◇ This Month in

# ANESTHESIOLOGY

## ■ Sensitivity of Processed Electroencephalogram Parameters to Opioid–Sedative Anesthesia. Manyam *et al.* (page 472)

Studies have shown that opioids reduce the clinical requirements of sedatives needed to provide adequate anesthesia. Manyam *et al.* designed a study to characterize how the addition of opioids to sedative drugs might influence processed electroencephalogram parameters, such as the Bispectral Index and the Auditory Evoked Potential Index.

The team recruited 24 healthy adult volunteers who received remifentanil and sevoflurane at various concentration pairs. During pseudo steady-state levels, the Bispectral Index and Auditory Evoked Potential Index were measured. The Observer's Assessment of Alertness/Sedation score was also measured by a single observer to control interrate variability. Adequate anesthesia was defined by the presence of all of the following: (1) a modified Observer's Assessment of Alertness/Sedation score of 1 or less; (2) no movement in response to a 5-s, 50-mA electric titanic stimulation; and (3) no change in heart rate ($>$ 20%) in response to the electrical stimulation. Pharmacodynamic response surface interaction models were built using pooled data for each pharmacodynamic endpoint.

The response surface models adequately characterized all pharmacodynamic endpoints. The authors validated that clinical sedation increased significantly by adding small to moderate doses of remifentanil to the sevoflurane anesthetic. However, the Bispectral Index and Auditory Evoked Potential Index were insensitive to this change in clinical state. Based on this result, it is possible that when using remifentanil "heavy" combinations (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) during sevoflurane–remifentanil anesthesia, targeting a Bispectral Index less than 60 or an Auditory Evoked Potential Index less than 30 could result in an excessively deep anesthetic state.

## ■ Transcutaneous Measurement of Fluorescence Dilution Signals: Useful for Gauging Cardiac Output? Maarek *et al.* (page 491)

In this issue, Maarek *et al.* report on a new indicator dilution method for assessing cardiac output and circulating blood volume. Previously, the team had validated the technique, based on the transcutaneous measurement of circulating indocyanine green fluorescence with an optical probe on the skin surface, in animals. For this phase I study, they recorded fluorescence dilution traces transcutaneously in six healthy human volunteers in resting conditions after rapid intravenous injection of 1 mg indocyanine green.

The team tested three placements of the optical probe: at the nose ala, the ear lobe, and the temple area. Recordings obtained from the nose ala and the ear lobe were twice as intense as those from the temple area. The fluorescence intensity at each site was related in a linear fashion to the local laser Doppler perfusion index. Signal-derived cardiac output and blood volume values were in the normal range. The authors suggest that their results offer an opportunity to compare this new technique with the traditional "gold standard" thermodilution method. If the fluorescence dilution technique can be successfully transitioned to a practical clinical device, it would offer simultaneous monitoring of cardiac output and circulating blood volume with minimal invasiveness.

## ■ Measuring Cerebral Blood Flow Responses to Pain Stimuli during Remifentanil Anesthesia. Wagner *et al.* (page 548)

Seven right-handed male volunteers participated in a study designed by Wagner *et al.* to measure response to experimental pain stimuli during remifentanil analgesia. Each subject underwent a total of 18 positron emission tomography scan measurements using $^{15}$O-water. Nine of the positron emission tomography scans were conducted during painful heat stimulation and nine during nonpainful heat stimulation, while subjects received, in randomized order, three different drug infusion regimes: saline, 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ("low dose") remifentanil, and 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ("moderate dose") remifentanil. After each stimulation and completion of the associated positron emission tomography scan, subjects were asked to rate their experience of pain on a visual analogue scale of 0 to 100 (with 100 connoting unbearable pain).

All volunteers rated the nonpainful heat stimulation during the control condition (saline infusion) as 0 on the visual analogue scale. The painful heat stimulus was rated as 68 $\pm$ SEM 5. Positron emission tomography scans revealed that the painful heat stimulus during control conditions (saline infusion) induced increased cere-

bral blood flow in the thalamus, insula, anterior cingulate cortex, S2, and frontal cortex areas. Remifentanil administration at both the low and moderate doses suppressed all detectable activations in the thalamus, insula, and anterior and posterior cingulate cortex and reduced the visual analogue scale pain rating to heat. However, remifentanil increased activation in the cingulofrontal cortex (including the perigenual anterior cingulate cortex) and the periaqueductal gray, as evidenced by increased regional cerebral blood flow. The authors conclude that these results provide evidence that opioidergic analgesia is mediated by activation of descending antinociceptive pathways.

## ■ Antinociceptive and Hyperalgesic Properties of Methadone Examined in Rats. Holtman and Wala (page 563)

To better understand the mechanisms of opioid-induced antinociception as well as opioid-induced hyperalgesia, Holtman and Wala designed a series of experiments in the rat model. Male and female rats were injected with *d,l*-methadone hydrochloride, *d*-methadone hydrochloride, *l*-methadone hydrochloride, and morphine sulfate, given as single doses or in combination. Tail flick responses to varying intensities of radiant heat were then measured to assess the drugs' antinociceptive or pronociceptive, hyperalgesic effects.

The investigators were able to demonstrate that *d,l*-methadone produced dose-related antinociceptive and hyperalgesic effects. Whereas *l*-methadone produced a greater degree of hyperalgesia, *d*-methadone produced no hyperalgesia. Apparently due to its antagonistic activity at the *N*-methyl-D-aspartate receptor, *d*-methadone reduced the pronociceptive effects of *l*-methadone, blocked morphine hyperalgesia, enhanced antinociception, and abolished sex-related differences in opioid analgesia. Because opioids are being used more frequently for management of pain, including chronic nonmalignant pain, it is increasingly important to understand the mechanisms by which opioids can increase pain sensitivity. Methadone may represent a better choice for long-term opioid treatment.

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