Midazolam and Somatosensory Evoked Potentials

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Summary

The effect of midazolam, a water-soluble benzodiazepine, on the somatosensory evoked potentials (SEPs) following strong electrical stimulation of the upper lip, was investigated in Wistar albino rats. SEPs were recorded from the surface of the skull in the contralateral temporal area. A computer was used to obtain the averaged SEPs. The rats received intraperitoneal dosages of 1.25, 2.5, or 5.0 mg/kg of midazolam, or physiological saline. Relative amplitudes of the P_1N_1 wave were reduced significantly after midazolam injection. Amplitude recovered to the control level about 120 min after the injection in the 1.25 mg/kg group. In 2.5 and 5.0 mg/kg groups, midazolam-induced suppression did not recover within 120 min. No significant differences were found in the latencies of P_1 and N_1 before and after midazolam injection. It is suggested that midazolam has a mild analgesic effect due to central suppression of the pain perception following noxious stimuli.

Introduction

Midazolam is a water-soluble benzodiazepine derivative which has sedative, hypnotic, anticonvulsive, amnestic, and muscle relaxing properties. It has been reported that midazolam has a mild analgesic action during intravenous sedation[1] similar to diazepam[2,3] and flunitrazepam.[4] (The mechanism of this mild analgesic action of midazolam remains to be clarified.) Cental suppression of pain perception or pain reaction would explain this analgesic effect. In the present study, effects of midazolam on the somatosensory evoked potentials elicited by upper lip stimulation in rats were investigated by recording from the surface of the skull.

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Methods

Experiments were carried out on 24 Wistar albino rats weighing about 400 g. Each rat was anesthetized with thiamylal sodium given intraperitoneally in a dose of 60 mg/kg. An endotracheal catheter was intubated by tracheotomy. The rat was placed in a sterotaxic frame (SN-2, Narishige, Tokyo). Somatosensory evoked potentials (SEPs) were recorded by the method of Toda et al.[5,6] Left temporal bone was exposed by removing soft tissues. A small cavity was formed with a dental drill on the temporal bone above the zygomatic arch close to the somatosensory area projected by trigeminal afferents. SEPs were recorded by a silver ball electrode of 0.8 mm in diameter, placed on the small cavity using a micromanipulator (SM-20, Narishige, Tokyo). An indifferent electrode was inserted into the neck muscle. A bipolar stimulating electrode (interpolar distance: 2mm) of stainless steel wire, 0.1 mm in diameter, insulated except for the tips, was inserted into the right upper lip. The upper lip was stimulated electrically by rectangular pulses with the duration of 0.1 ms at 1 Hz. The stimulus intensity employed was 2 mA which was stronger than the SEP threshold. A computer (ATAC-350, Nihonkohden, Tokyo) was utilized to obtain the averaged SEPs. The computer was set for a 100 ms analysis time with the external trigger at 1 Hz intervals. The pulse counter was used to stop

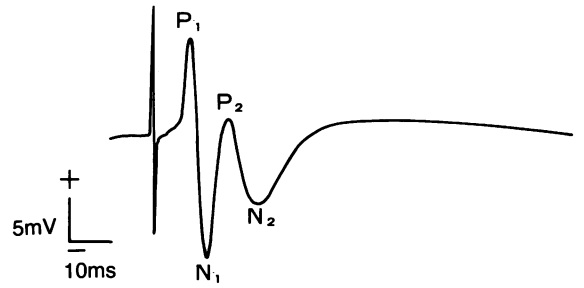

Fig. 1 — Typical example of SEP elicited by upper lip stimulation in a normal rat.

the triggering automatically after 200 responses. Before midazolam injection, it was confirmed that SEPs were recorded stably three times at intervals of 10 minutes. Midazolam was injected once intraperitoneally in a dose of 1.25, 2.5 or 5.0 mg/kg. Physiological saline was injected as a control. Changes in SEPs were measured at intervals of 10 minutes for as long as 120 min after injection.

Results

Figure 1 shows a typical example of the averaged SEP elicited by upper lip stimulation in normal rats. In all the rats, SEPs were composed of four components in a 100 ms analysis time; referred to as P_1 (first positive wave), N_1 (first negative wave), P_2 (second positive wave), and N_2 (second negative wave). In Figure 2, a typical example of the effect of 1.25 mg/kg

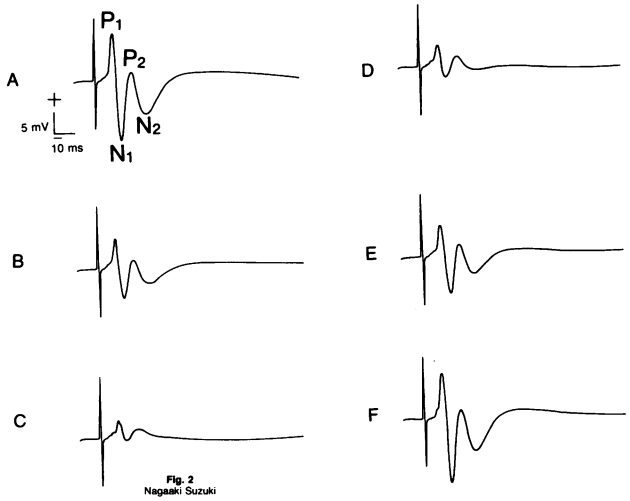

Fig. 2 — A typical example of the effect of midazolam (1.25 mg/kg, i.p.) on the contralateral SEPs elicited by upper lip stimulation. (A) control (before midasolam injection. (B) immediately after midazolam injection. (C) 10 min later. (D) 30 min later. (E) 60 min later. (F) 120 min later.

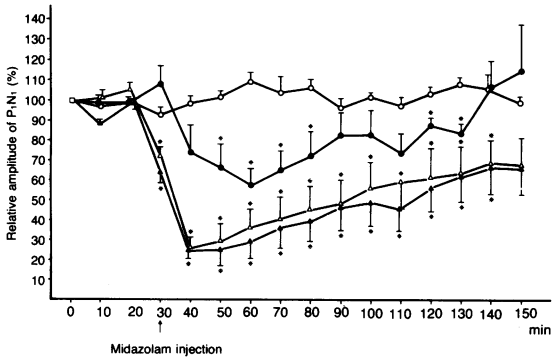

Fig. 3 — Changes in relative amplitudes of P_1N_1 waves after midazolam injection. ○: physiological saline i.p., ●: midazolam 1.25 mg/kg i.p., △: midazolam 2.5 mg/kg i.p., ▲: midazolam 5.0 mg/kg i.p. Vertical bars indicate SE. * $p<0.05$.

of midazolam is shown. Immediately after injection (B), the peak amplitude of the P_1N_1 wave was reduced significantly as compared to the control (A). The maximum effect was seen 10 min after injection (C). Gradually it recovered (D,E) and returned to the value before injection after 120 min (F). The latencies of P_1 and N_1 waves after midazolam injection were not changed significantly compared with the control. In Figure 3, the effect of midazolam on the relative amplitude of P_1N_1 is summarized from 24 experiments. Midazolam or physiological saline was injected 30 min after the start of SEP recording. The amplitudes of the P_1N_1 wave were suppressed immediately after injection. Within 10-30 min after midazolam injection, relative amplitudes of the P_1N_1 wave were suppressed 57.4±8.7% for the 1.25 mg/kg dose, 25.6±5.6% for the 2.5 mg/kg dose, and 24.6±3.9% for the 5.0 mg/kg dose, respectively. After 120 min, amplitude recovered to the control level in 1.25 mg/kg group, while the 2.5 mg/kg and 5.0 mg/kg groups did not achieve complete recovery to the control level. The latencies of P_1 and N_1 waves after midazolam injection did not change, as shown in Figure 4.

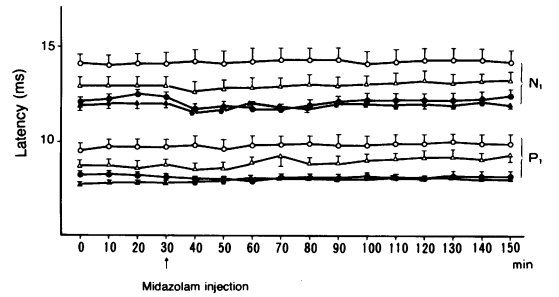

Fig. 4 — Changes in latencies of P_1 and N_1 waves after midazolam injection. Symbols are the same as in Fig. 3.

Discussion

Many dental procedures, including the administration of the local anesthetic itself, can result in moderate to severe pain. During intravenous sedation with midazolam, pain reaction following local anesthesia seems to be suppressed to some extent.[1] Moreover midazolam has good anterograde amnestic action; 26 out of 29 dental patients (89.7%) did not remember the receipt of local infiltration anesthesia prior to dental procedure.[1] These clinical observations suggest that midazolam may have a slight analgesic action due to suppression of pain perception and pain reaction.

In order to investigate the action of midazolam on the cerebral pain perception caused by noxious stimuli, somatosensory evoked potentials were recorded from the contralateral surface of the skull in the rat after midazolam injection. The SEPs consisted of early and late components as similarly shown by Toda et al.[5] In early components P_1 wave shows deep thalamocortical response and N_1 waves shows only superficial thalamocortical response.[7] Relative amplitudes and latencies of P_1 and N_1 were measured for the estimation of pain index following noxious stimuli applied to the trigeminal nerve. After midazolam injection, relative amplitudes of P_1N_1 were reduced significantly. This suggested that deep and superficial thalamocortical responses following trigeminal nerve noxious stimuli were inhibited. Latencies of P_1 and N_1 waves did not change after midazolam injection, indicating that the conduction and transmission of noxious stimuli from peripheral upper lip to contralateral cortical cells were not altered.

In conclusion, it is suggested that midazolam has a mild analgesic effect due not only to its sedative effect but also by the central suppression of pain perception following noxious stimuli.

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