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ADDENDUM

Two recently published papers describing assessment and management of perioperative risk from coronary artery disease in patients undergoing noncardiac surgery were published by Paida and Detsky of the American College of Physicians.[14,15] These are important "position papers" describing clinical guidelines for this patient population. Based on the findings of Mangano *et al.*,[16] the American College of Physicians recommends the perioperative use of atenolol in patients with coronary artery disease or risk factors for coronary artery disease as originally defined by Mangano *et al.*,[16] unless significant contraindications to the use of β blockers are present. — DCW

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Anesthetic Drug Interactions

An Insight into General Anesthesia—Its Mechanism and Dosing Strategies

IN this issue of ANESTHESIOLOGY, Katoh and Ikeda[1] present a study describing the interaction of sevoflurane and fentanyl to achieve loss of consciousness and ablation of somatic responses to skin incision. This is one of a few articles investigating the concentration response of the interaction between opiates and volatile anesthetics[2] or propofol.[3,4] What can we learn from these drug interaction studies?

The interaction between fentanyl, sufentanil, alfentanil, and remifentanil (analgesics) with either isoflurane, desflurane, sevoflurane, or propofol (hypnotics) for the prevention of purposeful movement at skin incision is remarkably similar. There is an initial steep decrease (40–50%) in the MAC/Cp_{50} with low (analgesic concentrations) of an opiate. Thereafter, the decrease in MAC/Cp_{50} with increasing opiate concentrations tends to flatten until a ceiling effect is observed. The interaction for loss of consciousness is different to that for skin incision, with only a 10–20% decrease in the MAC/Cp_{50} awake value when combined with an analgesic concentration of an opiate. The different interaction for these two endpoints is strong evidence that loss of consciousness and response to skin incision are not a single continuum of increasing "anesthetic depth" but

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Key words: Alfentanil; fentanyl; isoflurane; mechanisms of volatile anesthetics; opiates; remifentanil; sevoflurane; sufentanil.

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rather are two separate phenomena. To prevent a response at skin incision, the minimal concentration of the hypnotic when the plateau effect is reached, occurs at a volatile or propofol concentration equal to their MAC awake value. Propofol[5] or isoflurane,[6] when administered alone, requires concentrations far in excess of their MAC/Cp_{50} (skin incision) to prevent an autonomic response to a noxious stimulus. The addition of analgesic concentration of fentanyl to isoflurane or propofol ablates these autonomic responses and reduces the concentration of propofol needed for anesthesia.[5] It also has been shown that the prevention of movement by volatile anesthetics is a spinal action, and the MAC of isoflurane in an isolated brain preparation is double the MAC concentration in the intact animal (*i.e.,* brain and spinal cord).[7] If we combine these observations, it is possible to propose the following hypothesis of general anesthesia. General anesthesia is a process requiring a state of unconsciousness of the brain (produced primarily by the volatile anesthetic or propofol). If only unconsciousness is achieved, a noxious stimulus will cause arousal/awakening as a result of the intensity of the stimulus. To prevent arousal, the noxious stimulus needs to be inhibited from reaching higher centers. This is achieved by the action of the opiate at opiate receptors within the spinal cord (or, local anesthetics on peripheral nerves, or volatile anesthetics on the spinal cord when administered at concentrations equal to their MAC). Thus, it is proposed that general anesthesia consists of producing both loss of consciouness through the action of the drugs we administer on the brain, and, the inhibition of noxious stimuli reaching the brain through the action of the drugs we administer on the spinal cord.

Not only do these drug interactions provide an insight into the mechanism of general anesthesia, they also provide practical guidelines for optimal drug dosing during anesthesia. To achieve the objectives of a stable intraoperative course and rapid recovery to consciousness with adequate spontaneous ventilation, based on the interaction studies described previously, the hypnotic (propofol - volatile anesthetic) should be administered to concentrations, which at a minimum, equal the concentration producing loss of consciousness. To inhibit somatic or autonomic responses during the noxious stimuli of surgery, an opiate should be added, thereby lowering the concentration of the hypnotic. Although further increases in opiate concentration may enhance the control of somatic and autonomic response, a ceiling effect on the reduction of the hypnotic is reached. Also, as the opioid increases beyond that associated with adequate spontaneous ventilation, recovery is delayed. Thus, as explained by Katoh and Ikeda,[1] for the combination of fentanyl (and probably sufentanil and alfentanil) with sevoflurane (or other volatile anesthetics), the ideal combination (for optimal intraoperative anesthetic conditions and the most rapid recovery) is to administer the hypnotic at a concentration equal to its MAC_{awake} value and the opiate at an equivalent of 2 ng/ml of fentanyl. If this combination provides inadequate anesthesia in a given patient, either hypnotic or opiate concentration or both should be increased, but with the understanding that if the opiate is increased beyond the threshold for respiratory depression, recovery will be prolonged. Remifentanil, because of its extremely short context sensitive decrement time for even an 80% decrease, is an exception because it can be administered intraoperatively at concentrations 2 - 5 times that producing respiratory depression without delaying recovery.

Drug interaction studies as presented by Katoh and Ikeda have thus provided clinicians guidelines for optimal dosing during general anesthesia and potential insights into the mechanisms of general anesthesia.

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