Opioids as co-induction agents - the pros and cons

The term co-induction refers to simultaneous administration of two or more drugs to facilitate the induction of general anesthesia. Essentially, this concept originates from prudent use of different agents to achieve all components of anesthesia while minimizing adverse effects of any specific agent used singly to achieve the same, thus patching up the shortcomings of one agent with the other. The aim of co-induction is to achieve desired responses with the use of decreased dose of a primary agent while improving the quality of anesthesia with stable hemodynamics. Optimization of the time-course of drugs effects and a favorable ratio of desirable effects to adverse effects can be achieved with co-induction. This also reduces the consumption of expensive inducing agents such as etomidate and propofol, thereby reducing total cost.

The pharmacodynamics and pharmacokinetics, drug interaction at receptor level, the variation in pharmaceutical formulations, the adverse effect profiles, and economic constraints are to be considered.

A drug interaction may lead to antagonism, potentiation, summation, or synergism. Antagonism refers to the attenuation or prevention of pharmacological effects of agonists by other drugs. Potentiation refers to the enhancement of the effect of one drug by the other when the two drugs possess dissimilar pharmacological properties such as digoxin (inotropic) and thiazide (diuretic). When the action of one drug is facilitated or increased with the use of other agent, the interaction is called 'synergism' which is most likely to happen when drugs of different classes or even those with slightly different mechanisms are used to produce the same effects. Synergism refers to the supra-additive effects of two drugs with similar pharmacological activities and closely related sites of action, which produce an effect in combination which is greater than the anticipated summation.

Drug interactions have both pharmacodynamic and pharmacokinetic basis and may vary according to the particular combination used, the dose ranges of component drugs being used, and the specific clinical effect being measured. For example, midazolam having significant hypnotic properties shows significant synergism with propofol or thiopental when used to induce hypnosis. In contrast, fentanyl, primarily an analgesic, efficiently reduces propofol requirement for suppression of response to skin incision. Thus, the deficit of any particular property of an agent is supplemented by the other drug. Successful placement of a laryngeal mask airway (LMA) warrants adequate mouth opening and suppression of upper airway reflexes to prevent adverse events such as coughing, gagging and laryngeal spasm. In unpremedicated patients, when propofol alone was used, the dose requirements for smooth LMA insertion is quite high. Opioids can supplement or patch up the deficient analgesic component of propofol during introduction and tolerance of the LMA while minimizing the requirement of propofol for such purpose.

Till date, no intravenous induction agent can provide all the components of balanced anesthesia with an acceptable margin of safety and ease of titrability. co-administration of adjuvant drugs such as benzodiazepines, opioids, or alpha-2 agonists has shown to curtail the dose requirement of a primary induction agent. Opioids are used primarily for analgesia, anxiolysis, sedation, and attenuation of autonomic responses to surgery. Opioids do not have considerable amnestic properties. However, opioids alone can produce unconsciousness in humans, especially in higher dose. Certainly, the doses of opioids need to be individualized. Sufentanil was found to virtually replace halothane to prevent movement in response to a tail clamp in an experimental rat model. The clinical endpoint for titration of dose is unclear. The loss of eyelash reflex which is commonly used for titration during induction with barbiturates is not useful during induction with opioids. Responsiveness to a verbal stimulus may not be an adequate endpoint during induction with opioid, and instead, more intense stimulus might be useful for this purpose. Short et al. found that use of a small dose of alfentanil can curtail the induction dose of propofol to a half. Smaller dose of opioids usually does not produce amnesia. Butorphanol has been reported to produce considerable anterograde amnesia. In this issue, the authors compared butorphanol and fentanyl as co-induction agent with propofol and they found butorphanol as a preferable agent to fentanyl in respect of better respiratory profile (less apnea time). Although prolonged recovery time (prolonged sedation) and higher sedation scores were observed, it was considered as within clinically acceptable limit.

Propofol, ketamine, thiopentone, midazolam and opioids such as fentanyl, alfentanil, and sufentanil - all have been used in various combinations for different settings. As a part of co-induction, those agents have led to improvement in induction, maintenance, and...
recovery characteristics of anesthesia as well as a reduction in individual drug requirements. Ketamine balances the cardiodepressant effects of propofol with its sympathomimetic cardiotonist action thus resulting in a better hemodynamic profile, but at the cost of slight prolong recovery profile compared with propofol alone. Ketamine reduces the induction dose of propofol more efficiently than any other induction agents.[1,9] Infusion of low-dose ketamine-propofol combination was found to be more effective and safer sedoanalgesia than propofol-fentanyl infusion for emergency short surgical procedures in pediatric patients in terms of hemodynamic stability and lesser incidence of apnea.[10] In another study, Goyal et al. concluded that ketamine is a better premedicant than fentanyl with respect to hemodynamic stability and adverse effects. They found less incidence of apnea and respiratory depression with ketamine, while faster recovery was achieved with the use of fentanyl.[11]

However, synergistic effect may also amplify the undesirable interactions of the drugs such as cardiorespiratory depression and sedative effects. Thiopentone is not as effective as ketamine owing to the formers cardiovascular depressive properties. Midazolam causes minimal reduction in the induction dose of propofol compared with thiopeptone or ketamine as co-induction agents.

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