

Re: P890057s14a1

Memo Date: May 31, 2001

Preliminary Clinical Review:

Background:

The device is a high frequency oscillator ventilator. An earlier version of the device (3100A) has been approved for treatment of respiratory failure in infants and children. The version of the device now under review (3100B) has increased power capability and other modifications to allow treatment of adults. The intended use under review in this PMA supplement is:

The Sensormedics 3100B is indicated for use in the ventilatory support and treatment of selected patients 35 kilograms and greater with acute respiratory failure.

Technical:

In a simplified description the patient circuit of the ventilator is a high-flow CPAP system. Oscillations are superimposed on the gas in the patient circuit using an electrically-driven diaphragm, similar to an audio loudspeaker cone. The oscillation frequency and magnitude can be varied. Specifications are provided on page 9 of the PMA. The frequency can be set between 3 and 15 cycles per second. The mean airway pressure can be set from approximately 5 to 59 cmH₂O and the bias flow (continuous sweep flow through the circuit) can be set from 0 to 60 liters per minute. The maximum pressure swing is approximately 140 cmH₂O measured at the patient circuit. Corresponding pressure swings in the trachea would be in the range of 10% of this value because of attenuation in the tracheal tube (PMA page 598). The maximum tidal volume will be approximately 250 ml depending on the ventilator settings, tracheal tube size and the patient's pulmonary compliance. Typical settings are considerably less than these maximum values and are illustrated in the operators manual page 591 and page 593. The tidal volumes typically used are similar to the volume of the anatomic deadspace. Various mechanisms have been described to explain how these small volumes cause effective gas exchange (summarized in Krishnan and Brower, 2000).

The Sensormedics 3100 B includes alarms for overpressure and low pressures that will detect certain problems such as circuit disconnects, and some partial

obstructions. The air-oxygen blender, oxygen monitor, and humidifier are connected before the gas inlet to the patient circuit; these elements are conventional and are provided by the user.

The operator's manual PMA pages 497- 601, is reasonably complete. The operator's manual includes a section on clinical guidelines, (PMA pages 587-598), which appears to be based on information other than the information developed in this clinical trial.

Clinical:

Study design:

The clinical trial included adults and large child patients who have ARDS as defined by a PaO₂/FiO₂ ratio of less than 200 with a PEEP of 10 cmH₂O (PMA page 110). Patients were excluded if they had required an FIO₂ of greater than 0.8 for more than 48 hours. Patients were excluded also if they had a large air leak, shock, severe obstructive lung disease or a terminal prognosis. These entry and exclusion criteria seem reasonable.

The primary outcome measure was the combined variable of survival without chronic lung disease. Chronic lung disease was defined as "requiring respiratory support (O₂, CPAP or mechanical ventilation) 30 day after entry in the study" (PMA page 115).

The hypothesis for overall safety and effectiveness was that the rate of survival without chronic lung disease at 30 days was not more than 0.1 worse for HFOV, relative to conventional ventilation.

The trial was designed to randomize a total of 148 patients to either conventional ventilation or HFOV ventilation (PMA page 117). The sample size was based on a treatment effect similar to the treatment effect in a small randomized trial in children. The entry was block randomized assign to each group similar numbers of patients who were thought to have a poor prognosis (oxygenation index greater than 40)(PMA page 114).

The conventional ventilation treatment consisted of pressure controlled (pressure

limited) ventilation with a tidal volume of 6 to 10 ml/kg, PEEP at least 10 cmH₂O as high as 18 if needed for oxygenation an I/E ratio of initially 1:2, but as high as 2:1 if needed for oxygenation. PEEP and I/E ratios were maintained until the FIO₂ could be weaned to between 60 to 40%. Management of pCO₂ was not closely controlled in this protocol "The respiratory goal is to maintain the pH greater than 7.15 while minimizing peak pressures and treating metabolic acidosis. There is no pH target but a range of 40 to 70 torr is expected" (PMA page 113; see also PMA page 136).

HFOV management included an initial rate of 5 Hz, and a mean airway pressure 5 cm higher than used for the patient's pre-study mean airway pressure with conventional ventilation. Oscillator power was set by reference to the subjective adequacy of chest excursion, and blood gas results. Settings were adjusted to meet similar criteria for pCO₂, pO₂. When defined criteria were met for adequate improvement (including a mean airway pressure of less than 30), treatment was returned to conventional ventilation.

If patients could not be adequately treated using HFOV and met defined criteria the patients could be treated using conventional ventilation (PMA page 113 and 123). This aspect of the protocol was intended to allow conventional treatment if it appeared that the patient might benefit from conventional treatment, so that participation in the trial would not subject the patient to avoidable risks related to possible inadequacies of the HFOV method. However, patients who were not doing well with conventional ventilation were not to be changed to HFOV; since use of conventional ventilation was the best known practice, there seemed to be no ethical need to make an alternative available.

Actual enrollment was 75 HFOV treatment and 73 conventional treatment; the total was 148 patients, as planned (PMA page 21). Changes to the protocol during the trial (PMA pages 140 and 141) were minor and were unlikely to affect the interpretation of the results.

Results:

Patients in the two groups were similar at study entry (PMA page 21, 22). Analysis of outcomes was by intention to treat (page 115). For the primary outcome variable (death, mechanical ventilation, CPAP, or O₂ or at 30 days)

HFOV is worse (79%) vs Conventional (74%).

However, death was less frequent in the HFOV group - see following discussion.

The manufacturer has not presented much of the physiologic data acquired during treatment. The manufacturer did however identify differences in the physiologic variables during the treatment course: the mean airway pressure was, by design, higher in the HFOV group. The PaO₂/FIO₂ ratio was higher for in the HFOV group, as was the pH (page 25).

There were a considerable number of patients who were exited from the conventional arm of the study for "withdrawal of consent" (11 % page 22). Some of these were because the investigator undertook "rescue" treatment with HFOV. Most of these "rescue" patients died. As far as I can tell from the clinical summaries provided, these "crossovers" outside the clinical protocol are unlikely to have adversely or favorably affect the outcomes. The "intention to treat", statistical analysis also minimizes the effect of these protocol violations.

Discussion:

The failure, relative to the prospective hypothesis, may not preclude HFOV as reasonably safe and effective in adults. The hypothesis is based on the trials in infants and young children; at the time of the trial design, oxygen requirements at 30 days was considered to be a very important outcome for infants. This criteria was applied to adults, presumably in an attempt to reduce the required number of patients to be enrolled.

The death rate for patients in the HFOV group at 30 days was 37% as compared to 52% in the conventional ventilation group; Observed mortality at 6 months was also better, 47% HFOV vs 59% conventional. However, the observed mortality difference was not statistically significant.

The manufacturer constructed a post-hoc combined variable (death or mechanical ventilation at 30 days) which would have been statistically significant if it were a prospective hypothesis (page 32).

With respect to these matters FDA should ask the panel if the HFOV device can be found safe and effective on the basis of these data, even though the prospectively determined criteria for success has not been met.

The other main question relates to the control group outcomes, which showed a high mortality. If the control group did not meet current expectations for conventional ventilation, comparison of HFOV outcomes to this control group might not be informative. This question also would be addressed to the panel. The manufacturer notes, page 32, that the mortality in the control group is not related to the tidal volumes computed as ml/kg ideal body weight. However, the range of tidal volumes is above the low tidal volumes use in the ARDS network trial so the manufacturer's calculations page 32 does not explain the mortality difference.

Minimal information was provided on the physiologic variables observed during the course of the study. Data on these variables would aid in understanding aspects of the study results that are not apparent from the statistical outcomes alone. Summary information will be requested from the manufacturer.