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Title: EVIDENCE FOR RAPID ONSET OF ACUTE TOLERANCE WITH ALFENTANIL

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Introduction: Many of the agents used in anesthesia are well recognized to be associated with the development of tolerance when administered over a long period of time. The development of acute tolerance (i.e. tolerance developing within minutes to a few hours of initiation) is less well recognized. In anesthesia the development of acute tolerance may have significant ramifications. While studying the efficacy of alfentanil (A) in patients undergoing gynecological surgery, we noted what we postulate to be evidence of the rapid onset of acute tolerance to A.

Methods: Following IRB approval and informed consent, twenty female patients, ASA I and II, undergoing gynecological surgery were studied. All were premedicated with diazepam (10 mg/po) and atropine (0.4 mg/im). Standard monitoring was employed. Induction consisted of A 25-75 mcg/kg titrated to unresponsiveness to verbal command, followed by thiopentone 3-4 mg/kg. Succinylcholine 1.5 mg/kg facilitated endotracheal intubation. Maintenance of anesthesia was with N_2O/O_2 60:40% and a continuous infusion of A, initially 2 mcg/kg/min and then adjusted from 1-4 mcg/kg/min in an attempt to maintain hemodynamic variables within 15% of baseline. Pancuronium was titrated for relaxation. A infusion was discontinued approximately ten minutes before the end of surgery. At the end of surgery, the lungs were ventilated with 100% O_2 and neuromuscular blockade reversed with atropine and neostigmine. EEG signals were recorded from five minutes prior to induction until the patient left the OR. Blood samples were drawn from an indwelling venous catheter (heparin lock) from the preinduction period through the recovery room stay and analyzed for catecholamines (CAT) (radioenzymatic assay) and A (gas chromatography) concentrations.

Results: The mean loading dose of A was 55 ± 13 mcg/kg, total dose 270 ± 83 mcg/kg, and mean infusion rate 2.2 ± 0.4 mcg/kg/min. Hemodynamics remained stable throughout the study period. Following A administration the EEG changed to the low frequency, high voltage pattern of opioids. No EEG evidence of stimulation was seen during surgery. However, at recovery there was a distinct EEG effect of increased median frequency away from the delta region and towards an awake EEG pattern. CAT levels were constant except for a decrease in norepinephrine levels post-incision and an increase in epinephrine ($p < 0.05$) and norepinephrine levels in the recovery room compared to baseline (Table 1). The average plasma concentration of A increased over time with continuous infusion (Table 1). After discontinuation of A infusion, plasma levels rapidly declined. However, at extubation, plasma concentrations of A were significantly higher than following induction (Table 1).

Conclusion: The stable hemodynamics, EEG power distribution, CAT levels, and completed clinical recovery at significantly higher A levels than present post-induction are evidence of an increasing acute tolerance to A in those patients. The perceived pharmacokinetic and pharmacodynamic differences between drugs within a class may be a function of acute tolerance as much as a function of the specific drugs themselves.

TABLE 1

	Induction	Incision	Recovery
CAT: Norepinephrine	279 ± 111	200 ± 84[a]	377 ± 175[a]
Epinephrine	46 ± 17	62 ± 28	92 ± 43[a]
Systolic Blood Pressure	125 ± 10	117 ± 13	130 ± 16[b]
Plasma A [ng/ml]	180 ± 40	190 ± 28	300 ± 100

Note: (a) is significant $p < 0.05$ change from baseline.
(b) is significant $p < 0.05$ difference from induction.

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TITLE: THE REDUCTION OF HALOTHANE MAC BY EPIDURAL FENTANYL - A COMPARISON WITH INTRAVENOUS FENTANYL

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Fentanyl, a liposoluble opioid, produces strong analgesia by not only intravenous but also epidural administration. We designed this study to evaluate the analgesic potency of epidural or intravenous fentanyl in terms of its ability to reduce minimum alveolar concentration (MAC) of halothane.

We obtained our institutional approval and an informed consent from each patient before the beginning of this study.

Eighty-four ASA physical status I female patients, ages 22-50 yr and weights 40-65 kg, scheduled for simple or radical hysterectomy were studied. In the previous day of surgery, all patients received the epidural catheterization. An epidural catheter was inserted at the L1-L2 interspace, and 7cm of the catheter remained within epidural space. Through the catheter we then injected 2 ml of 1% lidocaine to rule out intravascular or subarachnoid injection. Twenty minutes after injection of test dose, we validated segmental analgesia from navel to groin by a pin-prick method following the injection of 7 ml of 1% lidocaine.

All patients received no premedication. ECG, oscillometric blood pressure, SpO_2, P_{ETCO_2}, and rectal temperature were continuously monitored. An intravenous catheter was inserted on the dorsum of left hand. Lactated Ringer's solution was infused at rate of 10 $ml \cdot kg^{-1} \cdot min^{-1}$ while the patients breathed pure oxygen through an anesthetic mask. The patients were randomly assigned to one of seven groups prior to anesthetic induction. Group A was given 10 ml of normal saline through the epidural catheter, and groups B, C and D were given 1, 2 and 4 μg/kg of fentanyl in 10 ml diluted with normal saline epidurally, respectively. Groups E, F and G were given 1, 2 and 4 μg/kg of fentanyl intravenously by a bolus injection, respectively.

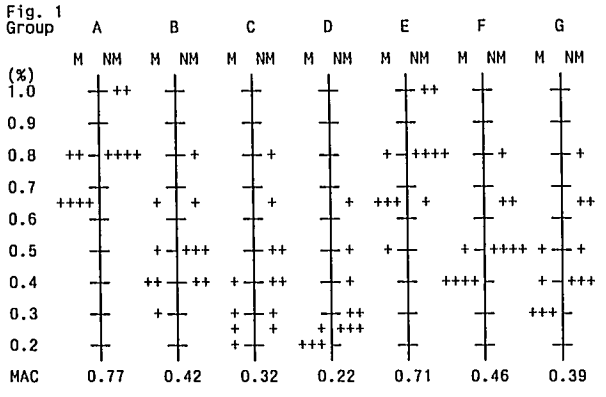
A patient, after receiving the prescribed dosage, inhaled halothane to attain a sufficient depth of anesthesia and the trachea was intubated with no adjuvant drugs. After intubation, end-tidal halothane concentration was rapidly brought to a predetermined level by the Dixon approach, and was maintained its level for at least 15 min. End-tidal halothane concentration and P_{ETCO_2} were continuously monitored by a mass spectrometer(Medical Gas Analyzer 1100,PERKIN-ELMER) and a capnograph (CAPNOMAC,DATEX). The mass spectrometer and the capnograph were calibrated by each standard gas before measurement. The lungs were mechanically ventilated to maintain P_{ETCO_2} between 30 and 40 mmHg. Patients were then observed for movement or lack of movement upon surgical incision. After observation, adjuvant drugs were administered for muscle relaxation with/without movement. MAC was calculated using the Dixon up-and-down approach.

Results are summarized in figure 1.

The analgesic potency of epidural fentanyl was stronger than that of intravenous fentanyl in same dose. The 71% reduction in halothane MAC occurred after epidural administration of fentanyl 4 μg/kg, while the 49% reduction after intravenous administration of fentanyl 4 μg/kg.

This phenomenon may arise as a result of spinal analgesic action produced by epidural fentanyl.

Fig. 1



M; movement, NM; not movement