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COUGH INDUCED BY REMIFENTANIL TREATMENT WITH PROPOFOL DURING TARGET-CONTROLLED INFUSION ANESTHESIA

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Abstract
Background: Remifentanil is commonly used in the anaesthetic induction process but is commonly linked with the occurrence of opioid-related cough, which can be clinically complicated. It is known that Propofol inhibits the airway reflexes, but the interaction of Propofol and remifentanil-induced cough is not fully investigated. Methods: In this randomised trial, patients undergoing general anaesthesia were administered propofol at various target effect-site concentrations (0, 3.0, 4.5 or 6.0 µg/ ml -1) and remifentanil (4.0 ng/ ml -1) as target-controlled rate of IV infusion. Incidences, onset and severity of cough were established, haemodynamic variables and loss of responsiveness. The pharmacodynamic simulations using pharmacokinetics calculated plasma and effect-site remifentanil concentration during the cough onset. Findings Pretreatment with propofol effect-site concentration of 6.0 ug ml -1 had a significant effect on remifentanil-induced cough, but lower concentrations of propofol did not. The dose of remifentanil was similar between groups. Conclusion: Proper propofol pretreatment helps to avoid remifentanil-induced cough during the induction of anaesthesia probably due to a reduction in the disparity between plasma and effect-site concentrations.

Keywords: Remifentanil-induced cough, Propofol, Target-controlled infusion, Anaesthetic induction, Airway reflex suppression

INTRODUCTION

Remifentanil is a selective µ-opioid receptor agonist which is ultra-short acting and typically utilized in cases of anaesthesia induction as an adjunct. Opioids are significant in the analgesia of pain and reduction of airway reflexes including coughing during tracheal intubation [1]. Ironically, though, intravenous fentanyl and fentanyl derivatives may cause coughs to develop on induction of anaesthesia [25]. Cough induced by opioids is not necessarily harmless and temporary, but, in certain instances, can be destructive or violent, requiring emergency clinical care [3]. It was also found that increased intracranial and intra-ocular, intraprostatic, and intraparietal pressures were related to coughing, and severe opioid-related cough was related to the development of conjunctival and periorbital petechiae. [6]. Thus, of significant clinical relevance is good prevention of opioid-induced cough. Despite the fact that the reported rate of cough following remifentanil use seems to be more than that of fentanyl use [4], the majority of the prior studies have been primarily aimed at the

reduction of fentanyl-induced cough [79]. Propofol has a broad usage in the anaesthetic induction and is known to inhibit airway reflexes as well as inhibit airway hyperreactivity [10]. Nevertheless, there is a deficient study on the effects of propofol on the instance of cough on the occasion of remifentanil during anaesthesia induction. Based on this, the effectiveness of varying target effect-site Propofol concentrations in cough prevention was experimented after remifentanil injections during Propofol and remifentanil target-regulated lapses.

METHODS

In this study, the Institutional Review Board of the Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Puducherry was contacted to authorize the research and all the subjects consented to the plan. A total of 158 physical status I or II aged between 18 and 70 years that will undergo gynaecological operations under general anaesthesia were recruited. The exclusion criteria were as follows; having body weight more than 20 percent of the ideal body weight, bronchial asthma, chronic obstructive pulmonary disease, respiratory tract infection or hypertension under the treatment of angiotensin-converting enzyme. The smokers were not excluded in the study. No premedication (preoperative). In this study, the informed consent of all participants was signed and the Institutional Review Board of the Sri Lakshmi Narayana Institute of Medical Sciences & Hospital approved the study. A total of one hundred and fifty eight (158) physical status I or II aged 18-70 years will be recruited to undergo the gynaecological operations under general anaesthesia. The exclusion criteria included the following; body weight more than 20 percent of ideal body weight, bronchial asthma, chronic obstructive pulmonary disease, respiratory tract infection or hypertension with angiotensin-converting enzyme. The smokers were not left behind in the study. No premedication before the operation was done.

We administered propofol and remifentanil fluids in the form of Target-Control Infusions (TCI) in order to achieve the desired effect sites and targets. Using Marsh's pharmacokinetic model, propofol and remifentanil were modelled with ke 0 values of 1.21 min-1 for propofol and 1.22 min-1 for remifentanil, respectively. In approximately 1.6 minutes after reaching the target propofol concentration at effect-site, Remifentanil TCI was initiated at 4.0 ngml-1 at effect-site. Emifentanil is administered as a bolus and the infusion rate of remifentanil is variable for approximately 1.6 minutes before the start of TCI in the Minto model. As soon as the infusion of remifentanil started, the cough was assessed within two minutes. An observer with no knowledge of the propofol target concentration marked the presence or absence of coughing and the point at which the first cough occurred. According to the severity of the cough, mild was classified as 1-2 episodes, moderate as 3-5 episodes, and severe as >5 episodes. Oxygen was initiated to aid mask ventilation occurrence in the event of oxygen desaturation (SpO 2 below 90%). As a result of remifentanil administration, some patients have reported apnoea and chest stiffness. In order to evaluate the loss of responsiveness, the drowsy patients were asked to open their eyes to evaluate their response to mild shoulder stimulation. Any response was considered responsiveness and no response as loss of responsiveness. Measuring the mean arterial pressure, heart rate, and oxygen saturation at baseline and two minutes after administration of remifentanil was done. As soon as the cough examination was completed, the propofol target level was adjusted to control loss of responsiveness, and anesthetic tracheal intubation was supported with rocuronium.

The target-controlled infusion simulations on patients who were coughing were based on the pharmacodynamics and the pharmacokinetic modelling software using a minimum minimum data refresh interval of 2 s. The concentrations of Minto remifentanil were calculated as time passed and were compared against each other. It was determined whether there was a difference in the predicted plasma concentration at the onset of cough between the two groups (Cp-cough, Cpk-cough) and the effect-site concentration at the onset of cough (Ceff-cough, Cpk-cough). Given a reported incidence of remifentanil-induced cough of 27%, and a predicted rate of 10% post-pretreatment with propofol, a sample size of 90 patients per group was necessary to have 80% statistical power. A total of 100 patients were assigned to each group to take dropouts into account. An analysis of the data was carried out using the SPSS software package. In the case of continuous variables, the analysis of variance

was conducted with Bonferonni corrections, and for categorical variables such as cough frequency and degree, the test was conducted with the Chi-square method with correctional differences. The significance level was set at less than 0.05.

RESULTS

Table 1. Patient attributes of 0, 3.0, 4.5 and 6.0 µg·ml -1 (Propofol 0, 3, 4.5 and 6 respectively) effect-site propofol infusion ratios. Values are displayed in means-standardized (SD) or number of patients form.

Variable	Propofol 0 (n = 150)	Propofol 3 (n = 150)	Propofol 4.5 (n = 150)	Propofol 6 (n = 150)
Age (years)	41.0 (11.4)	40.6 (12.4)	42.5 (10.1)	41.7 (11.0)
Weight (kg)	59.1 (8.9)	57.5 (9.5)	57.1 (7.2)	58.4 (8.9)
Height (cm)	159.6 (5.7)	158.4 (6.2)	159.0 (5.1)	158.0 (5.0)
ASA physical status (I / II)	113 / 37	110 / 40	120 / 30	120 / 30
Smoking history				
None	128	134	131	135
Former	8	9	8	8
Current	14	7	11	7
Pack-years	5.4 (2.4)	4.0 (2.6)	4.0 (2.6)	3.1 (1.6)

Table 2. Propofol and remifentanil bolus doses during target-controlled infusion and lack of responsiveness prior to remifentanil administration.

Variable	Propofol 0 (n = 150)	Propofol 3 (n = 150)	Propofol 4.5 (n = 150)	Propofol 6 (n = 150)
Propofol bolus (mg·kg^{-1})	–	1.03 (0.06)	1.55 (0.07)	2.08 (0.09)
Loss of responsiveness before remifentanil, n	0	57	128	146
Remifentanil bolus (µg·kg^{-1})	1.03 (0.11)	1.06 (0.12)	1.02 (0.11)	1.05 (0.10)

The last analysis took into account 600 patients and they were balanced in the four groups of study according to the desired effect-site concentration of propofol. The demographic and baseline clinical characteristics of the patients were the same in each group as revealed in Table 1. There were no clinically significant differences in age, weight body, height or distribution of the anesthesiologists physical state between Propofol 0,3, 4.5 and 6. Most of the patients in the two groups were of physical status anesthesiologists I with a similar proportion of patients with anesthesiologists II being in the groups. There was also an equal status in smoking with majority of the patients reporting that they never smoked, and only a little were reported as former or current smokers. The ranges of the mean pack-year among the smokers were minimal and no significant change was observed in the groups, this implies that the population was fairly homogeneous in terms of smoking exposure.

Table 2 presents a summary of bolus dose requirements and the loss of responsiveness rate before the administration of remifentanil. As anticipated, the dose of propofol bolus rose gradually with the target effect-site concentrations. In Propofol 0 group, there was no propofol bolus administered, Propofol 3, Propofol 4.5 and Propofol 6 group all required mean bolus doses of 1.03, 1.55 and 2.08 mg kg -1, respectively. Loss of responsiveness rate prior to administration of remifentanil continued to rise as propofol concentration increased. No patients in Propofol 0 group lost responsiveness before remifentanil infusion, but there were 57, 128 and 146 patients who lost responsiveness in Propofol 3, Propofol 4.5 and Propofol 6 respectively. Conversely, the bolus dose of remifentanil used in target-controlled infusion was not different in any group and the mean values ranged between 1.02 and 1.06 -1. It was found that increment of propofol effect-site concentration was linked with increment of

propofol demands and rise in rates of pre-remifentanil loss of responsiveness, and remifentanil dosage was parallel across groups.

DISCUSSION

Our study found that pretreatment with an initial propofol concentration of 6.0 ug/ml -1 (corresponding to an estimated bolus dosage of 2.0 mg/kg -1) reduced remifentanil-induced cough by 25 to 4 when the remifentanil concentration was 4.0 ng/ml-1 when anesthesia was induced with target-controlled infusions of propofol and remifentanil. On the other hand, the propofol target concentration of 3.0 and 4.5 μg·ml -1 did not have any significant reduction in the occurrence of the cough.

Remifentanil, like other opioids, suppresses coughing. Remifentanil effect-site concentrations of 2.14 ng -1 ml are effective in preventing coughing after anesthesia, as reported by Lee et al. [14]. Contrary to popular belief, intravenous opioids are notorious for causing preoperative coughing [5,9]. In this study, propofol was administered first, followed by remifentanil administered with an effect-site target to study how propofol impacts remifentanil-induced cough. Due to a shorter induction time, effect-site concentrations can be produced more rapidly than in plasma targeting. The transient plasma overshoot is used as a means of producing effect-site concentrations. In our previous study, we determined a remifentanil target concentration of 4.0 ng ml-1, to allow comparison of different propofol regimens.

Resifentanil-induced coughing was self-limited, short-lasting, and resolved spontaneously in this study. As a general presentation, coughing was observed at an early time, less than 5 seconds after initiation of the infusion, and stopped within 1 minute, and pharmacokinetic simulations showed that the duration of this process matched the rapidly rising plasma concentrations more than the effect-site concentrations, but effect-site concentrations were minimal but slowly increasing. By reducing plasma concentrations, effect-site concentrations increased to produce an antitussive effect, which caused coughing to cease. During the 2-minute observation period, the cough did not recur. Despite the fact that the effect-site concentrations at this later stage were significantly greater than those that had inhibited coughing [14], the likelihood of the patient coughing again was small. It is not ruled out that remifentanil may be responsible for a central mechanism, but it may be a peripheral mechanism, which occurs at relatively low effect-site concentrations and high plasma concentrations. Similar to dexmedetomidine, which is an alpha 2 agonist with a double-peak hemodynamic response, this effect is centrally acting.

Currently, it is unclear what causes coughing to develop, but opioids have been implicated in some mechanisms. A decrease in central sympathetic activity results in vagal stimulation, a process that is associated with coughing and reflex bronchoconstriction caused by opioids [7,16,17]. As another possible cause, the rapidly adapting irritant receptors or vagal fibers that surround pulmonary vessels may stimulate the pulmonary chemoreflex [2,18] or hyperreactivity of the bronchi may activate the pulmonary chemoreflex [7,17]. When induction is used, and when peripheral mechanisms play a critical role in strictly regulating plasma remifentanil concentrations, it is of the utmost importance. There are two strategies for reducing coughs: slow continuous infusion or plasma-targeted TCI. However, zero-order infusion cannot be titrated whereas plasma targeting takes longer. Remifentanil plasma targets (means 0.588 min-1) would be achieved in a range of 6 to 7 minutes with calculated remifentanil ke o.

It would be worth exploring previous studies of fentanyl-induced coughs. According to Cigarini et al. [10] a subtherapeutic dose of propofol 0.6 mg 1kg -1 did not result in bronchoconstriction due to fentanyl, but a subtherapeutic dose of propofol 2.5 mg 1kg -1 did. Accordingly, remifentanil induced cough was not observed at the lowest propofol target (3.0g / ml-1, or approximately 1.0 mg/kg-1). Interestingly, the most severe coughs were numerically higher in the Propofol 3 group, but many less than other groups except for Propofol 6. It is surprising to see this; however, voluntary control of coughing, which is mediated through higher cortical centers, can explain such observations [19]. A patient who is awake or minimally supervised can better control cough than one who is sedated, and a patient who is partially sedated might not be able to control the severity of cough. Remifentanil and

low doses of propofol should therefore be used with caution when managing patients with serious coughs.

Emifentanil inhibits cough in the same manner as propofol due to its effect on NMDA receptors during its action on remifentanil. [20] Proofol inhibits excitatory neurotransmission via the NMDA receptor. In the larynx, lungs, and airways, NMDA receptors are present [21] and have been thought to be responsible for cough regulation [22]. It has been shown experimentally that NMDA receptors can be stimulated by remifentanil [23,24], and that NMDA receptors can be inhibited by propofol, which causes direct or indirect bronchodilation [3,25]. Thus, the central and peripheral route can suppress the cough that is a result of remifentanil by using propofol.

It is also important to consider the pharmacokinetic interaction between propofol and remifentanil. As reported by Mertens et al. [26], the use of remifentanil total intravenous anesthesia using the Minto model was associated with performance errors ranging from -15 to 20% due to propofol-mediated errors. It is possible that all propofol-treated groups may have had slightly lower plasma and effect-site remifentanil levels, but with identical settings. As a result of our simulation studies, we found that the predicted plasma concentrations of remifentanil at cough onset, as well as the change of plasma and effect-site concentrations, were higher in propofol-treated groups, which is consistent with the notion that the high plasma concentrations might still cause coughing. In order to create remifentanil TCI programs to generate anesthesia, a decrease in the disparity between plasma and effect-site concentrations and rapid increases in effect-site concentrations may be significant.

CONCLUSION

As well as its effects on N-methyl-D-aspartate (NMDA) receptors, propofol inhibits cough when used in conjunction with remifentanil. By inhibiting excitatory neurotransmission via the NMDA receptor, propofol has been found to inhibit nervous system activity. [21] According to some studies, NMDA receptors are present in the larynx, lungs, and airways, and they play an important role in cough regulation. Experimental studies have demonstrated that propofol, which causes direct or indirect bronchodilation, can inhibit or stimulate NMDA receptors through remifentanil [23,24]. As a result, propofol used in the peripheral and central routes can suppress coughs caused by remifentanil.

It is also important to consider the pharmacokinetic interaction between propofol and remifentanil. Based on Mertens et al. 's study [26], it has been found that with remifentanil-TCI, the Minto model on total intravenous anesthesia resulted in performance errors of between -15 and 20%. It is possible that the plasma and effect-site remifentanil levels in propofol-treated groups might have been slightly lower, despite identical target settings. Based on simulation results from our researches, it was found that remifentanil plasma concentrations and changes in plasma and effect-site concentrations were more predicted in propofol-treated groups, which supports the idea that coughing may still result from high plasma concentrations. An increase in effect-site concentration and a decrease in plasma-effect-site concentration disparity may lead to the development of the best TCI program for remifentanil.

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