



BioPharmica Limited

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Encouraging Trial Results for Monitoring Brain Function

An Australian invention designed to decrease the likelihood of patients remembering parts of their surgery and improve their recovery from anaesthesia has just completed a further stage of clinical trials at Royal Melbourne Hospital. The positive results following the completion of this trial are a significant development for BioPharmica's investee Cortical Dynamics.

The Brain Anaesthesia Response Index (BAR Index) has been developed by Cortical Dynamics to quantify changes in the brain's electrical activity that occur in response to anaesthesia.

The purpose of this study was to establish whether a physiologically based method of analysing the brain's electrical activity (the electroencephalogram or EEG) developed by Associate Professor David Liley at Swinburne University of Technology was better able to monitor the depth of anaesthesia in the presence of opioid drugs when compared with the current industry standard, the Bispectral Index (BIS) monitor.

The trial was conducted by Associate Professor Kate Leslie, Head of Research, Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, and involved 45 elective surgery patients randomised to receive remifentanyl, a commonly used intraoperative opioid, at three different levels whilst anaesthesia was induced using propofol.

During this anaesthetic induction the EEG was monitored using electrodes placed on the forehead and connected to a BIS monitor. BIS index values and raw EEG were recorded and downloaded for later analysis, along with periodic assessments of the patient's level of consciousness. Each patient's study concluded when they were judged clinically to be fully unconscious. This required the absence of an eyelash reflex and being unresponsive to both verbal command and stimulation of the ulnar nerve.

The raw EEG was analysed offline using Cortical Dynamics proprietary algorithm to produce two theoretically derived measures of brain function known as the cortical state (currently referred to as the BAR Index) and the cortical input. The cortical state, cortical input and BIS Index corresponding to the recorded levels of consciousness and loss of responses were extracted, with some data excluded due to artefact. The results were initially analysed blind to the remifentanyl randomisation and then with respect to the three treatment groups.

Preliminary cortical state (BAR index) and cortical input results show that this physiologically based algorithm is capable of detecting drug induced changes in human EEG, with both measures showing clear trends with decreasing levels of consciousness.

Both the BAR and BIS indices were found to decrease with a reduction in the assessed level of consciousness. The spread of BIS values at low levels of awareness was significantly greater than that of the corresponding BAR values. Further initial analysis suggests that for a given clinically assessed level of consciousness a systematic variation in the recorded BIS value occurs for a given level of remifentanyl. In notable contrast the BAR index produced similar results across all target remifentanyl brain concentrations for a given level of consciousness, implying that the BAR index is potentially a more robust measure of functional brain state than the BIS.

These preliminary outcomes imply that the BAR index is more reliable in monitoring depth of anaesthesia in the presence of opioids.

EEG/EMG/Brain Function Monitoring

About the Current Clinical Trial:

The purpose of this study was to establish whether a physiologically based method of analysing the brain's electrical activity (the electroencephalogram or EEG) developed by Associate Professor David Liley at Swinburne University of Technology, was better able to monitor depth of anaesthesia in the presence of opioid drugs when compared with the current industry standard, the Bispectral Index (BIS) monitor.

The study involved 45 elective surgery patients randomised to receive remifentanyl, a commonly used intraoperative opioid, at three target brain concentrations of either 0, 2 or 4 ng/ml whilst anaesthesia was induced using propofol. Four minutes following the beginning of the randomised target remifentanyl infusion a propofol infusion was started at a brain concentration of 1.5µg/ml, and increased by 0.5µg/ml every four minutes until patients were fully unconscious. This meant that they had no eyelash reflex and had no response to either verbal command or electrical stimulation of the ulnar nerve. Each patient's study concluded when all responses were lost.

During this anaesthetic induction the EEG was monitored using electrodes placed on the forehead and connected to a BIS monitor. BIS index values and raw EEG were recorded and downloaded for later analysis. Haemodynamic measurements and event markers corresponding to the assessed levels of consciousness were also recorded.

Electroencephalographic Equipment

EEG equipment measures the weak electrical signals produced by the brain by means of one or more electrodes placed on the scalp. The recorded signal, while complex, contains a great deal of information that is useful diagnostically. Following amplification the recorded EEG can be analysed using a range of sophisticated on-line processing algorithms or stored for later offline analysis.

EEG recording and on-line processing equipment are being increasingly used during surgical interventions to monitor the patient condition. By recording the patient's brain activity this equipment provides valuable objective clinical measures regarding the patient's state of health during and after a surgery. Continuous EEG monitoring during surgery has been shown to significantly reduce the incidence of patient awareness and recall of the surgical procedure, to reduce post-operative recovery times and to reduce surgical costs. An EEG is widely considered as superior methodology for monitoring anaesthetic depth during surgery and other clinical interventions when compared to a range of other clinical monitoring approaches that include electrocardiography and oxygen saturation level monitoring.

EEG Processor Market Growing Sharply

The market for EEG processors is projected to grow at a brisk pace in future, owing to a rapid increase in the number of surgical procedures being performed world over. Currently, more than 40 million surgical interventions are carried out each year in the United States alone. The number of such incidences is poised to multiply swiftly in future with a rapid increase in the aging population.

Market

Worldwide market for EEG/EMG/Brain function monitoring totalled US\$690 million in 2005, and is independently estimated at US\$749 million for 2006. The market is further projected to grow at a compounded annual growth rate of around 7.7% to reach around US\$1 billion by 2010. In volume terms, the worldwide market is estimated to gross unit sales of 34,208 units for 2006. The market is anticipated to witness an annual growth of 8.9% through 2001-2010, to sales of 47,487 units by 2010.

Europe represents the largest market for EEG/EMG/Brain function monitoring worldwide, however, the US is the single largest global market with an estimated share of 37.3% for the same year.

Electroencephalograph (EEG) Equipment is the largest segment of the worldwide EEG/EMG/Brain function monitoring market. The segment is estimated to record sales of 28,999 units for 2006, valued at about US\$656 million. By the year 2010, the segment is expected to record sales of 42,180 units worth US\$908 million. EEG equipment is forecast to hold dominant position in the global EEG/EMG/Brain function monitoring, with its market share soaring to reach 91% by the end of 2010 in value terms.

Background

The BAR Index is a measure derived from the analysis of the EEG to quantitatively characterise the functional state of the brain. It is based on a detailed understanding of how the millions of neurons in the brain's cortex coordinate their activity to produce the EEG.

At present the monitoring of anaesthesia in the presence of opioids is unreliable using existing approaches and thus new methods are required in order to ensure optimal standards of clinical care. The current market leader is used in approximately 70% of hospitals in the USA, for clinical monitoring during anaesthesia containing an opioid. The competitor's market capitalisation in 2006 was approximately USD 400M.

When patients have a general anaesthetic, an anaesthetist may administer a combination of drugs through the intravenous drip in the patient's arm. These could include an anaesthetic drug to put the patient to sleep and a morphine-like drug as a pain-killer.

Once the patient is asleep, the anaesthetist keeps the patient in this state by continued administration of an anaesthetic drug through the drip or by giving the patient an anaesthetic gas to breathe. Using these combinations of drugs, the patient should be completely anaesthetised and unresponsive to any pain.

Anaesthetists currently quantify the effects of these anaesthetic drugs on the EEG using a widely available, market leading competing device. The market leader is used on many patients having general anaesthesia at hospitals. The competing monitor records EEG through a sticky sensor attached to the forehead. The monitor then produces a single number between 0 and 100 that the anaesthetist can use to adjust the depth of anaesthesia.

Studies have shown that the use of a monitor decreases the likelihood of patients remembering parts of their surgery and also improves their recovery from anaesthesia.

However, there is evidence to suggest that some monitors may not track the effects of a number of important anaesthetic agents. This may mean that the leading offering is less accurate when these agents are used. In particular, morphine-like drugs may interfere with the ability of the leading monitor to measure the depth of anaesthesia accurately by indicating a patient is less asleep than they really are. This means that patients may be receiving more anaesthetic than necessary.

The BAR Index method of analysing the EEG may overcome this limitation and provide a more accurate index of depth of anaesthesia in the presence of morphine-like drugs. The EEG information is obtained the same way, with a sticky sensor on the patient's forehead, but the monitor uses a physiologically more specific method in its analysis of the EEG.

Upon the completion of the review of the clinical trial involving opioids, BioPharmica and Cortical will be in a strong position to move towards commercialisation on development related to monitoring depth of anaesthesia, as well as making a case for development of other areas involving drugs, brain state and function.

The BAR Index has performed well in previous studies during midazolam and sevoflurane-nitrous oxide anaesthesia providing the first indication that the BAR Index is superior in a number of aspects to current approaches to measure brain function. The BAR Index (cortical state)—how responsive the brain is to input - and the associated measure of cortical input—the magnitude of input to the brain - provide physiologically more specific information regarding the effects of anaesthetics on brain activity and behaviour.

The BAR Index and the associated measure of cortical input have additional potential applications for the Alzheimer's and sedation markets. BioPharmica and partner Cortical Dynamics are working to develop the BAR Index as a monitoring tool in a number of neuro-diagnostic settings that include detecting the early onset of

degenerative diseases like Alzheimer's or Parkinson's as well as being used in drug discovery and evaluation associated with these conditions.

About BioPharmica Limited

BioPharmica [ASX: BPH] is an Australian Stock Exchange listed company developing biomedical research with academic and hospital institutes. The Company provides early stage funding for a direct collaboration, a spin out company or to secure a license. BioPharmica provides assistance with product development, funding and commercial strategies, whilst the institutional partner provides a majority of the infrastructure and research expertise.

Yours faithfully

A handwritten signature in black ink, appearing to read 'D. Breeze', with a stylized flourish at the end.

David Breeze
Managing Director

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