# Effect of Dimephosphon on Functional Recovery of Damaged Spinal Cord

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 141, No. 2, pp. 140-143, February, 2006
Original article submitted January 24, 2005

The effect of endolumbar dimephosphon perfusion in dogs with spinal cord contusion was studied by means of transcranial magnetic stimulation and stimulation electromyography. Treatment with dimephosphon contributed to preservation of conduction function of the spinal cord and decrease in excitability of spinal motoneurons in the perifocal zone.

**Key Words:** *spinal cord trauma; dimephosphon; transcranial magnetic stimulation; electromyography*

The incidence of spinal cord injury is very high. It should be emphasized that trauma of the first lumbar vertebra constitutes 40% of these disorders. High disability rate in these patients requires the search for new effective therapeutic methods and development of potent drugs. Dimephosphon is used in the therapy of various diseases. This drug exhibits neurotropic and cerebroprotective properties, produces an anticonvulsant effect, and stimulates electrical activity of the cortex. Previous studies showed that dimephosphon reduces local cerebral blood flow in tissues adjacent to the site of brain destruction [2,3,7].

Here we studied the effect of dimephosphon on functional recovery after experimental spinal cord injury.

## MATERIALS AND METHODS

Experiments were performed on 30 outbred dogs. Conduction in descending spinal nerves was studied before and after spinal cord injury by means of transcranial magnetic stimulation (TCMS). The state of sacrolumbar motoneurons was studied by the method of stimulation electromyography. Motor responses of the right and left anterior tibial muscle (ATM) were recorded during TCMS of the motor cortex using a Neirotest complex (transcranial magnetic stimulator and computer analyzer). The study was conducted using a Medikor electromyograph. Stimulation needle electrodes were introduced into the area of projection of the tibial nerve in the right and left popliteal space. Recording electrodes were fixed in the quadrate plantar muscles (QPM). Motor and reflex responses of QPM were recorded. Post-tetanic potentiation (PTP) of a QPM reflex response after high-frequency stimulation of the tibial nerve served as an additional criterion for the state of motoneurons [1,10].

Open vertebrospinal trauma was modeled at the level of the first lumbar vertebra. Laminectomy of the first lumbar vertebra was conducted under ketamine anesthesia. The dura mater remained intact. Spinal cord trauma was modeled according to a modified method [8]. A small metal cylinder (20 g) served as the traumatizing agent. The cylinder fell down in a sterile metal tube (length 20 cm) placed perpendicularly to the spinal cord. This tube was put on the roots of arches of the first lumbar ver-

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0007-4888/06/1412-0181 

tebra remaining after laminectomy. The weight and the tube were removed immediately after stroke. The optimum dose of the test drug was estimated empirically in 10 dogs. During endolumbar perfusion dimephosphon was administered in an optimal concentration of 2.5%. Group 1 dogs ($n$=10) with open vertebrospinal trauma did not receive dimephosphon. The wound was sewed tightly. The effect of dimephosphon on functional recovery of the spinal cord was studied in group 2 dogs ($n$=10). Wound hemostasis was performed before endolumbar perfusion of the drug. A chlorovinyl catheter was brought to the dura mater at the site of trauma. One end of the catheter was placed above the area of spinal cord contusion. Another end of the catheter passed through paravertebral muscles and was sewed to the skin. The outer end of the catheter was closed with a sterile cork. Dimephosphon (1 ml, 2.5% solution) was administered over 10 days. The state of motoneurons and spinal conduction were studied 1, 3, 7, 14, 21, 30, and 45 days after surgery. The results were analyzed using standard methods [6]. Histological examination of the spinal cord was performed at the level of injury under a light microscope (×20, hematoxylin and eosin staining).

## RESULTS

Motor responses of ATM in control animals before surgery were observed 18.3±0.7 msec after TCMS. The stimulation threshold was 78.7±3.0% of the stimulator output (4 T, Fig. 1). Reflex and motor responses of QPM in these animals were recorded upon stimulation of the tibial nerve. We found no asymmetric reactions to TCMS and stimulation of the right and left tibial nerve. The threshold of the reflex response varied from 1 to 35 V (7.8±2.6 V). This parameter was excluded from further analysis because of high variability. The maximum amplitudes of the reflex response and motor responses were 1.35±0.20 mV and 4.0±0.5 mV, respectively. The ratio between the maximum amplitudes of reflex and motor responses was 39±6% (Fig. 2). Study of PTP revealed typical changes in the amplitude of QPM reflex response (Fig. 3).

Group 1 animals survived for 3-30 days after surgery, and developed serious paraplegia or paralysis of the lower extremities. The response of ATM to TCMS was not observed 1 day after the incidence of spinal cord trauma, as well as in the follow-up period. The amplitude of the QPM reflex response underwent various changes after surgery. The mean amplitude decreased slightly compared to the control. The ratio between the maximum amplitudes in operated dogs was higher than in control animals. This parameter peaked on day 14 after surgery (83%, $p$<0.05), and returned to normal by the 30th day (Fig. 2). We revealed characteristic variations in PTP of QPM reflex response in animals of this group. However, potentiation of the reflex response in these dogs was more significant compared to control animals. The exception was day 7 of the posttraumatic period. The degree of potentiation was maximum on day 14 after trauma (Fig. 3).

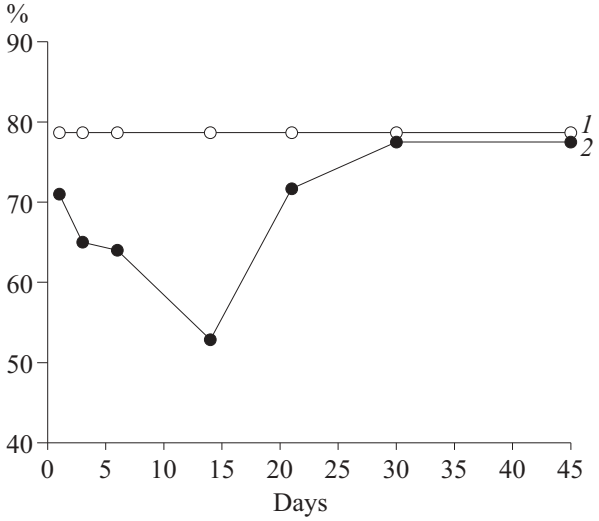


**Fig. 1.** Threshold for the motor response of the anterior tibial muscle to transcranial magnetic stimulation. Control (*1*), group 2 (*2*).

The severity of neurological deficit was much lower in experimental animals. Locomotor disturbances were not revealed during the postoperation period. On day 1 after trauma TCMS produced the motor response of ATM in 90% dogs. It should be emphasized that the strength of stimulation was

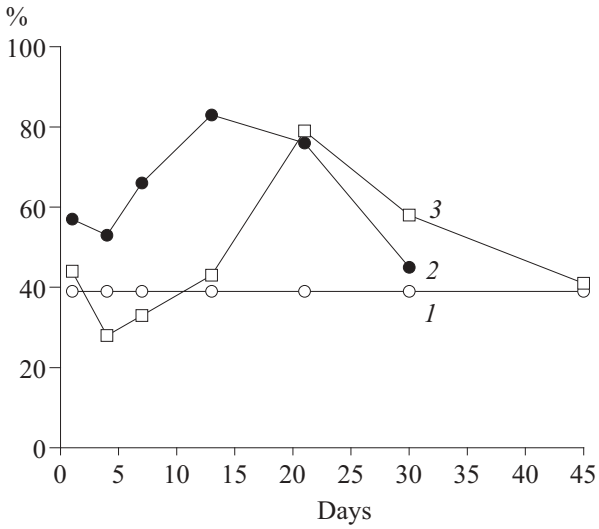


**Fig. 2.** Ratio between the maximum amplitudes of reflex and motor responses in the quadrate plantar muscle. Here and in Fig. 3: control (*1*); groups 1 (*2*) and 2 (*3*).

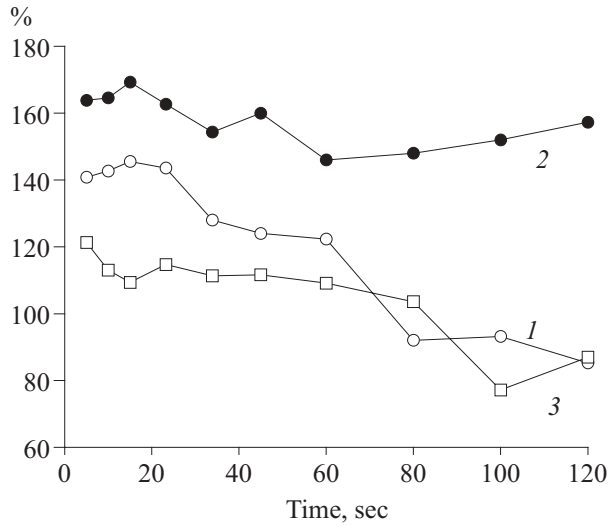


**Fig. 3.** Posttetanic potentiation of reflex responses in the quadrate plantar muscle.

71% of the stimulator output. The stimulation threshold decreased most significantly on day 14 after trauma (53%, $p<0.01$). By the 30th day this parameter approached the preoperation level (Fig. 1). On day 1 after surgery the ratio between the maximum amplitudes was 44% higher compared to the control. This parameter decreased to 28% on days 3-4, but increased in the follow-up period. The ratio between the maximum amplitudes was 43 and 79% on days 14 and 21 after trauma, respectively ($p<0.01$). This parameter decreased to the control level in the follow-up period (Fig. 2). Potentiation of the reflex response to high-frequency tetanization in experimental dogs was less pronounced compared to group 1 animals and control specimens. The minimum and maximum values of potentiation were observed on days 14 and 21, respectively (Fig. 3).

Histological examination revealed edema of the brain tissue and focal hemorrhage in group 1 animals. Necrosis of nerve cells was found in the area of contusion. The severity of brain tissue edema in group 2 animals decreased on day 7. Spinal neurons were characterized by insignificant dystrophic changes.

Our results show that treatment with dimephosphon contributes to preservation and/or recovery of the descending impulse conduction through the zone of the trauma. This effect is probably associated with vasoprotective and antiedemic activity of the drug [2,3,7]. The decrease in the threshold of motor responses in ATM to TCMS can be related to an increase in excitability of cortical neurons and/or spinal motoneurons. In animals receiving dimephosphon the minimum threshold for motor responses of ATM to TCMS was observed on day 14 after trauma. In this period the ratio between the maximum amplitudes of reflex and motor responses and PTP of a QPM reflex response were lower or approached the control level. Therefore, the decrease in the threshold of TCMS is mainly associated with the posttraumatic increase in excitability of cortical neurons (phenomenon of secondary generator) [4,5]. It cannot be excluded that the drug produces a direct stimulatory effect on the cortex [2,3,7].

Excitability of QPM motoneurons decreased in animals receiving dimephosphon. It should be emphasized that excitability of motoneurons progressively increased and peaked on day 21 after discontinuation of the drug. However, excitability of QPM motoneurons in untreated dogs was above the control level at different terms of the study. This parameter was maximum on day 14. The effect of dimephosphon was probably related to its protective activity. Excitability of QPM motoneurons decreased during the recovery of conduction through the zone of trauma. It can be hypothesized that these changes were primarily related to supraspinal influences. These influences should not be neglected. The presence of the excitation focus in the cortex (*e.g.*, secondary generator) can shift the balance between the descending influences on segmentary centers. It is difficult to evaluate specific features of a modified balance. Damage to the central nervous system is mediated by a variety of anatomical and physiological factors [9]. Intravenous infusion of dimephosphon (2.5%, 10 ml, 4 times a day) can be used in the treatment of patients with the acute stage of spinal trauma.

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