The Interactions of Narcotic Agonist-antagonists upon Spinal Analgesic Mechanisms

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Abstract

Narcotic agonist-antagonist butorphanol has the suppressive effects on single-unit activity of cells in Rexed lamina V. However, it is unknown whether the suppressive effects of butorphanol are antagonized or not by pentazocine, which is also narcotic agonist-antagonist analgesics.

We investigated the antagonisms by pentazocine upon spinal analgesic mechanisms of butorphanol by the single-unit extracellular recording technique using the spinal cat. Cats were divided into 4 groups.

In the first group, butorphanol 0.2 mg/kg alone was administered. In the second group, pentazocine 3 mg/kg was administered intravenously 5 minutes after the administration of butorphanol 0.2 mg/kg. In the third group, it was done 10 minutes after the administration of butorphanol. In the fourth group, it was done 20 minutes after the administration of butorphanol. And, also, the changes of spontaneous and evoked activities were investigated after pentazocine was administered and the recoveries were followed.

The antagonistic effects of pentazocine 3 mg/kg i.v. against spinal analgesia induced by butorphanol 0.2 mg/kg i.v. were not recognized on each group.

In conclusion the present study indicates that pentazocine after the administration of butorphanol could be applied in the patient clinically.

Key Words : pentazocine, butorphanol, Rexed lamina V single-unit, extracellular recording technique

INTRODUCTION

In the last decade, we have got several narcotic agonist-antagonist analgesics, which are known to exert a powerful inhibition on the spinal cord sensory interneurons, those are associated with the central transmission of pain message. Therefore, we will have a chance to use these analgesics together. However, there are few reports about the interaction of those analgesics administered together.

The purpose of this study was to investigate the effect of butorphanol tartrate on single unit activity of cells in Rexed lamina V of the feline lumbar spinal cord and to determine if pentazocine would antagonize these effects.

Considering above the effects, we could suppose the possibility of clinical usage in administering these two analgesics together.

METHODS

Details of the experimental methods have been reported elsewhere⁴⁾. Procedures specific to the present investigation are as follows: A total of 32 cats of either sex, weighing 2.5 to 4.0kg, were divided into groups given butorphanol tartrate alone (9 cats), 5 mins. interval from the administration of butorphanol tartrate to the administration of pentazocine (7 cats), 10 mins. interval (8 cats), 20 mins. interval (8 cats). Enflurane, nitrous oxide and oxygen anesthesia were used for tracheostomy, cannulation of the femoral artery and vein, and lumbar laminectomy. Each animal was rendered decerebrate by the bilateral electrolytic lesions placed in the midbrain reticular formation, and the spinal cord was transected at the T₁₂-L₁ level. Anesthesia was then discontinued and the animal was given pancuronium bromide and ventilated with 100% oxygen using a volume cycled ventilation connected to a non-rebreathing system. Femoral artery pressure, endotracheal pCO₂,

Fig. 1 Rexed laminae of feline lumbar spinal cord.

EKG, pulse rate, and rectal and spinal cord temperatures were recorded continuously on a polygraph.

These parameters were kept within the normal physiological range. Arterial blood gas analyses were performed from time to time and kept in the range of pO₂ 300 to 600 torr, pCO₂ 35 to 45 torr, and pH 7.30 to 7.45.

A glass rod platinum sheathed micro-electrode with a 1 to 2 μ m exposed tip was then inserted into the lumbar spinal cord near the L₇ root entry zone using a hydraulic microdrive. Neurons were characterized by their evoked responses to cutaneous pinching stimuli and by their spontaneous firing patterns. As a micro-electrode was passed ventrally through the dorsal column at a depth of about 2000 μ m from the cord dorsum, cells in lamina V displayed a spontaneous activity of bursts followed by steady

firing, responding primarily to high threshold stimuli with graded responses. The Rexed laminae⁵⁾ are illustrated above in **Fig.1**.

In this study, all lesions made were found and all physiological characteristics were anatomically correlated. Signals were recorded through a WP Instruments Inc. preamplifier on magnetic tape and displayed simultaneously on a cathode-ray oscilloscope.

1) Butorphanol tartrate alone (9 cats)

Single units were observed for about 30 minutes after isolation to obtain a stable firing pattern and to control the effect of transient tissue distortion produced by insertion of the microelectrode. The spontaneous and evoked activities of each single unit were counted electronically and instantaneous frequencies displayed on the polygraph.

A pinching methods, using the Nihon Kohden quantitative pain stimulating system, was used for the investigation of evoked activity. A 10 min. control period was then recorded, after which the effect of 0.2 mg/kg of butorphanol i.v. was studied upon spontaneous and evoked activities. The changes in spontaneous and evoked activities caused by pinching the center of the receptive fields were investigated every 5 min. until recovery of single unit activity.

The receptive fields characteristics of lamina V cells were studied before, during, and at the time of recovery from the effects of butorphanol. At the conclusion of each experiment, electrolytic lesions were placed through the recording microelectrode by passing a d. c. current of 20 to 50 μ A for 60 sec.. After fixation with 10% formalin, the spinal cord was sectioned in 30 μ m slices and stained with cresyl violet to study the cytoarchitecture of the spinal cord. Data were analyzed using a NEC PC-9801 VM Computer. The significance of the mean values obtained during the control period, during the administration of butorphanol, and during the recovery period was

assessed by the Student's paired t-test.

2) Butorphanol-pentazocine (5 min. interval) (7 cats)

Details of experimental methods have been described above. Procedures specific to the investigation of this group were as follows : After a 10 min. control period, 0.2 mg/kg i. v. of butorphanol was administered. Five min. after the administration of butorphanol, 3 mg/kg i.v. of pentazocine was administered.

3) Butorphanol-pentazocine (10 min. interval) (8 cats)

After a 10 min. control period, 0.2 mg/kg i.v. of butorphanol was administered. Ten min. after the administration of butorphanol, 3 mg/kg i.v. of pentazocine was administered.

4) Butorphanol-pentazocine (20 min. interval) (8 cats)

After a 10 min. control period, 0.2mg/kg i.v. of butorphanol was administered. Twenty min. after the administration of butorphanol, 3 mg/kg i.v. of pentazocine was administered.

RESULTS

The salient features of the physiological characterization of the lamina of the dorsal horn utilized in the study were reported previously⁴⁾. In the present study, the cells in Rexed lamina V responded primarily to high threshold peripheral cutaneous stimuli, deep squeezing, pinching, and the application of high intensity heat or ethyl chloride. Their spontaneous single unit activity was characterized by bursts followed by steady firing. Their average frequencies were 18.3 ± 4.2 (mean $\pm$ 1 S. E.) / sec. in the butorphanol alone group, 17.9 ± 3.5 (mean $\pm$ 1 S.E.) / sec. in the butorphanol-pentazocine (5 min. interval) group, 17.9 ± 2.4 (mean $\pm$ 1 S.E.) / sec. in the butorphanol-pentazocine (10 min. interval) group, and 18.7 ± 4.6 (mean $\pm$ 1 S.E.) / sec. in the butorphanol-pentazocine (20 min. interval) group.

Fig. 2 Effect of butorphanol on spontaneously firing lamina V cellular activity expressed as percent decrease from control.

Fig. 3 Effect of butorphanol on evokedly firing lamina V cellular activity expressed as percent decrease from control.

1) Butorphanol alone

The effect of butorphanol on spontaneously and evokedly firing lamina V cellular activity, expressed as percent decrease from the control values, and the time course are shown in **Figs. 2 and 3**.

Significant suppression of the spontaneous and evoked activities of neurons in Rexed lamina V was demonstrated 5 min. after 0.2 mg/kg of butorphanol i.v. ($p < 0.05$).

2) Butorphanol-pentazocine (5 min. interval)

Five min. after the administration of 0.2 mg/kg of butorphanol i.v., significant suppression of neurons in Rexed lamina V was observed ($p <$

Fig. 4 Effect of butorphanol-pentazocine (5 min. interval) on spontaneously firing lamina V cellular activity expressed as percent decrease from control. Note that a significant agonistic effect was observed after pentazocine.

Fig. 5 Effect of butorphanol-pentazocine (5 min. interval) on evokedly firing lamina V cellular activity expressed as percent decrease from control. Note that a significant agonistic effect was seen after pentazocine.

0.05). About 15 min. after 3 mg/kg of pentazocine i.v., a significant agonistic effect was seen ($p < 0.05$), as shown in **Figs. 4 and 5**. About 40 min. after pentazocine i.v., the complete recovery was observed.

3) Butorphanol-pentazocine (10 min. interval)

Five and 10 min. after the administration of 0.2 mg/kg of butorphanol i.v., significant sup-

Fig. 6 Effect of butorphanol-pentazocine (10 min. interval) on spontaneously firing lamina V cellular activity expressed as the percent decrease from control.

Fig. 7 Effect of butorphanol-pentazocine (10 min. interval) on evokedly firing lamina V cellular activity expressed as the percent decrease from control.

pression of the spontaneous and evoked activities of neurons in Rexed lamina V was observed ($p < 0.05$).

About 10 min. after 3 mg/kg of pentazocine i.v., a significant agonistic effect was seen ($p < 0.05$) as shown in **Figs. 6 and 7**. About 35 min. after pentazocine i.v., complete recovery was observed.

4) Butorphanol-pentazocine (20 min. interval)

Five and 10 min. after the administration of 0.2 mg/kg of butorphanol i.v., significant sup-

Fig. 8 Effect of butorphanol-pentazocine (20 min. interval) on spontaneously firing lamina V cellular activity expressed as the percent decrease from control. Twenty minutes after the administration of butorphanol, the suppressive effect of butorphanol already recovered. Then, the suppressive effect of pentazocine was observed newly.

Fig. 9 Effect of butorphanol-pentazocine (20 min. interval) on evokedly firing lamina V cellular activity expressed as the percent decrease from control. Twenty minutes after the administration of butorphanol, the suppressive effect of butorphanol already recovered. Then the suppressive effect of pentazocine was observed newly.

pression of the spontaneous and evoked activities of neurons in Rexed lamina V was observed ($p < 0.05$). About 15 min. after butorphanol i.v., the complete recovery of the firing was observed.

About 10 min. after pentazocine i.v., signifi-

cant suppression of the spontaneous and evoked activities of neurons in Rexed lamina V was observed ($p < 0.05$). About 35 min. after pentazocine i.v., the complete recovery was observed.

DISCUSSION

The neurophysiological basis of the interactions of butorphanol and pentazocine has been controversial with regard to an analgesic action.

At the spinal level, there are reports that systemically administered morphine, which is narcotic agonist, has a significant suppressive effect in spinal animals^{1,2}. However, there are few reports about the interaction of analgesic effects of narcotic agonist-antagonist analgesics administered together.

We have shown that butorphanol in a dose of 0.2 mg/kg i.v. significantly suppressed the spontaneous and evoked activities of cells in Rexed lamina V and that such depressed activity was more suppressed 5~10 minutes after 3 mg/kg i.v. of pentazocine.

The suppressive effect of butorphanol recovered about 15 minutes after the administration of butorphanol 0.2 mg/kg i.v. in butorphanol alone group.

Therefore, in a 20 minutes interval group, the suppressive effect of butorphanol diminished when pentazocine was given. So, the suppressive effect of pentazocine was seen newly.

There are some reports about the subpopulations of opioid receptors³. Both butorphanol and pentazocine are kappa and sigma receptor agonist. The difference of two drugs about the subpopulations of opioid receptors is that pentazocine is a mu receptor antagonist, on the one hand, butorphanol does not have any effect on mu receptor. Accordingly the effects of butorphanol and pentazocine on the subpopulations of opioid receptors are very similar. By reason of the above reports, pentazocine would not show an antagonistic effects to the suppressive effect of

butorphanol on single-unit activity of Rexed lamina V cells.

It is obvious that the antagonistic effects of pentazocine 3 mg/kg i.v. against spinal analgesic induced by butorphanol 0.2 mg/kg i.v. are not recognized under the single-unit extracellular recording techniques.

In conclusion, the present study indicates that pentazocine after the administration of butorphanol could be applied in the patient clinically.

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References

- 1) Hanaoka, K., Tagami, M., Toyooka, H. and Yamamura, H., Mechanisms of intrathecally administered morphine analgesia, *Anesthesiology and Intensive Care Medicine*, **144** (1982) 24-29.
- 2) Hanaoka, K., Ohtani, M., Toyooka, H., Dohi, S., Ghazi-Saidi, K., Taub, A. and Kitahata, L. M., The relative contribution of direct and supraspinal descending effects upon spinal mechanisms of morphine analgesia, *J. Pharmacol. Exp. Ther.*, **207** (1978) 476-484.
- 3) Jaffe, J.H. and Martin, W.R., Narcotic analgesics. In : L.S. Goodman and A. Gilman (Eds.), *The Pharmacological Basis of Therapeutics*, Macmillan Publishing Co., New York, 1985, pp. 491-530.
- 4) Kitahata, L. M., Taub, A. and Satoh, I., Lamina-specific suppression of dorsal horn unit activity by nitrous oxide and by hyperventilation, *J. Pharmacol. Exp. Ther.*, **176** (1971) 101-108.
- 5) Rexed, B., The cytoarchitectonic organization of the spinal cord in the cat, *J. Comp. Neurol.*, **96** (1952) 415-495.

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