J Anesth (1996) 10:33–38

Journal of
Anesthesia

A comparison of sympathetic adrenal nerve responses to intravenous high-dose morphine and fentanyl administration in rats

SUMIO AMAGASA, SEIJI TAKAOKA, MASAYA KUDO, and HIDEO HORIKAWA

Department of Anesthesia and Resuscitation, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-23, Japan

Abstract: We compared the effects of intravenous morphine (5 mg·kg^{-1}) and fentanyl (50 μg·kg^{-1}) on systolic blood pressure (SBP), heart rate (HR), and efferent sympathetic adrenal nerve action potentials (SANA) in rats. We also determined the extent of the reflex responses of these parameters to 9% carbon dioxide (CO_2) challenge during the above narcotic anesthesia. In the morphine group, SBP was elevated and the elevated levels were maintained, while changes in SBP in the fentanyl group were not significant. In the morphine group, SANA showed initial stimulation and subsequent depression, while in the fentanyl group, SANA showed sustained depression. CO_2 challenge induced only very small changes in SBP and HR, suggesting that during high-dose narcotic anesthesia the hypercapnic stimulus may not be reflected in circulatory parameters. In both groups, hypercapnia increased SANA to 30% of the baseline values from the pre-challenge level. However, these values were only 91% and 56% of the baseline value in the morphine and the fentanyl groups, respectively.

Key words: Morphine, Fentanyl, Sympathetic adrenal nerve action potential, CO_2 challenge

Introduction

High-dose morphine and fentanyl are used in cardiovascular anesthesia because of their low myocardial depressant effect. However, undesirable cardiovascular events, i.e., hypertension or hypotension, have been reported following morphine administration, whereas these events occurred less frequently after fentanyl [1]. Further, morphine increases plasma catecholamine levels in a dose-dependent manner in patients undergoing cardiac surgery, while fentanyl decreases rather than increases these levels [2,3]. These findings suggest that these two narcotics may exert different effects on the sympathetic nervous system.

The purpose of this study was to compare the effects of intravenous (i.v.) high-dose morphine and fentanyl on the sympathetic nervous system in anesthetized rats. We determined the spontaneous changes in systolic blood pressure (SBP), heart rate (HR), and sympathetic adrenal nerve action potentials (SANA) in response to these high-dose narcotics. We also determined the extent of the reflex responses of these parameters to carbon dioxide (CO_2) challenge after narcotic administration.

Materials and methods

Animals and surgical preparation

Approval for the animal experiment was obtained from our Institutional Animal Laboratory Committee. Twenty-four Wistar rats, weighing 350–500 g, were used for this study. Anesthesia was induced by intraperitoneal injection of pentobarbital (50 mg·kg^{-1}). Following a tracheotomy, ventilation was controlled mechanically, tidal volume was 10 ml·kg^{-1}, and the ventilatory rate was adjusted to maintain $PaCO_2$ at 40 mmHg. The left external jugular vein was cannulated for continuous infusion of Ringer's solution (10 ml·kg^{-1}·h^{-1}) and the administration of drugs. The left femoral artery was cannulated for measurements of SBP, HR, and blood gas analysis. Anesthesia was maintained with halothane in oxygen, and pancuronium bromide (0.1 mg) was given i.v. as required. Sodium bicarbonate was given to maintain arterial blood pH near 7.4. The rectal temperature was maintained at 36.5°–38.0°C with a water mattress.

A branch of the sympathetic adrenal nerve, exposed via a retroperitoneal approach, was severed near the

Address correspondence to: S. Amagasa
Received for publication on September 7, 1995; accepted on March 15, 1995

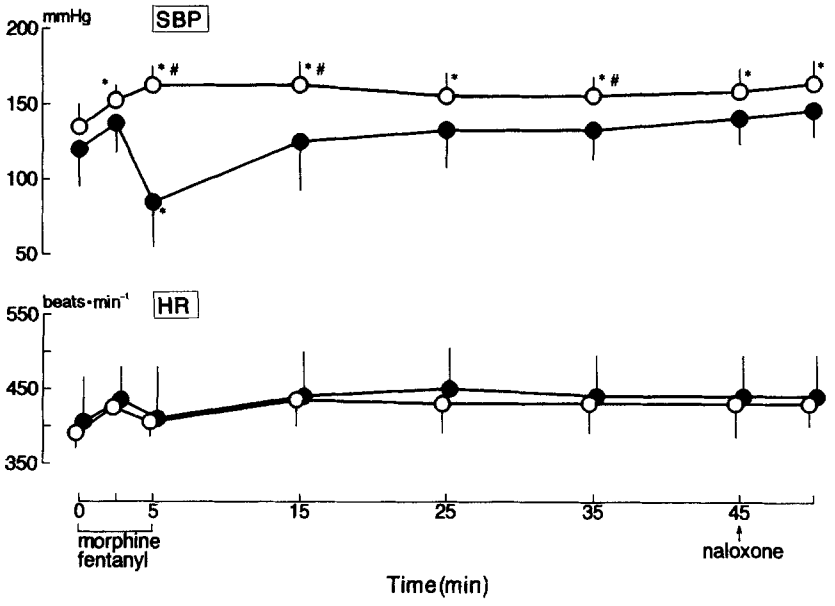

Fig. 1. Systolic blood pressure (SBP) and heart rate (HR) changes after i.v. 5 mg·kg^{-1} morphine, 50 μg·kg^{-1} fentanyl, and 200 μg·kg^{-1} naloxone administration. *vs 0 min ($P < 0.05$); #5 mg·kg^{-1} morphine group vs 50 μg·kg^{-1} fenganyl group ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

adrenal gland. The remaining branches were left intact. The proximal end of the cut nerve was placed on a pair of bipolar platinum–iridium electrodes in a pool of warm paraffin oil. Spontaneous efferent discharges of SANA were amplified (VC-10; Nihon Koden, Tokyo) and displayed on an oscilloscope (ATAC-350; Nihon Koden). Discharges greater than the background noise level were selected and counted every 10 s (DBA-1100; Nihon Koden).

Experimental procedure

The animals were assigned randomly to four groups of six animals each. Group 1 received i.v. high-dose morphine, Group 2 received i.v. high-dose fentanyl, Group 3 was exposed to CO_2 after high-dose morphine administration, and Group 4 was exposed to CO_2 after high-dose fentanyl administration.

Experiment 1: Groups 1 and 2. The surgical preparation took almost 3 h to complete. Halothane was then discontinued, and 10 min later α-chloralose (5 mg·kg^{-1}) was given i.v. to maintain anesthesia. Twenty minutes later, an equipotent dose of morphine (5 mg·kg^{-1}) or fentanyl (50 μg·kg^{-1}) was administered i.v. over a 5-min period. Changes in SBP, HR, and SANA were recorded. Forty minutes after the administration of the narcotics, α-chloralose was administered again, followed by 200 μg·kg^{-1} naloxone, via an i.v. route to reverse the residual effects of the narcotics.

Experiment 2: Groups 3 and 4. The drugs used in this experiment were the same as those used in Experiment 1. Seven minutes after the beginning of fentanyl administration and 9 min after the beginning of morphine administration, CO_2 challenge was applied for 12 min by introducing CO_2 into the inspired oxygen (CO_2 200 ml + O_2 2 1; 9%). The reflex responses in SBP, HR, and SANA were observed, together with changes in the blood gas levels. The timing of the CO_2 challenge was based on the times at which SANA changes in Groups 1 and 2 became stable after the narcotics administration in Experiment 1.

Statistical analysis of data

Values were expressed as means ± SD. Data collected repeatedly within each group were analyzed with ANOVA. When this test revealed a significant level, Tukey's multiple comparison test was used. Differences between the two groups at any given point were analyzed by unpaired t-test. Values were defined as significant when $P < 0.05$.

Results

Experiment 1

1. SBP and HR changes in response to i.v. high-dose morphine or fentanyl. There was a small but significant increase in SBP after morphine administration, and SBP then remained elevated throughout the experiment. In contrast, in the fentanyl group, SBP declined transiently to 80.8 ± 31.0 mmHg at the end of drug administration, but rapidly returned to almost the baseline value (Fig. 1). SBP was higher in the morphine group 5, 15, and 35 minutes after drug administration.

2. SANA changes in response to i.v. high-dose morphine or fentanyl. Figure 2 shows the percentage

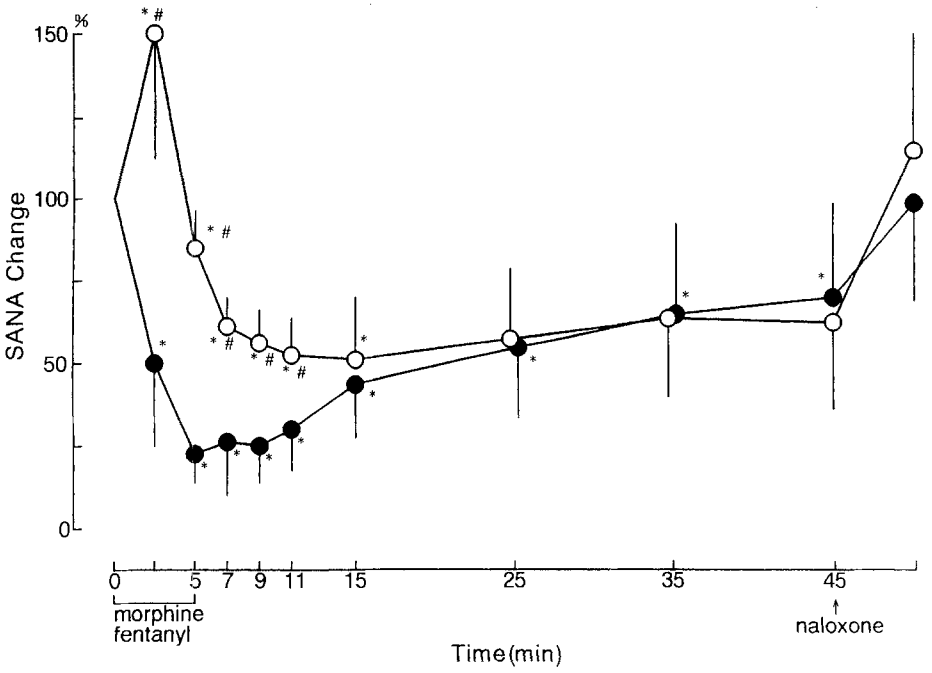

Fig. 2. Sympathetic adrenal nerve action potentials (SANA) changes after i.v. 5 mg·kg^{-1} morphine, 50 μg·kg^{-1} fentanyl, and 200 μg·kg^{-1} naloxone administration. *vs* 0 min ($P < 0.05$). #5 mg·kg^{-1} morphine group *vs* 50 μg·kg^{-1} fenganyl group ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

changes in SANA induced by morphine, fentanyl, and naloxone. In the morphine group, SANA increased transiently to 150.0 ± 37.8% of the baseline value, decreased rapidly to 84.2 ± 12.1% at 5 min, 56.3 ± 10.0% at 9 min, and 52.81 ± 11.7% at 11 min, and remained depressed until reversed by naloxone. The values then increased immediately to 114.6 ± 36.7%. In the fentanyl group, SANA decreased rapidly to 22.5 ± 10.4% of the baseline value at 5 min, 26.1 ± 16.7% at 7 min, and 29.9 ± 12.0% at 11 min, and remaining depressed until reversed by naloxone. The values then returned to 98.7 ± 31.1%. Significant differences were seen between the two groups in the early period after the beginning of drug administration.

Experiment 2

1. $PaCO_2$ and pH changes in response to CO_2 challenge during high-dose morphine or fentanyl anesthesia. At the end of the CO_2 challenge, $PaCO_2$ had increased to 73.8 ± 6.1 mmHg in the morphine group and to 79.0 ± 8.7 mmHg in the fentanyl group; pH in the morphine and fentanyl groups decreased to 7.17 ± 0.02 and 7.16 ± 0.03, respectively (Fig. 3).

2. SBP and HR responses to CO_2 challenge during high-dose morphine or fentanyl anesthesia. In the morphine group, SBP increased slightly but significantly from the baseline value during CO_2 challenge, while the change in SBP in the fentanyl group was not significant. No significant intergroup differences were seen in SBP or HR at any point during or after the CO_2 challenge (Fig. 4).

3. SANA response to CO_2 challenge during high-dose morphine or fentanyl anesthesia. Figure 5 shows the SANA changes provoked by CO_2 challenge during high-dose morphine or fentanyl anesthesia. In the morphine group, the drug-depressed SANA were elevated by CO_2 to 91.4 ± 16.1% of the baseline value and remained high until virtually the end of the CO_2 challenge. The values then returned to the pre-CO_2 challenge level. In the fentanyl group, SANA values, which had been depressed to 24.5 ± 11.9% of the baseline value by the drug, were increased by CO_2 to 55.6 ± 23.9% of the baseline value, and remained at this level until the end of the CO_2 challenge. The values then again declined to 27.8 ± 13.8% of the baseline value. SANA were completely restored to the baseline value by naloxone at the end of the experiment. The increases in SANA values in the morphine and fentanyl groups immediately after the start of CO_2 challenge were 27.8 ± 12.2% and 27.0 ± 14.1%, respectively, at 4 min, and 25.9 ± 9.1% and 30.5 ± 13.8%, respectively, at 12 min. At 4 min after the cessation of the CO_2 challenge, SANA were 1.4 ± 12.7% and 3.3 ± 3.6%, respectively, of their value at the start of CO_2 challenge (Fig. 6).

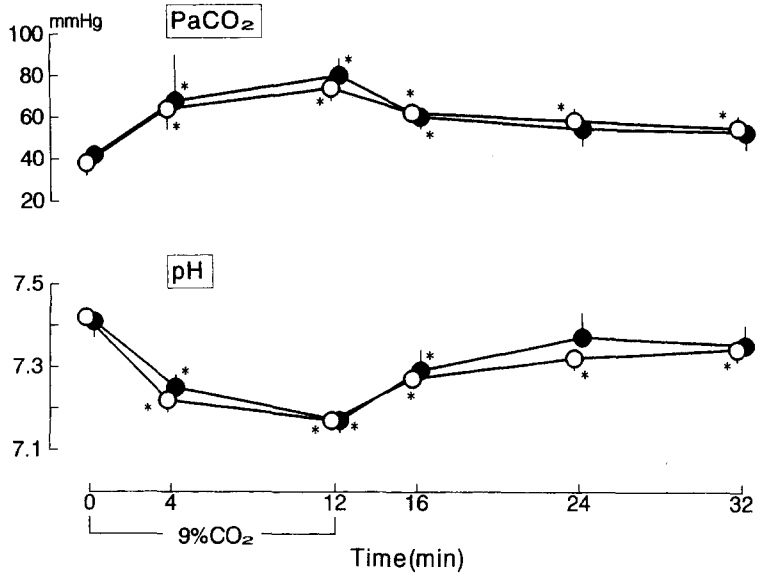

Fig. 3. $PaCO_2$ and pH changes in response to CO_2 challenge during high-dose morphine or fentanyl anesthesia. *vs 0 min ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

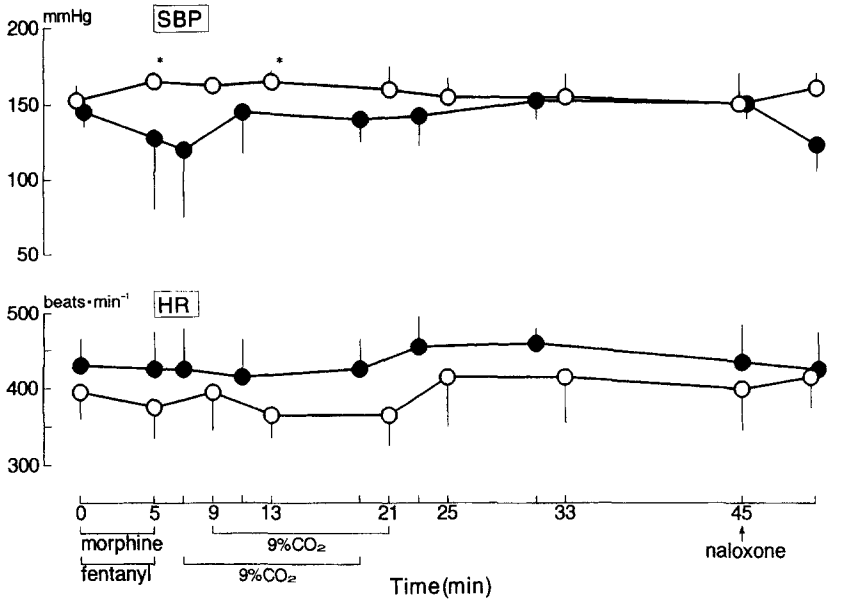

Fig. 4. SBP and HR changes in response to CO_2 challenge during high-dose morphine or fentanyl anesthesia. *vs 0 min group ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

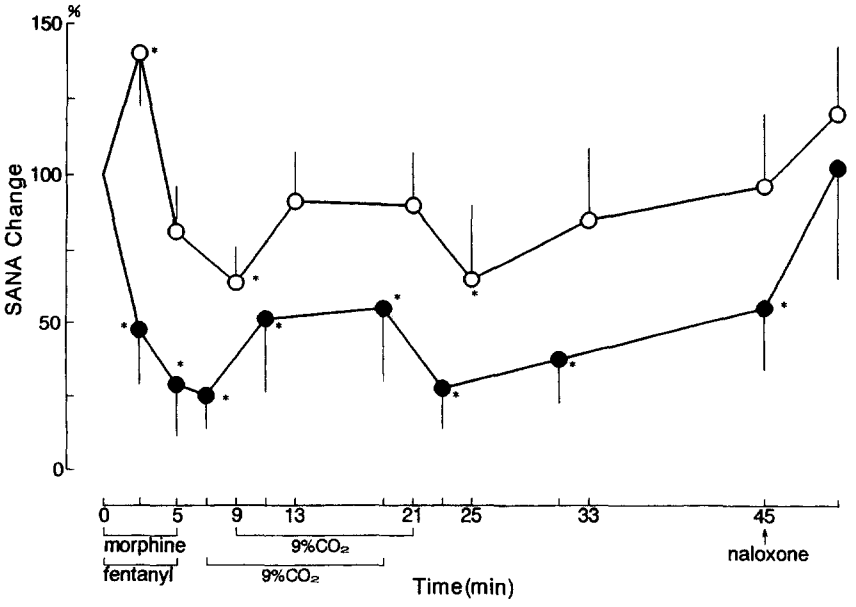

Fig. 5. SANA changes in response to CO_2 challenge during high-dose morphine or fentanyl anesthesia. *vs 0 min ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

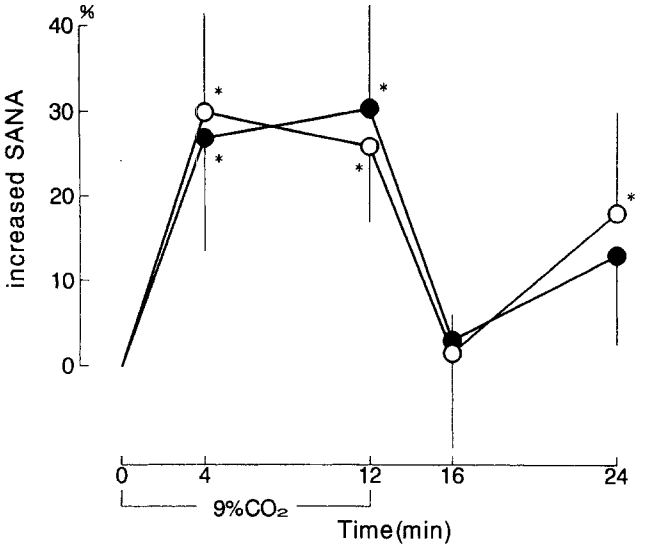

Fig. 6. Increased SANA changes from the pre-CO_2 challenge value. * *vs* 0 min ($P < 0.05$). *Open circles*, 5 mg·kg^{-1} morphine; *solid circles*, 50 μg·kg^{-1} fentanyl

Discussion

Our study showed that i.v. morphine elicited a transient stimulation and subsequent depression of SANA with a small but significant increase in SBP, while in the fentanyl group SANA showed sustained depression. The CO_2 challenge produced a significant increase in SANA associated with only small circulatory changes in both the morphine and fentanyl groups.

Delle et al. [4] demonstrated that i.v. morphine (1 mg·kg^{-1}) provoked a brief and immediate increase in SANA (to 150% of the baseline value), and that naloxone pretreatment virtually abolished this response to morphine in rats anesthetized with α-chloralose. In contrast, Togashi et al. [5] demonstrated an inhibition of SANA without an initial increase in response to i.v. morphine (10 mg·kg^{-1}) in rats anesthetized with α-chloralose and urethane. It is not clear whether these contradictory results are due to differences in the major anesthetic agents employed, differences in the infusion rates, or differences in the doses of morphine administered. The transient sympatho-excitatory finding in the morphine group in our study suggests that morphine may elicit opioid receptor-mediated sympathetic activation, which may be related to the hypertension or increase in catecholamines that is associated with morphine administration in humans [1]. Studies are required to investigate whether pretreatment with adrenegic antagonists prior to morphine administration blocks this initial increase in SANA.

The cardiovascular effects of narcotics, i.e., the pressor or depressor responses, vary depending on whether the animal is conscious or anesthetized at the time of administration [5,6]. In our study, rats were anesthetized with α-chloralose after halothane was discontinued. The SBP in the morphine group remained elevated throughout the experiment, although SANA was depressed after the end of morphine administration.

Daskalopoulos et al. [7] showed that i.v. fentanyl (10–30 μg·kg^{-1}) markedly suppressed splanchnic nerve discharges in cats anesthetized with α-chloralose and urethane. In our study, SANA in rats fell to 23% of the baseline value after i.v. fentanyl (50 μg·kg^{-1}), and this reduction lasted until it was reversed by naloxone.

There are regional differences in sympathetic nerve response to CO_2 challenge. Fukuda et al. [8] demonstrated that sympathetic cardiac and renal nerve discharges were 80% and 40% above the pre-CO_2 challenge level at 9% and 10% end-tidal CO_2, respectively, in rats anesthetized with urethane. Few reports have dealt with the sympathetic reflex responses to CO_2 challenge during narcotic anesthesia. In our study, SANA increased to 30% above the pre-CO_2 challenge level in both the morphine and the fentanyl groups. This maximum elevation of SANA provoked by CO_2 was only 91% and 56% of the baseline values in the morphine and fentanyl groups, respectively. However, since we had no control group, we did not determine to what extent morphine and fentanyl modified SANA responses to CO_2 challenge compared with responses in controls.

Fukuda et al. [8] also showed significant increases in both SBP and sympathetic nerve discharges at 9% end-tidal CO_2. However, we observed no significant changes in either SBP or HR during CO_2 challenge in either group in our study. This finding suggests that the circulatory effects of acute hypercapnia in rats may be obscured by high-dose morphine or fentanyl.

Kissin et al. [9,10] demonstrated that thiopental had dual interactions with morphine and fentanyl: a synergistic interaction in relation to loss of the righting reflex, and an antagonistic interaction in relation to the prevention of purposeful movement response to noxious stimulation. These findings suggest that pentobarbital or α-chloralose (used in our study) may also have a synergistic and/or an antagonistic interaction with morphine and fentanyl. However, since we had no control group, we cannot determine how these interactions may have been involved in the present results.

In conclusion, our study showed that spontaneous SANA changes were markedly different in the early period after high-dose morphine and fentanyl administration, whereas the reflex SANA responses to CO_2 challenge in relation to the pre-challenge level were similar in the two groups of rats.

Acknowledgments. The authors wish to thank Professor Emeritus Kunio Ichiyanagi, Department of Anesthesia

and Resuscitation, and Kenichi Ito, MD, Department of Physiology, for their helpful comments, and Tadayoshi Karube for his technical assistance.

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