Journal of
Anesthesia

Aminophylline reversal of prolonged postoperative sedation induced by propofol

Satoru Sakurai[1], Atsuo Fukunaga[2], Kenichi Fukuda[3], Masataka Kasahara[3], Tatsuya Ichinohe[1], and Yuzuru Kaneko[1]

[1] Department of Dental Anesthesiology, Tokyo Dental College, 1-2-2 Masago, Mihama-ku, Chiba 261-8502, Japan
[2] Professor Emeritus of Anesthesiology, UCLA School of Medicine, Los Angeles, CA, USA
[3] Department of Anesthesia and Orofacial Pain Center, Tokyo Dental College, Suidoubashi Hospital, Tokyo, Japan

Abstract
Propofol is frequently used for intravenous sedation or anesthesia in ambulatory and office-based anesthesia. Although awakening is usually rapid, there are instances of delayed recovery from propofol anesthesia. It has been reported that aminophylline antagonizes the sedative effects of several anesthetic and analgesic drugs. The case reports presented here demonstrate that intravenous aminophylline effectively reversed prolonged propofol-induced sedation/anesthesia in the postoperative period. There were no side effects or delayed re-sedation after the administration of aminophylline. Our study suggests that aminophylline could be a clinically useful propofol antagonist.

Key words Aminophylline · Propofol · Adenosine · Anesthesia · Sedation

Introduction

Propofol is frequently used for intravenous sedation and/or anesthesia in ambulatory and office-based anesthesia. Although awakening is usually rapid, there are instances when delayed emergence and recovery from propofol anesthesia can occur. Aminophylline (theophylline ethylenediamine), known as an adenosine receptor antagonist and also a potent bronchodilator, has been reported to antagonize the sedative effects of several anesthetic and analgesic drugs, including benzodiazepines [1–4], barbiturates [5,6], volatile anesthetics [7], and opioid analgesics [8]. Furthermore, we recently found that aminophylline antagonized the sedative/anesthetic effects of propofol in human volunteers. (S. Sakurai et al. ATP potentiates and aminophylline reverses propofol-induced sedative/hypnotic effects as assessed by BIS in human volunteers. Presented at the American Society of Anesthesiologists, 2004 Annual Meeting, and at the 13th Annual Meeting of the International Society for Anaesthetic Pharmacology, Las Vegas, 2004.) To our knowledge, the two case reports presented here are the first successful cases wherein the clinical use of intravenous (IV) aminophylline demonstrated a rapid reversal and effective postoperative recovery from prolonged propofol-induced sedation/anesthesia. The findings in these patients suggest that aminophylline could be a useful antagonistic agent when delayed postoperative recovery from propofol sedation/anesthesia occurs.

Case reports

Case 1

A 19-year-old man (60 kg; 173 cm) was scheduled for open reduction of a jaw fracture after a motor vehicle accident. The patient was premedicated with intramuscular midazolam (2.5 mg) 30 min before the induction of anesthesia. Because of severe trismus, fiberoptic nasotracheal intubation was facilitated with IV fentanyl (100 μg) and propofol (1 mg·kg^{-1}) injections. Anesthesia was maintained with continuous propofol infusion at 9 mg·kg^{-1}·h^{-1} for the first 55 min, and then the dose of the propofol infusion was gradually reduced to 6 mg·kg^{-1}·h^{-1} and was maintained at this level until the end of surgery. The duration of the propofol infusion was 150 min and the total dose administered was 855 mg. Supplemental fentanyl (150 μg) and regional infiltration analgesia with 2% lidocaine were also added during the surgery. After the conclusion of the surgical procedure and discontinuation of anesthesia, the patient remained unconscious, and was breathing slowly, but with a good tidal volume. Although we called his name loudly and

repeatedly, he did not respond for more than 20 min. Therefore, IV naloxone (0.3 mg) was administered in an attempt to antagonize the action of fentanyl. Five minutes later, flumazenil (0.3 mg) was given to antagonize the activity of midazolam. Neither drug was successful, as there was no change in the level of responsiveness. After another 15 min had elapsed, IV aminophylline (5 mg·kg^{-1}) was given slowly. The patient awoke within a couple of minutes after this injection and became responsive to verbal commands, with greatly improved ventilation, allowing the safe removal of the endotracheal tube. Although his heart rate increased transiently, from 75 to 90 beats per min, the systolic blood pressure (120–130 mmHg) and the diastolic blood pressure (80–90 mmHg) remained stable before and after the aminophylline injection. The patient was then taken to the recovery room safely. He remained alert and responsive and was well-oriented, with stable vital signs and without the need for further medical intervention in the following 90-min observation period. The patient was discharged from the recovery room without any other subsequent discomfort.

Case 2

A 30-year-old woman (54 kg; 131 cm) underwent extraction of impacted teeth under propofol general anesthesia. Anesthesia was induced with IV propofol (2.2 mg·kg^{-1}), and nasotracheal intubation was facilitated with vecuronium bromide (6 mg). The lungs were ventilated using a mechanical ventilator. Anesthesia was maintained with a continuous propofol infusion, at 9 mg·kg^{-1}·h^{-1} for the first 30 min, and then at 6 mg·kg^{-1}·h^{-1} until the end of the surgery. Regional infiltration analgesia with 2% lidocaine was also added. The duration of the propofol infusion was approximately 55 min, and the total dose of propofol was 350 mg. No premedication or additional muscle relaxant was used. After the end of the surgery and discontinuation of the propofol infusion, the patient remained deeply sedated, with slow spontaneous ventilation, and she was unresponsive to any stimuli, including loud verbal commands, for more than 30 min. In an attempt to expedite recovery, IV aminophylline (5 mg·kg^{-1}) was slowly administered. Within 1 min after the injection, the patient awoke and responded to verbal commands, and showed marked improvement in her ventilation. Systolic blood pressure (90–100 mmHg), diastolic blood pressure (60–70 mmHg), and heart rate (60–70 beats per min) remained stable during the procedure. After the safe removal of the tracheal tube, she was transferred to the recovery room. There she remained awake, alert, and responsive, with stable vital signs, for an observation period of over 60 min, and she was subsequently discharged from the recovery room safely.

Discussion

Although physostigmine has been reported to be effective in reversing propofol-induced unconsciousness in healthy volunteers [9], its clinical use as an anesthetic antagonist has been reported to have many undesirable side effects, such as nausea/vomiting, abdominal pain, and cadiac arrhythmias [10,11].

In the two patients we have described here, a relatively large dose of aminophylline was used successfully to rapidly antagonize and expedite postoperative recovery from propofol-induced residual sedation, without any acute side effects. However, it could be argued that the delayed postoperative awakening may have not necessarily been that of antagonism to propofol sedation in the first place. In our first patient, for whom we administered several drugs, including fentanyl, midazolam, and propofol, during surgery, we initially used naloxone, the most commonly used opioid antagonist, but could not reverse the sedative effect. We then administered flumazenil, a benzodiazepine antagonist, also without success. Based on these findings, we hypothesized that propofol was responsible for the delayed awakening in both of our patients. When aminophylline was administered, the deep sedation was successfully reversed.

Aminophylline, a theophylline derivative, exerts multiple pharmacological effects, either through phosphodiesterase inhibition (i.e., a potent bronchodilating action, which is often used for the treatment of bronchial asthma) or via adenosine receptor blockade [12]. It is generally considered that the majority of actions ascribed to therapeutic doses of xanthines (caffeine and theophylline) are due to their action as adenosine receptor antagonists [13]. The role of adenosine in sleep and its sedative/hypnotic activities are well known [14–18]. In our volunteer study noted above, we demonstrated the antagonistic actions of aminophylline on propofol sedation; these actions were assessed using both the bispectral index (BIS) and behavioral responses to verbal commands. Continuous propofol infusion, targeted at a plasma concentration of 1 µg·ml^{-1}, produced a significant reduction in BIS values (60–65) associated with the sedative/hypnotic behavioral responses, and co-administration of propofol and ATP (an adenosine precursor) further decreased the BIS values (50–55), suggesting that ATP enhanced the propofol sedation. During stead-state propofol sedation, and IV dose of aminophylline, at the same dose as the one used in the present study (5 mg·kg^{-1}), effectively reversed and totally eliminated the sedative/hypnotic activities of propofol, despite the continued administration of the propofol infusion. These results suggested that the sedative/hypnotic effects of propofol may have been mediated, at least in part, via central adenosinergic mechanisms,

because ATP potentiated and aminophylline reversed the sedative/hypnotic actions of propofol. Thus, the antagonistic action of aminophylline on the residual postoperative sedation seen in our two patients could be attributable, at least in part, to its action as an adenosine receptor antagonist.

Previous reports vary as to the toxic and efficacious dose of aminophylline and the modes of administering it safely. In conscious subjects, aminophylline can potentially produce a number of side effects, such as insomnia, anxiety, anorexia, abdominal discomfort, nauses, and vomiting. Serious toxicity has been reported to occur when aminophylline is given at very high doses as a continuous intravenous infusion for a prolonged time, and when the plasma concentration of theophylline exceeds 20 mg·l^{-1} [19]. Some studies have suggested that low doses of aminophylline (1–2 mg·kg^{-1}) safely reversed the sedation induced by benzodiazepines, barbiturates or opioids [1–4,6,8]. Other reports, on the other hand, recommended the use of higher doses (4–6 mg·kg^{-1}) [5,7,12] for awakening anesthetized patients effectively, because the lower doses produced only partial or incomplete reversal of the sedative and hypnogenic actions of the anesthetics. In our carefully monitored postoperatively sedated patients, a single injection of a relatively high dose of aminophylline (5 mg·kg^{-1}) was safely used to reverse the sedative effects after propofol anesthesia. The arousal response to aminophylline was prompt, and was not associated with any apparent side-effects, such as nausea or vomiting, or cardiovascular, respiratory, or central nervous system dysfunction that could cause delay in the patient's postoperative discharge. Furthermore, with the dose used, it was possible to prevent delayed resedation, because of the long mean half-life of theophylline (9.5 h) [20].

In conclusion, rapid reversal of residual postoperative sedation induced by propofol was achieved with IV aminophylline, without undesirable side-effects or delayed resedation. Aminophylline may be a clinically useful propofol antagonist in humans. However, further studies are necessary to elucidate the appropriate doses that would be adequate for antagonizing a determined level of sedation; the best method of aminophylline administration; and its desired plasma concentrations. Further studies are also needed to elucidate the mechanisms of action responsible for the antagonistic action of aminophylline on the sedative activity of propofol.

References

1. Arvidsson SB, Ekstrom-Jodel B, Martinell SAG, Niemand D (1982) Aminophylline antagonizes diazepam sedation. Lancet II:1467
2. Marrosu F, Marchi A, De Martino MR, Saba G, Gessa GL (1985) Aminophylline antagonizes diazepam-induced anesthesia and EEG changes in humans. Psychopharmacology 85:69–70
3. Gürel A, Elevli M, Hamula A (1987) Aminophylline reversal of flunitrazepam sedation. Anesth Analg 66:333–336
4. Hoegholm A, Steptoe P, Fogh B, Caldara A, Pedersen C (1989) Benzodiazepine antagonism by aminophylline. Acta Anaesth Scand 33:164–166
5. Krintel JJ, Wegmann F (1987) Aminophylline reduces the depth and duration of sedation with barbiturates. Acta Anaesthesiol Scand 31:352–354
6. Chen YC, Chan KH, Tsou MY, Wang H, Ho YY, Lee TY (1993) The reversal effect of low dose aminophylline on thiopental-induced sedation. Chin Med J 52:145–148
7. Turan A, Memis D, Karamanlyodthlu B, Pamukcu Z, Sut N (2004) Effect of aminophylline on bispectral index. Acta Anaesthiol Scand 48:408–411
8. Stirt JA (1983) Aminophylline may act as a morphine antagonist. Anaesthesia 38:275–278
9. Meuret P, Backman SB, Bonhomme V, Plourde G, Fiset P (2000) Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 93:708–717
10. Avant GR, Speeg KV Jr, Freemon FR, Schenker S, Berman ML (1979) Physostigmine reversal of diazepam-induced hypnosis. A study in human volunteers. Ann Intern Med 91:53–55
11. Hartvig P, Lindstrom B, Pettersson E, Wiklund L (1989) Reversal of postoperative somnolence using a two-rate infusion of physostigmine. Acta Anaesthesiol Scand 33:681–685
12. Niemand D, Martinell S, Arvidsson S, Ekström-Jodal B, Svedmyr N (1986) Adenosine in the inhibition of diazepam sedation by aminophylline. Acta Anaesthesiol Scand 30:493–495
13. Williams M, Jarvis MF (1988) Adenosine antagonists as potential therapeutic agents. Pharmacol Biochem Behav 29:433–441
14. Radulovacki M (1991) Adenosine and sleep. In: Phillis JW (ed) Adenosine and adenine nucleotides as regulatiors of cellular function. CRC, Boca Raton, pp 381–390
15. Satoh S, Matsumura H, Suzuki F, Hayaishi O (1996) Promotion of sleep mediated by the A_2a-adenosine receptor and possible involvement of his receptor in the sleep induced by prostaglandin D_2 in rats. Proc Natl Acad Sci USA 93:5980–5984
16. Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW (1997) A mediator of the sleep-inducing effects of prolonged wakefulness. Science 276:1265–1268
17. Tanase D, Baghdoyan HA, Lydic R (2003) Dialysis delivery of an adenosine A_1 receptor agonist to the pontine reticular formation decreases acetylcholine release and increases anesthesia recovery time. Anesthesiology 98:912–920
18. Tung A, Herrera S, Szafran MJ, Kasza K, Mendelson WB (2005) Effect of sleep deprivation on righting reflex in the rat is partially reversed by administration of adenosine A_1 and A_2 receptor antagonists. Anesthesiology 102:1158–1164
19. Piafsky KM, Ogilvie RI (1975) Dosage of theophylline in bronchial asthma. N Engl J Med 292:1218–1222
20. Horai Y, Ishizaki T, Sasaki T, Chiba K, Suganuma T, Echizen H, Ohnishi A (1983) Biovailability and pharmacokinetics of theophylline in plain uncoated and sustained-release dosage forms in relation to smoking habit. I. Single dose study. Eur J Clin Pharmacol 24:79–87