What’s New in Critical Illness and Injury Science? The Quest for Effective and Safe Co-induction Agents in Spontaneously Breathing Patients Undergoing General Anesthesia

In this issue, Dwivedi et al. describe their use of the laryngeal mask airway (LMA) in spontaneously breathing patients undergoing general anesthesia for surgery. They supplemented propofol administration with either fentanyl or butorphanol as co-induction agents to minimize apnea caused by propofol. In their comparison of fentanyl versus butorphanol, they reported that the respiratory and recovery profile of the butorphanol group was a superior alternative to the fentanyl group, although the butorphanol group seemed to be sedated for a longer period of time in the postanesthesia recovery unit (PACU).

A view of the Dwivedi et al. findings in a historical context is of interest. Butorphanol was developed by Bristol-Myers as a synthetically derived morphinan-type mixed agonist–antagonist opioid analgesic. It was first approved by the Food and Drug Administration in 1978 (brand name Stadol), but now it is only available generically as a solution in two dosage forms for intravenous or intramuscular injection and intranasal spray. Butorphanol is a κ-receptor agonist with partial agonist–antagonist μ-receptor activity providing analgesia and sedation with less respiratory depression and a lower risk for physical dependence than classic, morphine-like opioids. This drug can commonly cause nausea and vomiting, as well as dysphoria (through the κ-receptor). The most common use of butorphanol is for migraine (nasal spray). It has also been used for labor, as well as in general anesthesia. The first study comparing butorphanol with other narcotics occurred in 1978. It was at this time that the antagonistic properties of butorphanol, demonstrating respiratory depressant effects in patients under general anesthesia, were confirmed in a clinical comparison. Thirty-eight years later, Chari and Ghai demonstrated the use of butorphanol, and thiopentone was superior to fentanyl and thiopentone in LMA insertion in relation to jaw relaxation, ease of insertion, swallowing, coughing/gagging, limbs/head movement, and laryngospasm. Also, Cheng et al. demonstrated that a fentanyl-induced cough occurring during induction of general anesthesia can be suppressed by butorphanol pretreatment. Previous to these findings of Philip et al. enrolled sixty healthy women in a randomized, double-blind trial where each patient received equianalgesic doses of fentanyl or butorphanol before induction of anesthesia. While postoperatively there were no differences in analgesic needs or discharge times, butorphanol had longer sedation times, but patients reported a more satisfying anesthetic experience. These findings were also supported by Pandit et al. Pandit et al. also reported interesting results when checking vital signs in the operative period during laparoscopy and using higher doses of fentanyl and butorphanol (2 μg/kg and 40 μg/kg, respectively). Here, they found that butorphanol caused smaller increases in heart rate and systolic blood pressure 120 s after intubation. In addition, Sklar et al. reported that butorphanol, with a sedative (diazepam), had a significant thiopental-sparing effect, although the butorphanol/diazepam group had a longer PACU stay due to sedation. In support of these positive findings on behalf of butorphanol, Bowdle et al. determined that butorphanol improved the CO2 response and ventilation after fentanyl anesthesia as was evident by the onset of spontaneous breathing in apneic patients, increased respirations, tidal volume, and minute ventilation.

All in all, butorphanol presents itself as a reasonable alternative to other opioid agents for the induction of anesthesia in the scenario where it is desirable to keep the patient spontaneously breathing. If PACU times are not unreasonably extended, and complications are not more prevalent, nor is it an increased cost associated with its use (larger trials with a more encompassing collection of data would be necessary to determine such findings), then the common use intravenous butorphanol in general anesthesia may become a reality.
this successful clinical effort. However, the authors could have made their case stronger and given the readers a better understanding of the study if they had reported: (1) the time period of the study, (2) the surgical procedures for which anesthesia was provided, (3) how the authors arrived at the number of study subjects (power analysis or was this an observational pilot study), (4) whether the patients were consecutively enrolled, (5) postoperative opioid administration, and (6) anesthetic complications. The well-known risks of prolonged apnea make analgesics like butorphanol attractive alternatives to pure opioid agonists. However, the complex nature by which mixed opioid analgesics exert their pharmacological effects requires appropriate patient selection. When administered by itself, 2 mg of butorphanol results in similar respiratory depressive and sedative effects to that of morphine 10 mg.\(^\text{[13]}\) While higher doses of butorphanol are associated with longer durations of central nervous system impairment, a “ceiling effect” is observed with respect to the degree of respiratory depression as well as analgesia which may pose a challenge to maintaining adequate intraoperative pain control if used for induction or as an adjunct to balanced anesthesia. Full agonists and mixed agonists–antagonists can have additive pharmacodynamic effects in combination, but butorphanol may also reduce the efficacy of other opioids and has been shown to precipitate symptoms of withdrawal similar to naloxone in chronic opioid users.\(^\text{[14–16]}\) For this reason, butorphanol labeling carries warnings which recommend against its use in those dependent on narcotics. Butorphanol requires judicious use, accounting for specific patient characteristics and history, type of surgical procedure, and concomitant agents used. It would be interesting to evaluate the demographics of the patients included and the surgeries described by Dwivedi et al. to learn more about butorphanol’s place in therapy since it is otherwise difficult to make broad conclusions.

Nonetheless, the anesthesiology community is still in search of the “perfect” opioid. All opioids have undesirable effects, and our job, as anesthesiologists, is to mitigate the harm; these unwanted effects could have on our patients by choosing the right drug for the right patient and the right surgery and that was the intended endeavor of this study’s authors. Anesthesiologists, by and large, train with only a select group of agents and most of us are largely unfamiliar with many of the choices that may be appropriate for a given task. Many anesthesiologists in the United States have rarely seen (if ever) a vial of butorphanol, let alone used it during an anesthetic. This may well be a shortcoming in the way we train anesthesiology residents, and this shortcoming may need to be addressed. Our specialty needs to be adaptable as volatility in the availability and ever increasing cost of drugs continues. This is especially true of opioid agents given the current worldwide public health crisis regarding opioids.\(^\text{[17–19]}\) We should be ready to use what is available to us in this era of drug shortages, decreasing reimbursements, and/or new regulations.

We encourage our colleagues to perform further multicenter studies into the use of butorphanol, and other opioid options as co-induction agents, to better determine the safest, most economical, and effective approaches to the anesthetic care of the surgical patient.

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Stroud, et al.: The quest for effective and safe co-induction agents

2018 Feb 09].

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