

**Titre:** PLASMA CONCENTRATIONS OF SUFENTANIL REQUIRED TO SUPPRESS HEMODYNAMIC RESPONSES TO NOXIOUS STIMULI DURING NITROUS OXIDE ANESTHESIA

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**Introduction.** Sufentanil (SF) is proposed in clinical practice as an analgesic supplement to anesthesia. However, it remains a controversy about the ability of opioids to suppress completely cardiovascular responses to surgery. A recent study demonstrated that a concept similar to MAC for halogenated anesthetics may be determined with alfentanil: Cp50, that is the plasma concentration which suppresses response in 50% of patients. The present study was designed to determine the Cp50 of SF to different noxious stimuli.

**Patients.** Fourteen patients (ASA I) scheduled for elective surgery were studied. All patients gave informed consent and institutional approval was obtained. Premedication consisted of lorazepam, 2.5 mg and atropine, 1 mg p.o.. Induction was achieved with SF, 2 mcg/kg in 2 min and 66% N<sub>2</sub>O in oxygen. Trachea was intubated using vecuronium or succinylcholine 5 min later. Patients were ventilated to normocapnia. Just after induction, a continuous infusion of SF, 0.66 mcg/kg/h was started. Infusion rate was adjusted in steps of 0.33 mcg/kg/hr between 0.33 and 2 mcg/kg/hr and bolus doses of SF, 0.1 or 0.2 mcg/kg were given to suppress any responses indicating inadequate anesthesia. A "response" state was present if: 1) systolic or diastolic blood pressure increased for more than 15% above preoperative values; 2) heart rate exceeded 90 bts/min; 3) movements or somatic responses were present. SF infusion was discontinued 25 min before the anticipated completion of surgery and N<sub>2</sub>O was stopped at the end of operation. Naloxone was administered 10 min after, if no efficient spontaneous ventilation was present. Arterial plasma concentrations of sufentanil (SFcp) were measured repeatedly during the operation by radioimmunoassay, when the patients did and did not respond to noxious stimulation. The Cp50 of SF was determined by non linear computerized fitting of data according to the following logistic equation:<sup>2</sup> Probability of no response =  $SFCp \gamma / (Cp50 \gamma + SFCp \gamma)$  where gamma is the steepness of the slope. Statistical analysis was performed using ANOVA. Values are given as mean±SD.

**Results.** Plasma sufentanil concentration required along with 66% N<sub>2</sub>O to suppress responses to tracheal intubation in 50% of the patients was 1.08±0.17 ng/ml. Plasma concentration at intubation varied between 0.73 and 2.55 ng/ml (mean: 1.52). The Cp50 for satisfactory spontaneous ventilation after the discontinuation of N<sub>2</sub>O was 0.25±0.2 ng/ml (significantly lower if compared to that required for intubation: p < 0.01). Plasma concentration at this time varied between 0.09 and 1.04 ng/ml (mean: 0.51). Between skin incision

and skin closure, multiple determinations of no response and response made for each patient indicate that individual Cp50 ranged from 0.2 to 2.3 ng/ml. In 5 patients, individual Cp50 could not be calculated since no response was observed during surgery (n = 3) or because of marked variability in the relationship between response and no response during surgery (n = 2).

**Discussion.** This study shows that it is possible to determine for sufentanil the plasma concentrations which suppresses responses to noxious stimuli in 50% of patients. Our findings support the data reported with alfentanil indicating a potency ratio of 1/400 to 1/800 between alfentanil and sufentanil plasma concentrations. However, it should be noted that the range of concentrations required to suppress responses to surgery is very large, indicating an important variation in the intensity of noxious stimuli during surgery and suggesting a great inter-individual variability in responsiveness. Further studies are needed to determine if this variability may be related to differences in opioid receptors.

#### References

1. Ausems ME, Hug CG, Stanski DR, et al.: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* 63:362-373, 1987
2. De Lean A, Munson PJ, Rodbard D.: Simultaneous analysis of families of sigmoidal curves: application to bioassay, radioligand assay, and physiological dose-response curves. *Am J Physiol* 235:E97-E102, 1978