STUDY SYNOPSIS

Study Number: GHBA-533

Title: A Phase II, Randomized, Open-Label Study to Compare the Safety and Efficacy of Sevoflurane Versus Halothane Administered with Nitrous Oxide and Oxygen in ASA Class I and II Pediatric Patients.

Investigators: 

Removed for privacy reasons


Objective: The objective of this study was to evaluate the safety and efficacy of sevoflurane in nitrous oxide/oxygen or oxygen versus halothane administered in nitrous oxide/oxygen, in children (ages 1-12 years) who require overnight hospitalization for surgery of 1-5 hours anticipated duration.

Study Design: This study was a Phase II, randomized (1:1:1), multi-center (2 sites), open-label study in which 120 pediatric patients (60 per site) received either sevoflurane in oxygen (20 patients per site) or sevoflurane in nitrous oxide/oxygen (20 patients per site) or halothane in nitrous oxide/oxygen (20 patients per site) for the induction and maintenance of anesthesia for surgery of 1-5 hours anticipated duration.

Accountability: A total of 120 patients (60/site) were enrolled in the study as follows:

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th>Sevoflurane</th>
<th>Halothane</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O₂</td>
<td>N₂O/O₂</td>
<td>N₂O/O₂</td>
<td></td>
</tr>
<tr>
<td>1-&lt;5 years</td>
<td>6</td>
<td>15</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>5-12 years</td>
<td>34</td>
<td>25</td>
<td>25</td>
<td>84</td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>24</td>
<td>25</td>
<td>77</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>16</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>120</td>
</tr>
</tbody>
</table>

All enrolled patients completed the study and were included in safety and efficacy analyses.

Study Drug Administration: Anesthesia was induced by administering incremental doses of 0.5-1.0% halothane or 1.5-2.0% sevoflurane every 3-5 breaths until an adequate depth of anesthesia was achieved to facilitate intubation. It was permissible for the inspired concentration of anesthesia to be increased more rapidly as required and/or tolerated by the patient. However the maximum inspired concentration was not to exceed 7.0% for sevoflurane and 4.5% for halothane.

Sevoflurane and halothane were administered using a vaporizer exclusively calibrated for each anesthetic agent. Sevoflurane was administered using an Ohmeda Sevotec 3 vaporizer. For each patient the same anesthetic was used for induction and maintenance of anesthesia.
anesthesia. Halothane was administered in 60-70% nitrous oxide and 30-40% oxygen (Group C). Sevoflurane was administered in either oxygen (Group A) or 60-70% nitrous oxide and 30-40% oxygen (Group B). Patients randomized to receive sevoflurane in oxygen were allowed to receive supplemental nitrogen. Anesthesia was induced through a partial rebreathing circuit without carbon dioxide absorber (Mapleson D or F) and a non-scented mask. Fresh gas flow was adjusted according to the patients' requirements in all groups. Steady state end-tidal anesthetic concentrations corresponding to 1.0 to 1.3 MAC in oxygen were to be established and maintained after induction.

Results:

The three treatment groups were statistically comparable in all demographic and baseline characteristics except in race and age. In Group A there was a higher percentage of Caucasian patients and a lower percentage of patients aged 1 to less than 5 years, compared to the other 2 groups. The most common primary diagnoses overall were within the categories "congenital abnormalities" (40/120, 33%, the most common was male hypospadias) and "nervous system and sense organs" (29/120, 24%, the most common were cholesteatoma and perforation of the tympanic membrane). The most common secondary diagnoses were within the categories "nervous system and sense organs" (33/120, 28%, the most common was otitis media) and "injury and poisoning" (29/120, 24%, the most common was unspecified adverse effect of drug, medicinal or biological substances). Primary and secondary diagnoses were comparable among treatment groups.

With regard to duration of surgery (mean ± s.e.) there was no statistically significant difference among Group A (95.2 ± 8.5 min), Group B (88.4 ± 8.5 min) and Group C (80.1 ± 8.5 min).

Efficacy:

Efficacy was measured by time to anesthesia events and evaluation of clinical anesthesia events. Time to anesthesia events (mean ± standard error) were as follows:

<table>
<thead>
<tr>
<th>Time To#</th>
<th>Group A Sevo/O₂</th>
<th>Group B Sevo/N₂O/O₂</th>
<th>Group C Halo/N₂O/O₂</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>1.7 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>A=B=C</td>
</tr>
<tr>
<td>Extubation</td>
<td>7.8 ± 0.5</td>
<td>8.3 ± 0.5</td>
<td>11.4 ± 0.5</td>
<td>A=B, A or B&lt;C*</td>
</tr>
<tr>
<td>Hip Flexion/Bucking</td>
<td>5.1 ± 0.4</td>
<td>5.9 ± 0.4</td>
<td>6.8 ± 0.4</td>
<td>A=B, B=C, A&lt;C*</td>
</tr>
<tr>
<td>Emergence</td>
<td>12.5 ± 1.5</td>
<td>15.5 ± 1.5</td>
<td>25.7 ± 1.5</td>
<td>A=B, A or B&lt;C*</td>
</tr>
<tr>
<td>Respond to Commands</td>
<td>11.5 ± 1.2</td>
<td>14.3 ± 1.2</td>
<td>24.1 ± 1.2</td>
<td>A=B, A or B&lt;C*</td>
</tr>
<tr>
<td>First Analgesia</td>
<td>85.0 ± 29.2</td>
<td>88.5 ± 30.4</td>
<td>136.2 ± 32.3</td>
<td>A=B=C</td>
</tr>
<tr>
<td>Suitable for Discharge from Recovery</td>
<td>46.2 ± 2.9</td>
<td>50.0 ± 2.9</td>
<td>60.2 ± 2.9</td>
<td>A=B, A or B&lt;C*</td>
</tr>
</tbody>
</table>

* Statistical significance at p<0.05 level.
# Time from start of anesthesia or end of anesthesia, as appropriate.

Sevo = sevoflurane, Halo = halothane.
A=B=C refers to no statistically significant differences among groups.
Sevoflurane-treated patients (Groups A and B) demonstrated a more rapid recovery than halothane-treated patients (Group C), as evidenced by statistically significant shorter times to extubation ($p<0.001$), emergence ($p<0.001$), respond to commands ($p<0.001$) and suitability for discharge from recovery ($p<0.05$).

The induction success rate was statistically significantly higher in Group B (83%) and Group C (75%) than in Group A (40%). The overall success rate was statistically significantly higher in Group B (80%) and Group C (68%) than Group A (40%). The difference was due to a higher incidence of excitement during induction in Group A. There were no significant differences in the emergence success rates between Group A (98%), Group B (98%) and Group C (93%).

There were no statistically significant differences among groups in the times at which patients achieved the best total score for any evaluations or total score in the Objective Pain-Discomfort Scale, with the exception of the verbal evaluation. More patients in Group C achieved the best score for verbal evaluation earlier than patients in Group A. There was no difference between Groups B and C, or Groups A and B, with regard to times at which patients achieved the best score for verbal evaluation.

There were few statistically significant differences among groups with regard to the Modified Aldrete Scores in recovery. However, Group A patients, had better scores for activity and consciousness than Group C patients and better total scores than Group B patients.

Sevoflurane patients (Groups A and B) achieved the best score for level of consciousness sooner than halothane patients (Group C). The best level of consciousness was reached by 100% of Group A within 40 minutes, 95% of Group B within 50 minutes, and 95% of Group C within 70 minutes of admission to the PACU.

None of the patients questioned had any intra-operative recall.

**Pharmacokinetics:**

**Plasma Inorganic Fluoride Pharmacokinetics**

Mean peak inorganic fluoride concentrations obtained in pediatric patients undergoing an average surgery of 2.1 hr duration, receiving an average dose of 2.8 "adult"-MAC-Hr, was 15.8 μM. The maximum $C_{\text{max}}$ observed was 28 μM. Peak concentrations generally occurred within 1.3 hours after the end of anesthesia. The mean half-life of inorganic fluoride was 4.04 hr. In comparison to adults in other studies undergoing surgeries of similar dose and duration, pediatric patients exhibit shorter half-lives and lower peak inorganic fluoride concentrations.
Safety:

Adverse Experience Incidence

No statistically significant difference was observed in the incidence of patients reporting one or more adverse experiences among treatment groups. The incidence rates within groups for all adverse experience reported were: 88% in Group A, 83% in Group B and 93% in Group C.

Two patients in Group A had adverse experiences reported which were considered by the investigator to be serious but not related or unlikely to be related to the study drug. One patient, (who underwent surgery for hypospadias) had atelectasis and pulmonary edema secondary to fluid overload resulting in respiratory distress which was rated as severe in intensity and was treated with medication. One patient had mild vomiting which resulted in prolonged hospitalization.

When adverse experiences with no relationship or unlikely relationship to study drug were excluded, no significant difference in the overall incidence of patients reporting one or more adverse experiences was observed between treatment groups. The incidence rates of reported study-related adverse experiences were; 80% (32/40) in Group A, 63% (24/40) in Group B and 73% (29/40) in Group C.

Patients in Group B had significantly fewer (p < 0.05) study-related adverse experiences associated with the "respiratory system" than did patients in Group C. There was no difference between Groups A and B in the incidence of "respiratory system" adverse experiences.

Patients in Group A had significantly more (p < 0.01) study-related adverse experiences associated with the "body as a whole" than did patients in Group C. These adverse experiences in Group A were reported to be "lack of drug effect". Patients in Group A also had significantly more (p < 0.001) study-related adverse experiences associated with the nervous system than either of the other groups of patients. this was due mainly to agitation.

The most commonly reported study-related adverse experience for all treatment groups was vomiting.

There were no serious study-related adverse experiences in the study. Almost all of the study-related adverse experiences were rated mild or moderate in intensity. Five patients had study-drug related adverse experiences that were rated as severe by the investigator. These included 1 incident of agitation during induction and 1 incident of lack of drug effect in Group A patients, 1 incident of difficult intubation in a Group B patient, and 1 incident each of nausea and coughing in Group C patients.

No clinically significant changes from pre-study to final examination were observed in physical examination results or in clinical laboratory values.
Conclusions:

In pediatric patients;

- sevoflurane patients had better recovery characteristics than halothane patients, as evidenced by shorter times to extubation, emergence, response to command and suitability for discharge from recovery.

- sevoflurane patients achieved higher levels of consciousness faster during recovery than halothane patients,

- sevoflurane in nitrous oxide/oxygen patients had fewer study-related adverse experiences associated with the respiratory system than halothane in nitrous oxide/oxygen,

- sevoflurane in nitrous oxide/oxygen was at least as safe and effective as halothane in nitrous oxide/oxygen, based on induction and emergence success rates, overall adverse experiences and evaluations during recovery, and

- sevoflurane in nitrous oxide/oxygen proved to be the best regimen for mask induction in children.