Optimal propofol and fentanyl combination during aneshtesia

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For intravenous anesthetics, the index of potency has been defined in terms of the plasma concentration required to prevent a response in 50% and 95% of patients (Cp50 and Cp95) to stimulation by skin incision, and this index is a guide for therapeutic concentrations.(1-8) However, the intensity of stimulation varies during surgery with varying kinds of stimuli. Ideally, the anesthetic infusion rate should be adjusted in each patient according to the expected intensity of an impending stimulation, and the plasma concentrations should be maintained slightly above the minimum level required to maintain satisfactory anesthetic conditions to allow rapid recovery (4-6) and stable hemodynamic conditions. However, there are often marked increases in blood pressure during the early phase of abdominal surgery empirically, even in patients who are administered doses above the Cp95 for skin incision during propofol and fentanyl anesthesia. These findings suggest that skin incision may not be the most intensive stimulus and that somatic response will be different from hemodynamic response to noxious stimulus. Ausems reported that skin incision is not the most intensive stimulus encountered in the perioperative period.(1)

Moreover, there exist various combinations of propofol and fentanyl for the purpose to suppress only somatic response to stimuli. In the viewpoint of maintaining both stable somatic and hemodynamic anesthesia, there are no indexes for noxious stimuli. In addition to preventing somatic response, the prevention of a hyper-hemodynamic state that occurs in response to surgical stimulation is a basic concern of clinical anesthesia and is of obvious interest to all clinicians. We have investigated the optimum combination of propofol and fentanyl for various surgical stimulations.

1) Effects of Propofol and Fentanyl on Somatic Response to Skin Incision, Peritoneum Incision, and Abdominal Retraction

The interactions between propofol and fentanyl in relation to somatic responses to skin incision, peritoneum incision, and abdominal retraction were shown in figures 1, 2, and 3. The reductions in propofol Cp50si, Cp50pi, and Cp50ret by fentanyl were significant. Propofol and fentanyl had a synergistic action on somatic response.

We determined the plasma concentration of propofol Cp50 of required for upper abdominal peritoneum incision and abdominal retractor that are about 1.47 times of Cp50 for skin incision. Ausems reported alfentanil Cp50 required for breast, lower abdominal, and upper abdominal surgery as 270, 309, and 412 ng/ml when supplemented 66% of nitrous oxide, and also determined the Cp50 for skin incision as 279 ng/ml.(6)Thus the ratio of alfentanil Cp50 for upper abdominal surgery to Cp50 for skin incision was 1.48.

Peritoneum incision and abdominal retractor are clearly more intense stimuli than skin incision encountered in the beginning of upper abdominal surgery. Although skin incision can be still used as the representative of all noxious stimuli in non-abdominal surgery, it should be considered that peritoneal incision and peritoneal retraction would be the more intense stimulation than skin incision in abdominal surgery.
A plasma fentanyl concentration of 1 ng/ml resulted in a 44% reduction of propofol Cp50si, a 31% reduction of propofol Cp50pi, and a 30% reduction of propofol Cp50ret. Increasing the plasma fentanyl concentration to 3 ng/ml resulted in a 76% reduction of propofol Cp50si, a 65% reduction of propofol Cp50pi, and a 56% reduction of propofol Cp50ret. The 50% reductions in Cp50si, Cp50pi, and Cp50ret were provided by fentanyl concentrations of 1.2, 1.8, and 2.8 ng/ml respectively.

2) Interaction between Propofol and Fentanyl without Surgical Stimulation

Propofol and fentanyl concentrations at which 50% of patients did not respond hemodynamically by showing various sBP and HR decreases without surgical stimulation are shown in figures 4 and 5. Without fentanyl, 15%, 30%, and 40% decreases from normal sBP were provided by 3.6, 8.1, and 17.7 µg/ml of propofol in 50% of patients. SBP was decreased mainly by propofol during the prestimulation period, and this decrease was dose dependent (figure 4). Propofol combined with fentanyl exerts a synergistic effect on sBP. HR decreased with increasing propofol concentrations (figure 5). No consistent data set was obtained for a 40% decrease from normal HR, and therefore the propofol-fentanyl interaction to induce 40% decrease could not be determined. The two drugs had a synergistic action on HR during the prestimulation period.

3) Effects of Propofol and Fentanyl on Hemodynamic Response to Skin Incision, Peritoneum Incision, and Abdominal Retraction

The average of the %increase of sBP in each concentration of propofol and fentanyl are also given in figures 1, 2, and 3**.** Clinically, 15 per cent increase of systolic pressure after noxious stimulation can be approved to be a reasonable clinical response to various stimuli.
According to this viewpoint of 15 per cent increase response of systolic pressure, visual inspection revealed that increasing propofol could not attenuated sBP increase after each of stimulation. However, increasing fentanyl concentration reduced the sBP increase. The increase in blood pressure is most closely related to the type of the stimulation pattern, followed by plasma fentanyl concentration.

4) Optimum Combination of Propofol and Fentanyl to suppress both Somatic and Hemodynamic Responses to Skin Incision, Peritoneum Incision, and Abdominal Retraction

Propofol decreased sBP significantly more than fentanyl did without surgical stimulation. These findings have leaded to increase propofol blood concentration when hypertension was observed in response to surgical

stimulation during surgery. However, this treatment was usually ineffective in clinical cases especially during peritoneum incision or peritoneum retraction. There are two reasons why the unsuccessful clinical treatment. First, peritoneum incision and retraction were more intensive stimuli than skin incision. Although almost somatic responses to skin incision should be suppressed in Cp95 for skin incision, those responses to peritoneum incision or retraction would not be suppressed even in that concentration. Second, hemodynamic effects of propofol and fentanyl without surgical stimulation are not different from those with surgical stimulation. Propofol decreased sBP effectively during no surgical stimulation rather than fentanyl, however it could not decrease sBP effectively that caused with surgical stimulation. Fentanyl suppressed responsive hypertension effectively rather than propofol.
We found the optimum combination of propofol and fentanyl to suppress both somatic and hemodynamic responses to skin incision, peritoneum incision, and abdominal retraction. Those crossing points of somatic Cp50 lines and 15% increase of sBP hemodynamic response lines were shown as the optimum combinations of propofol and fentanyl in figures 1, 2, and 3.

When considering both specific somatic and hemodynamic responses for surgical stimulations at once, propofol therapeutic band is from 3 to 5 μg/ml, and fentanyl therapeutic band is from about 3.5 to 9.0 ng/ml. According to these findings, the fentanyl concentration should be changed more than propofol concentration to maintain a stable anesthesia.

Propofol and fentanyl should be given using a pharmacokinetic model-driven TCI system, such that equilibrium between blood concentrations and their theoretical effect compartment was obtained at the time drug effect was assessed. The degree of hysteresis is reflected by the time constant for equilibration between blood and brain, which for propofol is 3.4 min (9,10) and which for fentanyl is about 9.5 min.(11) Although it is reasonable to change fentanyl concentration rather than propofol, these findings shows the difficulty of changing fentanyl concentration rapidly.

Summary
Although propofol decreased BP more than fentanyl, it could not suppress hypertensive responses effectively rather than fentanyl. In addition to the concentrations to suppress somatic response, it is innevitable to consider the concentrations to suppress hemodynamic response at once in clinical anesthesia management.

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