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Original Article

The Effects of Aminophylline Reversal of Propofol Sedation on the Emergence and Recovery Profiles: Comparison with Spontaneous Recovery as Assessed by the Bispectral Index and Psychometric Behavior Responsiveness in Volunteers.

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Purpose: *The aim of this study was to investigate if aminophylline could effectively reverse propofol sedation, thus shorten recovery times when compared with spontaneous recovery from propofol sedation.*
Methods: *In this double-blind study, 10 healthy volunteers were assigned on two different days to receive either saline or aminophylline during propofol infusion in a randomized, cross-over manner. Propofol infusion was initially targeted to achieve bispectral index (BIS) around 60 and loss of consciousness (LOC), and thereafter this infusion rate was maintained constant for 50 min. At 40 min of continuous propofol infusion, each subject received one of the study drugs either saline or aminophylline (5 mg/kg). Changes in BIS, psychometric behavior responsiveness to verbal command (BRVC), cardio-pulmonary variables, plasma concentrations of propofol and theophylline were measured during the entire study periods for 70 min.*
Results: *Propofol reduced BIS to 61 ± 10 in 30–35 min, which was associated with negative BRVC (LOC) in all subjects. At 40 min, saline administration had no effect. In contrast, aminophylline rapidly reversed propofol sedation (within a min): BIS acutely increased associated with rapid awakening and accelerated restoration of positive BRVC. Aminophylline could also rapidly normalize all the cardio-pulmonary variables that were suppressed by propofol. No deleterious side effect was observed.*
Conclusion: *This study clearly demonstrates that the use of aminophylline can effectively and rapidly reverse propofol sedation, and thus significantly shorten emergence and recovery times with improved psychometric as well as cardio-pulmonary functions, compared with spontaneous recovery after discontinuation of propofol infusion.*

Key words: propofol sedation, aminophylline, adenosine receptor antagonist

Introduction

Propofol is today one of the most widely used intravenous (IV) sedative anesthetic drug. Although propofol is known to allow rapid emergence and recovery following its use during short procedures, delayed awakening (>20min), significant impairments of psychometric functions, and a high overall incidence of side effects were noted after propofol infusion in major surgical procedures[1]. The drug also carries serious risks of cardio-pulmonary depressions[2], but no reliable specific antagonist has been reported. Aminophylline (theophylline ethylenediamine) has been shown to reverses (antagonizes) sedative/hypnotic effects of variety of intravenous as well as inhaled volatile anesthetics drugs[3–8]. Similar antagonistic interactions between propofol and aminophylline have been observed[9–12]. However, these previous reports are difficult to interpret because of multiple confounding variables including use of multiple drugs, varied dosages, differing mode of administration and varying level (depth) of sedation and anesthesia. Recently, we have reported two successful clinical experiences of rapid and complete reversal by aminophylline after midazolam/propofol/fentanyl anesthesia, but unknown level of sedation/anesthesia[9]. In the current study, we wished to evaluate, in detail, the effect of a single IV dose of aminophylline administration during the well defined level of propofol sedation. Therefore, the randomized, double-blind study was designed to investigate if IV injection of aminophylline (5 mg/kg) could safely and effectively achieve the reversal (antagonism) during recovery phase of light plane propofol sedation [bispectral index (BIS): approximately 60] in healthy volunteers. We employed two commonly used methods of assessing the level of sedation: BIS and psychometric behavioral responsiveness to verbal commands (BRVC), which have been used previously[13–15]. The aim of this study was to investigate if the use of aminophylline, (given at the end of surgery), could effectively reverse propofol sedation, thus shorten emergence and recovery times and improve recovery profiles when compared with spontaneous recovery after stopping propofol infusion.

Methods

This study was approved by the Ethics Committee of Tokyo Dental College (Approval No. 160). Prior to the study, we explained study plan to each participants and a written

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informed consent was obtained from 10 healthy young adult (27 ± 3 yr) male volunteers. Each fasted and refrained from smoking or taking caffeine and theophylline containing food and drinking for at least 8 h before each study day. In a supine position and after local infiltration anesthesia, a 22−gauge IV catheter was inserted into the left brachio-cephalic vein for the study drugs administration, and another 20−gauge catheter was inserted into the right brachio-cephalic vein for blood sample collections.

Study Protocol

Each subject participated on 2 separate days (at least 2 weeks apart) for study drug administration either IV saline (placebo-control, group−1) or IV aminophylline (Neophylline®, Eisay, Tokyo, Japan, 5mg/kg, group−2) during the continuous propofol (Diprivan®, Astra Zeneca, Osaka, Japan) infusion.

Propofol was IV infused continuously using a diprifusor TCI pump (Graseby®3500pump; Graseby Medical Ltd., Watford, UK). The initial infusion dose (6 mg/kg/h for 5 min and followed by gradual decrements) was targeted to achieve BIS value around 60 and LOC, and thereafter, the infusion rate was maintained constant (approximately 3 mg/kg/h) until the end of infusion for 50min. Study drug administration: At 40min of continuous propofol infusion, one of the study drugs was slowly injected IV (over 30seconds) in a randomized, double-blind, cross-over manner: In group−1, saline (placebo-control) was administered during continuous propofol infusion, and followed by spontaneous recovery after stopping propofol infusion. In group−2, a single dose of 5mg/kg aminophylline was administered during continuous propofol infusion for 50min. Neither the investigators nor the volunteers knew whether saline or aminophylline was given on any particular study day.

Assessment of the level (depth) of sedation

The level of sedation was continuously assessed by using BIS. A BIS plus® sensor (Bis™ Quatro; Covidien Ireland Ltd., Mansfield, MA, USA) was placed on the forehead of each subject which was connected to a BIS monitor (Version2. 21, A−2000, Aspect Medical System, Newton, MA, USA). In addition, intermittent BRVC was evaluated (every 5 min) to determine that (A) if they could respond to the verbal commands positively (wakefulness, consciousness) or negatively (LOC, unconsciousness, asleep), and (B) if they could respond properly as instructed before the study (as a simple cognitive function test) : They were instructed ; (a) to move a sponge from one hand to the other hand when they heard a bell sound, and (b) to perform simple arithmetic calculations.

Cardio-pulmonary parameters

Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), pulse-oxymeter saturation (SpO_2), respiratory rate (RR), end-tidal carbon dioxide tension ($ETCO_2$), tidal volume (V_T) and minute volume (V_E) were monitored using non-invasive, automated monitoring equipments (Moneo BP−88R, Nippon Collin, Tokyo, Japan), CAPNOMAC ULTIMA® (Datex Ohmeda) and a Rite® flow-meter by continuous sampling from the junction of the face mask and the semi-closed anesthesia circle breathing system (total gas flow rate = 6L/min with air, $FiO_2 = 0.21$). These variables were measured, every 5min, before and after the start of propofol infusion for a total study periods of 70min. In addition, we measured blood (venous) plasma concentrations of propofol and theophylline. Each blood sample was analyzed using reverse-phase high-performance liquid chromatography with fluorescence detection for plasma propofol concentration (SRL Incorporation, Tokyo Japan), and the plasma theophylline concentration was analyzed by enzyme-linked immunosorbent assay (SRL Incorporation, Tokyo Japan).

Statistical analysis

A power analysis based on a preliminary pilot study suggested that a sample size of 10subjects for each group should be adequate to detect a difference in the BIS values between the 2 groups with a power of 0. 8 (alpha = 0. 05). Baseline data points were recorded prior to the drug infusion. Data are presented as mean ± SD. Intra-group comparisons of time-dependent variables were made with repeated measures ANOVA followed by Dunnett post hoc test. Inter-group comparisons were made with a paired student t-test. P values less than0. 05were considered significant.

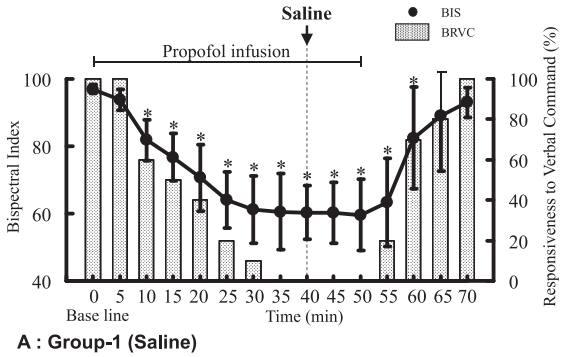
Results

Changes in BIS and BRVC

Continuous IV propofol infusion resulted in progressive BIS reduction attaining target level (BIS : 61 ± 10) in 30−35min, which was associated with deep sedation and negative BRVC (unconsciousness, LOC, asleep). Thereafter, this level of sedation was maintained stable with constant rate of propofol infusion (approximately 3 mg/kg/h) for 50min in both groups. At 40min (during continuous propofol infusion), administration of placebo-saline had no effect. At 50min (soon after discontinuation of propofol infusion), spontaneous recovery began, but progressed slowly requiring another 20min to return to the pre-infusion level (Fig. 1−A). In contrast, aminophylline given during steady-state propofol sedation rapidly reversed both BIS and BRVC (Fig. 1−B). Immediately after IV injection of aminophylline (5 mg/kg), BIS began to increase from 61 ± 8 to 92 ± 4, associated with rapid awakening and regaining consciousness (despite the continued propofol infusion and steady-state maintained plasma propofol concentration), as well as faster restoration of positive BRVC as evidenced by the complete recovery of BRVC (wakefulness with clear cognition) within 5 min after aminophylline administration. (Fig. 1−B, Table 1).

Changes in cardio-pulmonary variables

Continuous propofol infusion for 50min resulted in significant depressant effects on all SBP, DBP, V_T, V_E, SpO_2 and $ETCO_2$, and they continued to remain depressed for another 5 −20min after stopping the propofol infusion. At 40 min (during continued propofol infusion), placebo-saline administration had no effects on cardio-pulmonary variables in group−1 (Fig. 2). In contrast, when aminophylline (5 mg/kg IV) was injected, it effectively counteracted



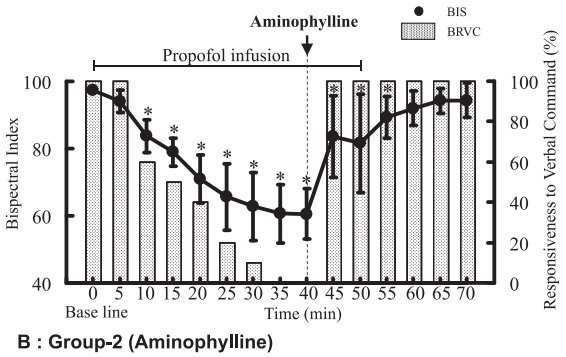
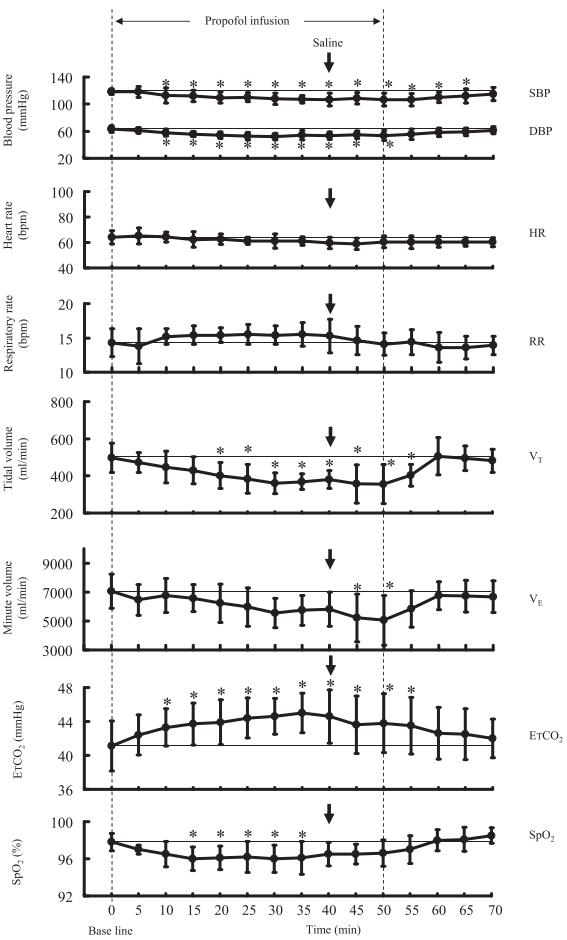


Fig. 1

A: Time courses of bispectral index and behavioral responsiveness to verbal command during propofol infusion and recovery for 70min. At40min, saline (placebo−control) was administered. Date are presented as mean ± SD, n = 10. *p＜0. 05versus baseline control (BIS). BIS, bispectral index. BRVC, psychometric behavioral responsiveness to verbal command.

B: Time courses of bispectral index and behavioral responsiveness to verbal command during propofol infusion and recovery for 70min. At 40min, aminophylline (5 mg/kg) was administered. Date are presented as mean ± SD, n = 10. *p＜0. 05versus baseline control (BIS). BIS, bispectral index. BRVC, psychometric behavioral responsiveness to verbal command.



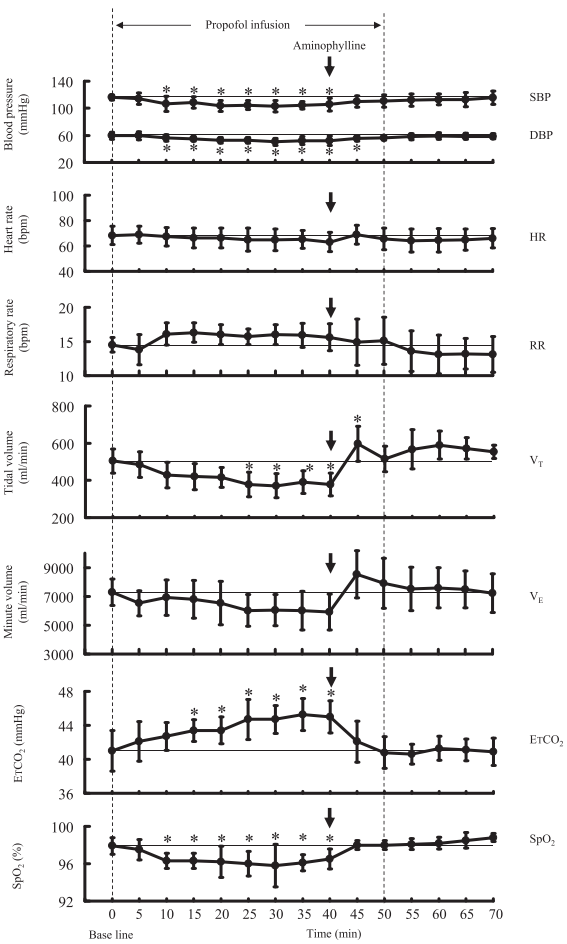


Fig. 2

Changes in cardio-pulmonary variables during propofol infusion and recovery for 70min. At 40min, saline (placebo-control) was administered. Data are presented as mean ± SD, n = 10. *p＜0. 05versus baseline control. SBP, systolic blood pressure. DBP, diastolic blood pressure. HR, heart rate. RR, respiratory rate. V_T, tidal volume. V_E, minute volume. $ETCO_2$, end-tidal carbon dioxide. SpO_2, oxygen saturation.

Fig. 3

Changes in cardio-pulmonary variables during propofol infusion and recovery for 70min. At 40min, aminophylline (5 mg/kg) was administered . Data are presented as mean ± SD, n = 10. *p＜0. 05versus baseline control. SBP, systolic blood pressure. DBP, diastolic blood pressure. HR, heart rate. RR, respiratory rate. V_T, tidal volume. V_E, minute volume. $ETCO_2$, end-tidal carbon dioxide. SpO_2, oxygen saturation.

Table1. Plasma propofol concentration during and after propofol infusion

Time after start of propofol infusion (min)		0	20	40	50	60	70
Plasma propofol concentration (μg/ml)	Propofol infusion + Saline	0.00 ± 0.00	0.78 ± 0.04	0.80 ± 0.05	0.81± 0.07	0.24 ± 0.05	0.14 ± 0.05
	Propofol infusion + Aminophylline	0.00 ± 0.00	0.78 ± 0.06	0.84 ± 0.05	0.84 ± 0.06	0.23 ± 0.05	0.15 ± 0.07

Data are mean ± SD

No statistical difference between two groups

Table2. Plasma theophylline concentration after aminophylline administration

Time after aminophylline administration (min)		0	1	5	10	30
Plasma theophylline concentration (μg/ml)	Propofol infusion +Aminophylline	0.0 ± 0.0	29.6 ± 8.4	17.2 ± 2.2	12.0 ± 1.6	8.7 ± .07

Data are mean ± SD

propofol-induced cardio-pulmonary depressant effects; all the SBP, DBP, V_T, V_E, SpO_2 and $ETCO_2$ rapidly recovered to the base-line normal levels within 5 −10min after aminophylline administration in group−2 (Fig. 3).

Plasma propofol concentration

In both groups, similar and stable level of plasma concentrations were achieved and maintained during continuous propofol infusions, particularly between 20−50min, respectively. At 40min, IV injection of one of the study drugs (saline or aminophylline) had no effect on plasma propofol concentration, and they declined rapidly after the discontinuation of propofol infusion (Table 1).

Plasma theophylline concentration

At 40min of continued propofol infusion, when a single dose of aminophylline (5 mg/kg IV) was injected, the plasma theophylline concentration reached at peak level : 29.6 ± 8.4μg/ml, a min after its administration. Thereafter, the plasma theophylline concentration rapidly declined to lower therapeutic plasma concentration ranges : 17.2 ± 2.2μg/ml and12.0 ± 1.6μg/ml in 5 to10min after aminophylline administration, respectively (Table 2). No serious side effects were seen during and after aminophylline administration.

＊A safe plasma theophylline concentration range : 5 −20 μg/ml for the intravenous administration in clinical situations[20].

Discussion

In the current study, we have focused our examination primarily on three aspects of aminophylline reversal of propofol sedation: 1) safe and effective IV dosage of aminophylline, 2) speed of actions (reversal effects from sedation), and 3) side effects after a single IV injection of aminophylline under propofol sedation in healthy volunteers. Our results clearly demonstrate that IV aminophylline can safely, effectively and rapidly reverse (antagonize) propofol sedation, thus allowing rapid emergence (within a min) and faster recovery with full restoration of consciousness and cognitive function (within 5 min), when compared with spontaneous recovery after discontinuation of propofol infusion, which required over 20min to return to the baseline control levels in both BIS and BRVC. It is also worthwhile to note that under propofol sedation/anesthesia, a slow IV injection of aminophylline (5 mg/kg) was well tolerated and did not cause any deleterious side effect, which corroborate our previous reports[9]. Once brought to a lighter sedation level, no subject relapsed into deeper plane (resedation) because theophylline has a longer action of 8 to 9 hours[16].

Assessment of the level (depth) of sedation

The continuous BIS monitoring has become a reliable measure for assessing the level of sedation/anesthesia for intravenous as well as volatile inhaled agents[17]. However, during sedation and anesthesia, BIS measurement alone can not clearly distinguish between wakefulness (awake, consciousness) and LOC (asleep, unconsciousness). LOC under anesthesia occurs abruptly at a threshold separating wakefulness (positive BRVC, consciousness) from asleep (negative BRVC, unconsciousness). An abrupt LOC occurred at a measured BIS threshold of approximately70−65[13], 62 ± 11[18] and 61[19]. Therefore, in the current study, continuous BIS monitoring was combined with intermittent assessments of BRVC (in every 5 min) in order to ascertain that the subject was wakefulness (positive response) or asleep (negative response) during the entire study periods. Thus, the BRVC confirmed the changes of BIS and ensured that the subject was wakefulness or asleep.

Antagonistic interaction between aminophylline and anesthetic drugs

Previously, antagonistic interactions between aminophylline and anesthetic drugs have been observed in a number of surgical patients after sedation and anesthesia with various drugs[3-8]. More recently, similar antagonistic interaction between aminophylline and propofol has been de-

scribed. Taylor et al.[10] found in ICU that propofol sedation proved a difficult problem during aminophylline infusion in an asthmatic patient for the treatment of status asthmatic: propofol requirements (doses) were very high, 400–500mg /hour was necessary at times. Turan et al.[11] found in volunteer study that propofol requirement (total dose) was larger at LOC, and the time to recovery of consciousness (ROC) was shorter during IV aminophylline infusion (1.5 mg/kg/h). Hupfl et al.[12] found that their clinical study result was of little clinical relevance. They injected aminophylline (3 mg/kg IV) during deep plane of surgical anesthesia with propofol/remifentanil (BIS: approximately38), and their results showed only a small overall increase of 3－6 BIS units over the 10 min observation period after aminophylline administration. However, these previous reports are difficult to understand and questionable as for their clinical utility and applicability. In these studies, the mode and dosage of aminophylline administration varied widely, as well as the observations were made under different depth of sedation/anesthesia with various drugs, which might have contributed to the inconsistent, erroneous results and/or misleading conclusions.

Therapeutic use and dosage of aminophylline

In unanesthetized asthmatic patients, continuous IV infusion of aminophylline for longer period of times have been used, which could potentially produce a number of side effects such as insomnia, anxiety, anorexia, abdominal discomfort, nausea/vomiting and seizure activity or convulsion were reported[13]. In the current study, we used a single IV dose of aminophylline (5 mg/kg), administered slowly over 30seconds, under well defined propofol sedation level. This therapeutic dose was chosen on the basis of their demonstrated safety and effectiveness for the treatment of variety patients, such as bronchial asthmatics[20], pulmonary emphysema with congestive heart failure[21], angina pectoris[22–25], myocardial ischemia[22, 23], as well as under sedation/anesthesia with benzodiazepines[26], barbiturates[5], enflurane/nitrous oxide[7], sevoflurane /nitrous oxide[8] and propofol/midazolam/fentanyl[9]. More recently, we have shown successful use of aminophylline (3－5 mg/kg IV) during similar level of midazolam sedation (BIS：60), without causing any deleterious side effects on cardiopulmonary variables in healthy young volunteers[27]. In fact, in the present study, a single dose of aminophylline (5 mg /kg IV) given during propofol sedation, effectively counteracted all the propofol-induced effects; not only sedative effect, but also cardio-respiratory depressant effects of propofol, thus rapidly restored and normalized them to their base-line control levels, without causing any undesirable side effect.

In conclusion

These results clearly demonstrate in healthy volunteers that a single IV dose of aminophylline (5 mg/kg) given after propofol sedation is safe and effective in reversing propofol effects as evidenced by the concomitant changes in both BIS and BRVC as well as cardio-pulmonary variables, without causing any undesirable side effect. Thus, the use of aminophylline facilitates faster recovery from propofol sedation when compared to the spontaneous recovery after stopping propofol infusion. We believe our results could provide convincing evidence of aminophylline reversal (antagonism) of propofol sedation in human and clinically relevant information regarding safe and effective antagonism against propofol sedation, by a readily available, inexpensive drug that could be used in patients whose recovery from propofol is unexpectedly prolonged. Further usefulness proof clinical study is required to determine the clinical importance of these findings.

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アミノフィリンのプロポフォール鎮静からの回復への影響：bispectral indexと行動応答による評価

後藤隆志　櫻井　学

本研究では，アミノフィリン投与によりプロポフォール鎮静からの回復を促進できるかを検討した．

被検者は有志の健康成人10人とし，各被験者に対し2回の実験を行った．実験ではプロポフォールを投与して鎮静状態とし，鎮静中に生理的食塩水あるいはアミノフィリンを投与した．生理的食塩水とアミノフィリンの投与は2週間以上開けた異なる日に投与し，それぞれの鎮静からの回復状態を比較した．また，これらの研究はダブルブラインド，無作為，クロスオーバー法で行った．プロポフォールは，意識が消失しbispectral index（BIS）が約60になるような状態を維持するように50分間持続投与した．生理的食塩水あるいはアミノフィリン（5 mg/kg）は，プロポフォール投与中の40分の時点で投与された．実験中はBIS，指示行動に対する反応，呼吸・循環のパラメーター，プロポフォールとテオフィリンの血漿濃度を記録した．

プロポフォール投与により，30–35分にはBIS値は61±10となって，全ての被験者は指示行動に反応しなくなり，意識消失状態となった．プロポフォール投与後40分に生理的食塩水あるいはアミノフィリンを投与したが，生理的食塩では効果が認められなかったのに対し，アミノフィリンは急激（1分以内）にBIS値を上昇させ，完全覚醒も可能とした．また，アミノフィリンはプロポフォールによって抑制された心肺機能も急速に正常化した．アミノフィリン投与に伴う重篤な副作用は認められなかった．

今回の結果はアミノフィリンの投与がプロポフォール鎮静からの回復促進に有効であることを示した．

キーワード：静脈内鎮静法，プロポフォール，アミノフィリン，アデノシン

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（平成26年4月3日受理）