Title: EFFECTS OF OXYMORPHONE OR FENTANYL ON SYSTEMIC HEMODYNAMICS AND PLASMA CONCENTRATIONS OF HISTAMINE, CATECHOLAMINES, AND IMMUNOREACTIVE BETA ENDORPHIN

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Introduction. Oxymorphone (Numorphan) is a semisynthetic opioid analgesic, which is about ten times the potency of morphine. There are scanty reports of its use in anesthesia. The present study is a double-blind comparison of equianalgesic doses of oxymorphone and fentanyl during nitrous oxide-relaxant anesthesia.

Methods. Forty consenting adult patients, scheduled for major orthopedic procedures, were randomly assigned to receive either oxymorphone, 0.1 mg/kg, or fentanyl, 0.01 mg/kg. The protocol was approved by the Human Studies Committee. The drugs were dispensed in identical syringes, which contained either 0.5 mg/ml of oxymorphone or 0.05 mg/ml of fentanyl. Patients were premedicated with oral diazepam, 0.1 mg/kg. Intravascular catheters were inserted under local anesthesia, while the patients breathed oxygen via a face-mask. Pancuronium, 0.02 mg/kg was administered to prevent rigidity. After control hemodynamic measurements and arterial blood samples were obtained, 0.2 ml/kg of the opioid drug was injected intravenously. Measurements and blood samples were obtained 2, 5, 30, and 60 minutes following drug injection. Patients were encouraged to breathe and report any subjective changes. Upon completion of the 5-minute measurement, anesthesia was induced with thiopental, 4 ml/kg, and endotracheal intubation facilitated with succinylcholine, 1 mg/kg. Nitrous oxide and oxygen (3:2L/min) were used for maintenance of anesthesia, and d-tubocurarine, 0.4 mg/kg, provided muscle relaxation. Increments of the opioid drug were given to control elevations (15 percent above preanesthetic values) of systolic blood pressure and/or pulse rate. Thiopental, 50-100 mg, was administered if the study drug were ineffective. Increments of curare were given to maintain muscle relaxation, determined by the response to peripheral nerve stimulation. Atropine, 0.8-1.2 mg, and neostigmine, 2.5-5 mg, were given to reverse neuromuscular blockade. Cardiac output (dye dilution), heart rate (ECG), and arterial and right atrial pressures were determined before and 2, 5, 30, and 60 minutes after drug injection. Plasma histamine (radioenzymatic assay) was measured before and 2 and 5 minutes after drug administration. Plasma catecholamines (HPLC) were determined before and 2, 5, 30, and 60 minutes following drug injection. Beta endorphin (RIA) was measured before and 30 and 60 minutes after the drug. Hemodynamic responses to intubation and skin incision were recorded. Recovery times from discontinuation of N_2O to opening of eyes on command, and to orientation to place and date were recorded.

Results. Both groups of patients were comparable in age, sex, weight, height, and control measurements. There were no significant hemodynamic changes after either drug. Cardiac outputs (L/min) were 5.9±0.4 (control), 6.2±0.3 (after 2 min), and 6.3±0.4 (after 5 min) with oxymorphone, and 5.8±0.4 (control), 6.0±0.3 (after 2 min), and 6.1±0.4 (after 5 min) with fentanyl. At corresponding time periods: (a) mean arterial pressures (mmHg) were 96±4, 93±5, and 92±3 with oxymorphone, and 97±3, 93±4, and 91±4 with fentanyl; (b) plasma histamine concentrations (pg/ml) were 313±299, 212±198, and 217±167 with oxymorphone and 301±276, 203±147, and 156±104 with fentanyl. These changes were not significant. Plasma epinephrine and norepinephrine concentrations demonstrated a small significant decrease with fentanyl only. Immuno-reactive beta-endorphin levels decreased significantly after oxymorphone only (from 51.3±11 to 34.1±10 and 32±9 pg/ml after 30 and 60 min, respectively). Durations of anesthesia were comparable in both groups. Recovery times were significantly shorter ($P<0.05$) in the fentanyl group. Dose requirements for oxymorphone were 7.5 times more than those for fentanyl. Four patients in the fentanyl group complained of pain on awakening; none complained of pain in the oxymorphone group. Nausea and vomiting occurred in five patients in each group. Incremental doses of the drug and thiopental were required at approximately similar intervals. Duration of postoperative respiratory depression, determined by measuring arterial blood gases, was longer with oxymorphone.

Discussion. This study demonstrates that oxymorphone is a useful analgesic supplement to N_2O-relaxant anesthesia. Both drugs were associated with stable systemic hemodynamics and no histamine release. In these respects, they differ from morphine. Both groups of patients had comparable operative procedures, thus surgical stimulus was similar. Dose requirements were seven and a half times more for oxymorphone (0.15 vs. 0.02 mg/kg). This would be expected from their potencies relative to morphine.

Both drugs suppressed the hemodynamic responses to both intubation and the surgical incision. Postoperative nausea and vomiting were comparable with both drugs. However, recovery times and the duration of postoperative respiratory depression were longer with oxymorphone. Although no pharmacokinetic data is available for oxymorphone, our results suggest that its pharmacokinetic profile resembles that of morphine.

The decreased level of beta-endorphin with oxymorphone is an interesting phenomenon; we are currently examining this observation.

Oxymorphone is an effective supplement to nitrous oxide-relaxant anesthesia. It is associated with stable hemodynamics, little or no histamine release, longer recovery times and prolonged respiratory depression. This drug deserves further studies and its pharmacokinetic profile should be delineated.