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Diazepam Alters Electrical Activities of the Human Spinal Cord

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Abstract. The effects of intravenous diazepam (0.2 mg/kg) on the evoked electrospinogram recorded with an epidural electrode in the posterior epidural space of the lumbar enlargement and on the evoked electromyogram recorded with disc electrodes on the gastrocnemius muscle were studied following posterior tibial nerve stimulation in fourteen subjects. Following administration of diazepam, the amplitude of P_1, a reflection of afferent input through the dorsal root, was significantly depressed 3 min after intravenous administration. The amplitude of P_2 of EESG, a reflection of primary afferent depolarization in the spinal cord was significantly increased 10 to 30 min after administration. The amplitude of the H-reflex of the evoked electromyogram decreased significantly 3 to 30 min after administration, whereas that of the M-wave remained unchanged. These results may indicate that diazepam in the clinical doses directly affects the function of the human spinal cord.

Key Words: diazepam, evoked electrospinogram, evoked electromyogram

Introduction

Diazepam is widely used as a premedicant and an anesthetic adjuvant in anesthetic practice. The effects of diazepam on the supraspinal portion of the central nervous system have been extensively studied in both men and animals[1]. However, little is known of the effects of diazepam on the human spinal cord. Recent developments in epidural recording of the evoked electrospinogram (EESG), originally described by Shimoji, et al[2]. revealed differential effects of anesthetics on the human spinal cord. In the present study this approach was extended to determine the effects of diazepam on the human spinal cord, and it was found that diazepam affected the function of the human spinal cord.

Methods

Subjects were four volunteers and ten patients free of neurological abnormalities who underwent minor surgical operations under a combination of epidural and general anesthesia. EESG and the evoked electromyogram (EEMG) were recorded in seven and four subjects, respectively, and simultaneous recording of EESG and EEMG was made in three subjects. The age of subjects ranged from 21 to 50 years. Informed consent was obtained from all subjects. The fasting subjects arrived at a quiet operating room without premedication. The

Table 1 Changes in latencies and amplitudes of each components of EESG and EEMG after diazepam (0.2 mg/kg).

	Minutes after diazepam administration		Control Mean	Control SE	3 Mean	3 SE	5 Mean	5 SE	10 Mean	10 SE	20 Mean	20 SE	30 Mean	30 SE
EESG (n=10)	Latency (msec)	P_1	10.8	0.2	10.7	0.2	10.7	0.2	10.7	0.2	10.7	0.2	10.8	0.2
		N_1	13.9	0.5	13.8	0.5	13.9	0.5	13.9	0.5	13.9	0.5	14.0	0.5
		P_2	31.6	0.8	31.8	0.9	32.6	0.9	33.2	0.8	33.3	0.7	32.7	0.7
	Amplitude (μV)	P_1	2.4	0.5	1.9	0.4	2.3	0.5	2.2	0.5	2.2	0.5	2.2	0.5
		N_1	11.3	1.6	11.6	1.6	11.8	1.9	12.6	1.8	12.4	1.8	12.3	2.0
		P_2	7.3	0.9	7.5	0.7	8.0	0.8	8.8	1.0	8.2	1.0	8.4	1.0
	Half decay time of (msec)	P_2	11.8	1.1	12.0	1.2	11.4	1.0	11.1	1.1	12.3	1.6	13.3	1.2
EEMG (n=7)	Latency (msec)	M	11.9	1.3	11.9	0.8	11.9	0.9	11.9	1.2	11.9	0.9	11.9	2.4
		H	35.9	1.1	36.3	1.0	36.3	1.2	36.3	1.1	36.3	1.1	36.3	1.0
	Amplitude (mV)	M	7.1	2.9	9.0	4.5	9.2	5.1	10.2	5.3	11.2	5.6	11.0	5.4
		H	12.5	3.4	4.2	1.6	4.3	2.0	6.3	2.2	5.8	1.2	5.6	1.2

patients participated in the study before the start of surgery. The subjects were placed first in the lateral recumbent position for insertion of the electrodes, then in the supine position for observation. Venous cannulation was performed for the administration of Ringer's lactate solution at the rate of 2 ml/kg/hr throughout the study. According to Shimoji's method for EESG[2], a recording electrode was introduced into the dorsal epidural space between T_{11} and L_1. The electrode was a stainless steel wire 150 μm in diameter and insulated up to 5 mm of tip by a polyethylene tube. An indifferent electrode, a non-polarizable silver needle, was inserted into the adjacent supraspinous ligament. A pair of disc electrodes was attached on the skin overlying the gastrocnemius muscle, 2 cm apart, to record EEMG. The time constants for EESG and EEMG recording were 0.3 and 0.05 sec, respectively. The spontaneous electrospinogram and electromyogram were recorded on an ink-writing polygraph (Nihon Kohden Medicalcorder). Two non-polarized stimulating needle electrodes were inserted into the skin close to the posterior tibial nerve at the popliteal fossa. Square-waves, 0.5 msec in duration and with sufficient intensity to produce twitch of the gastrocnemius muscle, were generated by a constant current stimulator (Nihon Kohden, MSE-3) with an isolation unit. Stimulus intensity, about 10 V, produced submaximal H-reflex amplitude. Since EESG was so small and easily obscured by the electrocardiograph (ECG) artifacts, the stimulus was delivered after every other QRS complex of the ECG between T and P waves of the ECG. EESG and EEMG tracings were led into a computer (Nihon Kohden, ATAC-250) for averaging 20 or 30 individual responses and were plotted on an X-Y recorder. The subjects were encouraged to relax as much as possible. They had some discomfort but easily tolerated the stimulation. After two to four control recordings, a single dose of 0.2 mg/kg diazepam was administered intravenously within half a minute. Observations began 30 seconds after the administration of diazepam and continued for 30 min. Arterial blood pressure was measured by sphygmomanometry and the ECG was continuously monitored in all subjects. In six subjects, arterial blood was sampled for blood gas analysis before and 5 to 10 min after the administration of diazepam. The per cent control of latencies and amplitudes were tested by paired t-test and $P<0.05$ was considered statistically significant.

Results

Stimulation of the posterior tibial nerve produces a potential change in dorsal epidu-

ral space of the same or the adjacent segment corresponding to the nerve, as has been reported previously by Shimoji et al[3]. The potentials consist of an initially positive spike (P_1), which is sometimes not recordable, subsequent sharp negative (N_1) and slow positive (P_2) waves.

A secondary component of P_2 appears in its decaying phase (Fig. 1 and arrows in Fig. 2) when the stimulus is strong enough. The nomenclature of each component follows that of the previous reports[3]. P_2 occasionally consisted of two positive peaks. The main peak whose amplitude was measured in this study followed an early peak which probably appeared due to the difference in recording conditions. Detailed analysis of an early peak was not made in this study because its origin was considered to be the same as that of the main peak. Typical control recording and measurement of EESG and EEMG are illustrated in Fig. 1.

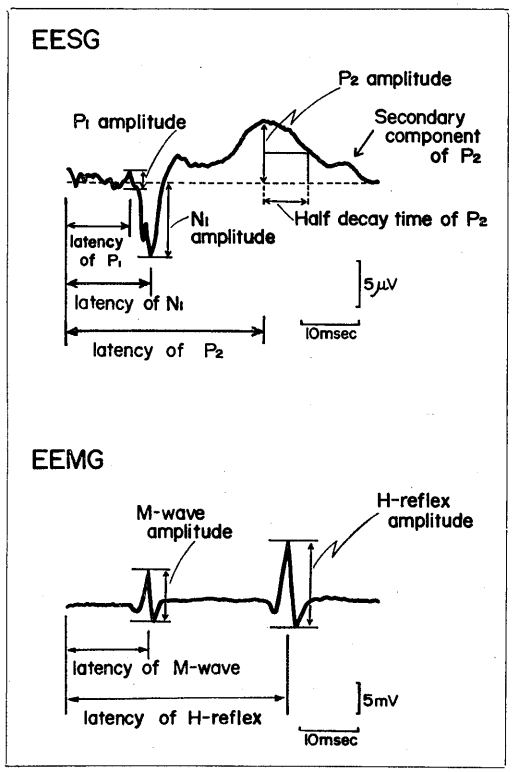

Fig. 1 Examples of evoked electrospinogram (EESG) and evoked electromyogram (EEMG) are labelled to show the nomenclature and measurements adopted. P_1, N_1 and P_2 in EESG denote the initially positive spike, the sharp negative wave, and the slow positive wave, respectively. An arrow indicates the "secondary component of P_2". Amplitudes of all components of EESG were measured from the base line except those of the spike potential (P_1) in which peak-to-peak amplitude was calculated. In EEMG, the peak-to-peak amplitude was measured. Latencies were measured from the onset of stimulus to the peak of each components (Table 1).

The changes in peak latency and amplitude of EESG and EEMG after diazepam are summarized in Table I and their per cent control are shown in Fig. 2. Large variation of individual values necessitated the statistical testing in per cent changes. Fig. 3 shows the alteration of EESG and EEMG after diazepam in a representative case. With diazepam, the amplitude of P_1 decreased significantly only at 3 min. On the other hand, the amplitude of P_2 did not change by 5 min after diazepam, but significantly increased from 10 to 30 min with prolongation of peak latency. The secondary component of P_2 was too small and variable to be quantitated, but clearly appeared in three cases of this study. This component disappeared within 3 min after diazepam and recovered to control within 30 min (Fig. 3). The latencies of M-wave and H-reflex were not affected by diazepam. The average amplitude of H-reflex was significantly reduced to about 50 per cent of control 3 to 30 min after diazepam.

All subjects went to sleep 2 to 3 min after diazepam and woke up 20 to 40 min later. Maximum decrease in systolic blood pressure averaged 91 ± 3 (mean $\pm$ S.E.) per cent of control. $PaCO_2$ levels averaged 39 ± 3.0 (mean $\pm$ S.E.) and 39 ± 2.7 mmHg before and after diazepam, respectively. PaO_2 remained above 83 mmHg in all subjects. Body tem-

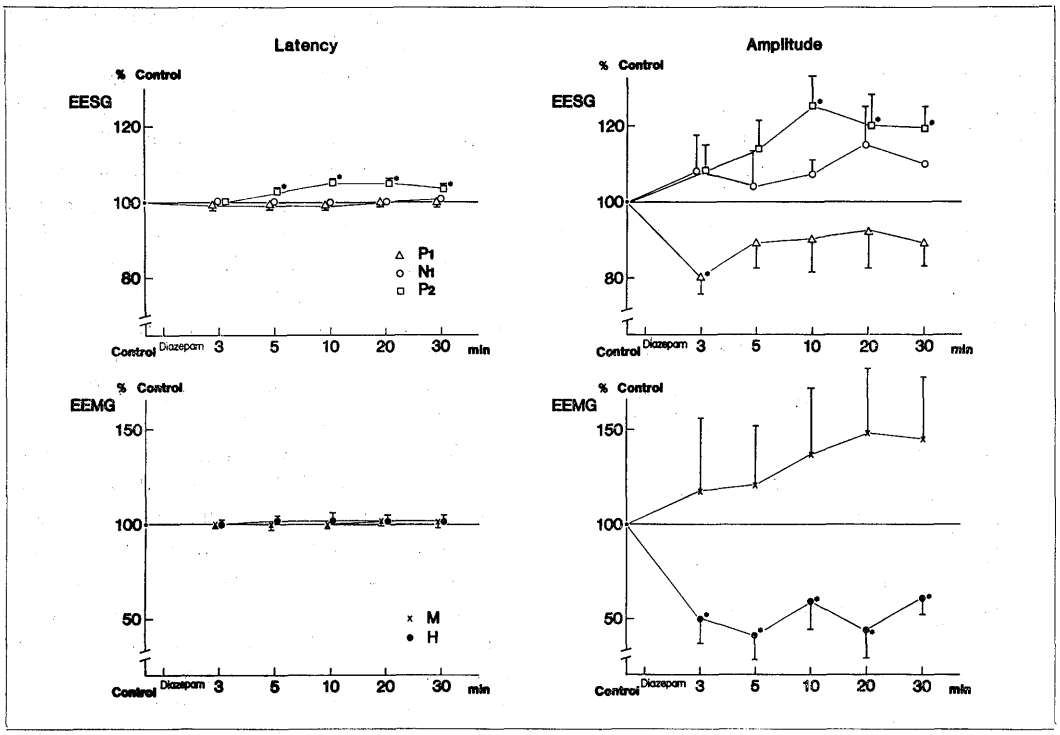

Fig. 2 Per cent control of latency and amplitude of EESG and EEMG after diazepam (0.2mg/kg). Each points represent the mean±SEM.
*Significantly different from control ($P<0.05$).

perature remained constant throughout the study.

Disscusion

In this study, diazepam transiently suppressed the amplitude of P_1 in the early stage after its administration. P_1 is thought to be the result of afferent input through the dorsal roots[3]. Therefore, the results suggest that afferent nerve conduction is transiently depressed by diazepam at the site of dorsal roots. Although N_1 has been variously interpreted by different authors, synchronous depolarization of interneurons in the spinal cord is one possible explanation[4]. N_1 has been reported enhanced by thiamylal[5], ketamine[6], N_2O-halothane anesthesia[3], but depressed by neuroleptanalgesia[6]. In contrast, diazepam did not cause any significant change in N_1 in the present study. The amplitude of P_2, however, increased significantly 10 to 30 min after the depression of P_1 had returned to control. The origin of P_2 is thought to be the same as the "P wave" recorded directly from the dorsal surface of the spinal cord in decerebrated animals, which reflected electrotonic spread of primary afferent depolarization and hence presynaptic inhibition[4,7]. There is little evidence to suggest that P_2 reflects recurrent inhibition due to antidromic discharge of motoneurones[4]. Enhancement of presynaptic inhibition as manifested by the increase in P_2-amplitude has been reported with diazepam in animals[8-10]. The result of P_2 change is in contrast to the reports that P_2 is depressed by ketamine[6], morphine[11], neuroleptanalge-

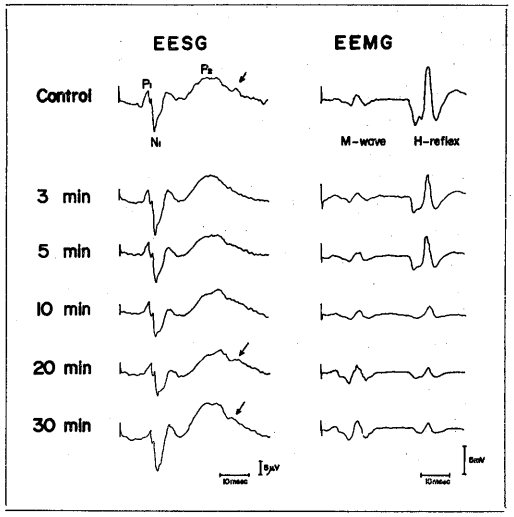

Fig. 3 Effects of diazepam on evoked electrospinogram (EESG) and evoked electromyogram (EEMG) elicited by tibial nerve stimulation. EESG and EEMG were recorded from the posterior epidural space at T_{12} vertebral level and from the gastrocnemius muscle, respectively. Arrows indicate the "secondary component of P_2". Each tracing is the average of 30 individual responses.

sia[6], N_2O-halothane[3], and deep thiamylal anesthesia[5]. The decrease in H-reflex amplitude which accompanies a decrease in inputs into the spinal cord, as demonstrated in the diminution of the P_1, indicates possible inhibition of the monosynaptic reflex arc within the spinal cord, since the M-wave remained unchanged. Depression of the H-reflex and augmentation of P_2 may indicate that the presynaptic inhibitory action prevails within the spinal cord by diazepam. Depression of the H-reflex has also been observed with neuroleptanalgesia, but it was not accompanied by an increase in P_2[6]. Thus, the effects of diazepam on the human spinal cord are different from the effects of other drugs which have been reported previously[3,5,6,11]. The secondary component disappeared after diazepam although the amplitude of P_2 was increased. The secondary component is thought to be the primary afferent depolarization caused by a feedback loop via supraspinal structures[12]. The results indicate that diazepam may also have blocking effects on the inhibitory mechanism via supraspinal structures. Similar effects on this component have been observed with barbiturate, morphine and natural sleep[11,13]. The observed changes in EESG were influenced by the action of diazepam on the supraspinal nervous structure. The slight hemodynamic change induced by diazepam is not believed responsible for its differential action on EESG and EEMG.

In conclusion, intravenous diazepam in clinical doses affects the function of the human spinal cord. The most significant findings were the increase in P_2 of EESG and the decrease in H-reflex of EEMG which suggest enhancement of presynaptic inhibition.

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