Title: MORPHINE AND FENTANYL ANESTHETIC INTERACTIONS WITH ETOMIDATE

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Introduction. Thiopental and opiates (fentanyl and morphine) have been found to interact differently regarding different components of anesthesia: with synergism in relation to hypnotic effect, relative antagonism in relation to movement response to noxious stimulation, and antagonism in relation to cardiac acceleration to noxious stimulation.[1,2] One of the agents in the studied combinations, thiopental, is a barbiturate. It is known that barbiturates have an antianalgesic action. The question arises whether nonbarbiturate intravenous anesthetics interact with opioids in a way different from the way barbiturates do. The aim of the present study was to define the type of interaction between morphine and fentanyl, on the one hand, and etomidate, on the other, in relation to the following three end-points of anesthesia: loss of the righting reflex, blockade of purposeful movement to tail clamping, and suppression of cardiac acceleration response to tail clamping.

Methods. Experiments were performed in Sprague-Dawley male rats weighing 275-325 g. Interaction for each end-point of anesthesia was studied in a separate series of experiments. ED_{50} values for the agents given separately and jointly in binary combinations were determined with the probit procedure[3] and compared with an isobolographic analysis.[4] Each animal was given (i.v. injection) one predetermined dose of an agent or a combination of agents. Times between injections of agents and the end-point test were based on the times to peak effect for these agents: 15 min for morphine, 5 min for fentanyl, and 2 min for etomidate. The animals were placed in a chamber with oxygen 15 min before the first injection. Doses of the agents (used for determination of the dose-response curves and ED_{50} values) were selected on the basis of the pilot experiments. Each series of experiments consisted of 60 animals. In the righting reflex series of experiments, the test was regarded as positive when the rat failed to right itself within 15 sec after being placed in a side position. In the purposeful movement series of experiments, the animals were stimulated by clamping the tail (60 sec, 300 g/mm^2). Only one stimulation was induced in each animal. In the cardiac acceleration series of experiments, the heart rate was obtained from an electrocardiogram. After injection of the anesthetics, the animals received tubocurarine, 1 $mg \cdot kg^{-1}$, followed by endotracheal intubation. Controlled ventilation was provided by a rodent respirator. The response was induced by tail clamping (60 sec, 300 g/mm^2). An increase in heart rate of less than 5% was determined as an end-point. The effect of morphine-etomidate and fentanyl-etomidate combinations on $PaCO_2$ were studied separately in rats with arterial catheters implanted before the day of the experiment. Arterial blood gases were measured using an IL System 1301 Blood Gas Analyzer.

Results. The interaction regarding loss of the righting reflex resulted in a synergism with deviation from the additive effect (expected ED_{50}/observed ED_{50}) of 1.13 ($p<0.05$) for etomidate-fentanyl and 1.56 ($p<0.001$) for etomidate-morphine. The effect of the opiate-etomidate combinations on the somatic response (purposeful movement) to noxious stimulation resulted in a summation; expected ED_{50}/observed ED_{50} ratio was 1.03 with etomidate-fentanyl and 1.1 with etomidate-morphine. The effects of the opiate-etomidate combinations on the sympathetic response (cardiac acceleration) to noxious stimulation resulted in an antagonism; the deviation from the additive interaction was 0.41 ($p<0.001$) with etomidate-fentanyl and 0.37 ($p<0.001$) with etomidate-morphine. In an attempt to explain the difference between the expected/observed ratios in the etomidate-fentanyl and the etomidate-morphine righting reflex series of experiments (1.13 vs 1.56) by the possible role of ventilatory depression (hypercarbia) which might be quite different with the two combinations, we performed $PaCO_2$ experiments. With etomidate-fentanyl and etomidate-morphine combinations, at the ED_{50} level, the $PaCO_2$ was increased to a similar degree: 15.1 ± 4.0% with etomidate-fentanyl vs 14.4 ± 2.4% with etomidate-morphine.

Conclusion. It was found that etomidate and opiates (fentanyl and morphine) interact differently regarding different end-points of anesthesia: synergism for loss of the righting reflex, summation for loss of movement response to noxious stimulation, and antagonism for suppression of cardiac acceleration response to noxious stimulation. The results in most respects are similar to those obtained in the studies with barbiturate-opiate interactions.[1,2] They suggest that the anesthetic action probably represents several actions (components of anesthesia)[5] with different mechanisms for various components of anesthesia. As a result, depending on the specific component in question, the effect of the combination of etomidate with an opiate varies.

References.

1. Kissin I, Mason JO, Bradley EL, Jr: Morphine and fentanyl anesthetic interactions with thiopental in relation to movement response to noxious stimulation. Anesth Analg 65:1149-1154, 1986
2. Kissin I, Mason JO, Bradley EL, Jr: Morphine and fentanyl anesthetic interactions with thiopental in rats. Federation Proceedings 46:1302, 1987
3. Finney DL: Probit analysis. London, Cambridge University Press, 1952
4. Loewe S, Aldous RA, Fox SR, Johnson DG, Perkins W: Isobols of dose-effect relations in the combination of trimethadione and pentylenetatrazole. J Pharmacol Exp Ther 113:475-480, 1955
5. Woodbridge PD: Changing concepts concerning depth of anesthesia. Anesthesiology 18:536-550, 1959