery, cortisol and norepinephrine concentrations were significantly higher in A than B or C.

DISCUSSION Our findings indicate that during a TIVA technique it is preferable to maintain F constant and titrate P to maintain adequate anesthesia. P as a sole anesthetic requires very high concentrations resulting in prolonged recovery. P alone was also not as effective at ablating the stress response

REF. 1. Glass PSA et al, Anesthesiology 73: 1082-90, 1990

Mean ±SEM	Group A (n=22)	Group B (n=18)	Group C (n=22)
Age (years)	35 ±2.3	34.4±2.1	33.8±2
Weight (kg)	82.4 ±3.7	75.4±3.5	84.8±3.8
Propofol conc (µg/ml)	9.4 ±0.4	2.5 (pred)	3.4 ±0.2
Duration (min)	223±26	193±33	203±25
P maintenance µg/kg/min	267±16	78±4	126±11
F maintenance µg/kg/min	0	0.12±.02	0.04± 0.003
Time to orient (min)	34.4±4.8*	18.2±4.7	15.6±3
Spont ventilation	10.2±3 *	9.8±2	6±1
Respond to command	26.7±5.3*	8.6±1.2	11.7±2
Aldrete score of 10	54.2±6*	40±5.8	28.8±3.3

* $p< 0.05$ A vs both B or C