Catecholamine Surge in Opioid-addicted Patients Undergoing Detoxification under General Anesthesia

To the Editor—We read with interest the article by Kienbaum et al.\(^1\) regarding the hypothesis that \(\mu\)-opioid receptor blockade by naloxone induces cardiovascular stimulation mediated by the sympathoadrenal system. This study confirms that clinicians who have detoxified heroin addicts for 20 yr have known, \textit{i.e.}, clonidine, an \(\alpha_2\)-agonist, is essential to avoiding hyperadrenergic crisis and pulmonary edema. Riordan and Kleber\(^2\) in 1980 first demonstrated that utility of clonidine in controlling the hemodynamic changes seen in the withdrawal syndrome. Naloxone has also been previously associated with pulmonary edema\(^3,4\) presently because of this sympathoadrenal surge.

It is very dramatic to document the extent of catecholamine secretion. This has been elegantly demonstrated in the study by Kienbaum et al.\(^1\) We also agree with the authors that because of this cardiovascular stimulation secondary to a surge in sympathoadrenal system, the procedure of acute opioid detoxification should be done by trained anesthesiologists in an intensive care setting. However, in order to make this procedure safe, it is imperative to use an \(\alpha_2\)-agonist, such as clonidine before \(\mu\)-opioid receptor blockade, even if the patient is under general anesthesia.

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\textit{In Reply.—} We appreciate the interest of Drs. Gevirtz, Subbedar, and Choi in our recent publication.\(^1\)

On the clinical side, consistent with our experience, clonidine reduces withdrawal symptoms during detoxification. Accordingly, it has been favourably administered during detoxification from opioids in \textit{awake} addicts for more than 20 yr.\(^2\) However, it has been claimed by psychiatrists that cardiovascular responses and withdrawal symptoms to detoxification from opioids both can be minimized by administration of large amounts of \(\mu\)-opioid receptor antagonists alone when administered during sedation or general anesthesia.\(^3,4\) In our study, we had to reject this hypothesis by demonstrating extensive increases in catecholamine concentrations in plasma and cardiovascular stimulation associated with \(\mu\)-opioid receptor blockade by naloxone during general anesthesia. Furthermore, the need for additional drugs such as \(\alpha_2\)-adrenergic agonists, \textit{e.g.}, clonidine, was described.\(^1\)

We pointed attention to the fact that (1) marked sympathoadrenal activation and cardiovascular stimulation may be observed during detoxification from opioids by administration of \(\mu\)-opioid receptor antagonists alone, despite deep general anesthesia, and (2) the need for trained anesthesiologists/intensivists in performing this treatment, as also proposed by Dr. Gevirtz and coworkers. Whether and why clonidine helps in minimizing cardiovascular and sympathoadrenal stimulation during detoxification even during conditions of general anesthesia is the subject of ongoing investigation.

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Possible Mechanism(s) of Opioid-induced Coughing

To the Editor.—Doctors Bennett and Yemen recently exchanged letters addressing the issue of opioid-induced coughing. Doctor Yemen, in particular, expressed his curiosity as to the mechanism whereby opioids, known more as cough suppressants, could stimulate coughing. Dr. Yemen speculated that opioid-induced coughing might be related to opioid actions recently documented to occur at the level of the vocal cords. I would like to bring to attention information not mentioned in their letters that is relevant to the question asked.

It is known that the antitussive actions of opioids are central in origin. However, fentanyl, sufentanil and alfentanil, elicit a brief cough in up to 50% of patients when injected by intravenous bolus. Opioid-induced coughing is elicited within seconds of drug injection. A pulmonary chemoreflex, mediated by C-fiber receptors (also known as J receptors), is thought to underlie this phenomenon. Opioid receptors have been shown in smooth muscles of the trachea and bronchi and in alveolar walls, but not in the small airways. Alveolar wall opioid receptors may be associated with J receptors.

The cough reflex after opioid injection is not likely to be vagally mediated because atropine pretreatment does not affect it. Opioids may also elicit cough by stimulating irritant receptors in the central smooth muscle. Interestingly, pretreatment with inhaled β-adrenergic agonists significantly reduces the incidence of cough associated with intravenous opioid injection.

In my experience, any opioid of the fentanyl series can elicit this usually brief cough response. Opioid-induced coughing is frequently more noticeable in patients who smoke. I have not witnessed an opioid-induced cough reflex that was not self-limited. As an aside, the elicitation of the cough reflex after opioid administration seems to be temporally related to circulation time and may serve as a clinical clue to “vein-to-brain” time, or cardiac output.

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