TITLE: PHASE II-III CLINICAL TRIAL WITH DESFLURANE (I-653) IN ASA I ADULT PATIENTS

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Desflurane (DF) is a new inhalational anesthetic with favorable results observed in Phase I human trials. Following are preliminary results of an independent phase II-III clinical study, in comparison with isoflurane (IF).

With institutional approval, we studied 48 informed and consenting adult patients undergoing elective orthopedic surgery, ASA I, 18-48 y.o., 59-109 kg (72±9.1 S.D.). As premedication, midazolam 3 or 4 mg was given i.v. in divided doses. We monitored ECG, O_2 saturation, BP, core temperature, ventilatory rate, volume and pressure, end-tidal CO_2, concentrations of N_2O, O_2 and inhaled and exhaled DF or IF (Datex^R), as well as any body, airway, or salivary responses. Following thiopental 5 mg/kg, anesthesia continued with DF (N=24) or IF (N=24), N_2O and O_2 under mask. Subsequently, N_2O was withdrawn. At approximately 2 MAC of DF or IF, the trachea was sprayed with 4% lidocaine (4 ml) and intubated without the use of any relaxant. Anesthesia was then maintained at DF 9% or IF 1.6% exhaled (both 1.25 MAC). End-expiratory CO_2 was controlled at 32-35 torr by a respirator. Towards the end of surgery, normal tidal CO_2 was restored, DF or IF was turned off, and the patient's first spontaneous motion, cough, reaction to painful pinch, response to verbal command, and orientation to age, name, and body parts were examined minute by minute. Delirium, shivering, nausea, or vomiting was noted. Data were compared by t or chi-square tests for $p < 0.05$.

There is no significant difference between DF and IF during maintenance of anesthesia, but cough and laryngeal closure occurred more frequently during the induction of anesthesia with DF, 62.5% vs. 29.2%, $p < 0.05$. All laryngospasms were overcome by higher ventilatory pressure without complications. There was no cardiac dysrrhythmia, salivation, or bronchospasm. Spontaneous ventilation was markedly reduced when the exhaled concentration of DF or IF reached 1-2 MAC. All patients had relaxed jaw for easy intubation of the trachea at 1.5 MAC. No patients moved on incision. On termination of anesthesia, starting from 1.25 MAC, it took DF 16.9±7.1 (S.D.) min, and IF 28.5±10.8 min, $p < 0.05$, for the patient to be able to tell name, age, and right from left. DF patients had less delirium and shivering. The duration of anesthesia was similar: DF 142±53 (S.D.) min, IF 122±46 min, $p > 0.05$.

We conclude that DF is faster and cleaner than IF in emergence from anesthesia. Laryngeal reaction during mask induction with DF may be due to its pungency and may have more significant implication in pediatric anesthesia. A 12-15% exhaled concentration permits tracheal intubation with relaxed jaw. A 9% exhaled concentration permits incision in young, healthy adults. It is safe and efficacious.

TITLE: UPTAKE, EQUILIBRATION AND ELIMINATION OF DESFLURANE (I-653) IN HEALTHY ADULT PATIENTS IN A CLINICAL SETTING

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Desflurane (DF) has lower solubility coefficients than isoflurane (IF). Initial clinical studies have indicated its rapid equilibration in non-surgical volunteers and surgical patients at low MAC.[1,2] We determined (1) its uptake during induction of deep anesthesia by mask, (2) its equilibration between inhaled and exhaled concentrations while maintaining anesthesia at 1.25 MAC, and (3) the decay of its concentration under controlled ventilation at the end of surgery.

Twelve informed and consenting adult patients, ASA I, age 18-40 y.o., weight 76±7 (S.D.) kg, undergoing elective orthopedic surgery received DF with institutional approval. The end-tidal PCO_2, the breathing circuit O_2 and N_2O, and the inhaled and exhaled concentrations of DF were monitored at the junction of the endotracheal tube or the mask (Datex^R). Following oxygenation, anesthesia began with thiopental 5 mg/kg i.v. and N_2O 60% in O_2 (total flow 5-7 l/min). DF was added to the breathing circuit, increased or decreased as required and ventilation was spontaneous, assisted, or controlled, with a goal of establishing as rapidly as possible a deep level of anesthesia suitable for intubation of the trachea without the use of muscle relaxant. N_2O was then withdrawn and the trachea intubated. During surgery, ventilation was controlled at end-expiratory PCO_2 32-35 torr. The exhaled concentration of DF was held at 9%. The required inhaled concentration was noted. At the end of surgery, DF was discontinued and O_2 was supplied at 8 l/min. The decay of the DF concentration in this semi-closed system was recorded minute by minute for 5 minutes before attempts were made to establish spontaneous breathing and extubate the trachea. Another 12 similar patients received IF, IF 1.6% as equipotent to DF 9.06%. DF and IF were compared with t tests for $p < 0.05$.

Results: We induced anesthesia with DF and IF at similar speed, achieving 9% DF exhaled at 5.7±1.7 (S.D.) min, vs. 1.6% IF at 4.3±1.7 (S.D.) min, $p = 0.08$. At the 45th minute of exposure, DF was inhaled at 106±1% (S.D.) of the exhaled concentration, vs. IF at 147±22% (S.D.), $p < 0.01$, indicating more complete equilibration with DF. On termination of the anesthetics, the time constant of decay was 1.3 min for DF and 2.2 min for IF. The total duration of exposure was 143±57 min (DF) vs. 122±29 min (IF), $p > 0.05$.

We conclude that in this clinical setting, DF has a shorter time constant of elimination than IF and during surgery, equilibrates faster. What is delivered closely approximates what is in the patient. For induction of anesthesia under mask, laryngeal reactivity may prevent the expected rapidity from being realized.

References
1. Anesth Analg 70:S444, 1990
2. Anesth Analg 70:S378, 1990