The Effects of Nicardipine Given after 10-minutes Complete Global Cerebral Ischemia on Neurologic Recovery in Dogs

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The effect of nicardipine (NC) on neurologic recovery from ischemic insult after 10-minutes complete global cerebral ischemia was evaluated in dogs by examination of neurologic recovery score (NRS: complete recovery = 100, death = 0). Ischemia was achieved by occlusion of ascending aorta, and NC, 10 $\mu g \cdot kg^{-1}$ in bolus followed by infusion of 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 2 hours, was administered immediately after re-establishment of circulation. The mortality at 7th day was 2/9 in the control (C) and 1/9 in the NC group (ns). NRS on 2nd day was 52.3 $\pm$ 6.8 in the C and 70.6 $\pm$ 6.5 in the NC ($P < 0.05$), but that on 7th day did not differ between the two groups. The numbers of dogs recovered to over 80 in NRS on the 2nd day was 1/9 in the C and 5/9 in the NC ($P < 0.05$), but that on the 7th day increased to 3/9 in the C and remained at 5/9 in the NC (ns). These results suggest that NC accelerates the early neurologic recovery from ischemic damage, but influences little the final outcome. (Key words: nicardipine, cerebral ischemia, neurologic recovery)

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Since calcium ion (Ca^{2+}) which is excessively accumulated intracellularly is considered to be a major factor contributing to final cellular death after ischemia[1–3], calcium channel blockers (CCBs), which reduce Ca^{2+} entry into cells, have been extensively studied as drugs for cerebral resuscitation. A beneficial effect of nimodipine (NM), flunarizine (FL) and lidoflazine (LF) on neurological recovery from ischemic insult have been reported in experimental animals[4–7]. Two reports of trials using NM in humans have recently appeared. The open trial by Roines et al.[8] suggested the efficacy of NM for cerebral resuscitation, but the randomized blind trial by Forsman et al. did not reveal any potential benefits[9].

Nicardipine (NC), known to be a CCB with a potential vasodilatative effect on cerebral vessels, has been demonstrated to prevent the development of post-ischemic cerebral hypoperfusion when given after ischemia[10]. Since post-ischemic hypoperfusion may be one of the contributing factors influencing post-ischemic neurologic recovery, NC treatment may have a beneficial effect on neurologic recovery. NC administration after ischemia ameliorated brain damage which was produced by incomplete forcal ischemia, forebrain ischemia, in the rat[11]. However, the

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Table 1. Neurologic recovery score (NRS)

Consciousness: 0–15
normal=0, clouded=5, stuporous=10, comatose=15
Respiration: 0–15
normal=0, slight abnormal=5, severe abnormal=10, on ventilator=15
Cranial Nerve Response: 0–16
pupil size=0–2, light reflex=0–2, corneal reflex=0–2, eyelid reflex=0–2, eye position=0–2, facial sensation=0–2, auditory response=0–2, gag reflex=0–2
Motor and Sensory Response: 0–6
muscle tone=0–2, pain response=0–2, body position=0–2
Behavior: 0–8
cleaning=0–2, feeding=0–2, drinking=0–2, sitting=0–2
Gait: 0–20
normal=0, able to walk but with a little ataxia=2.5, able to walk with ataxia and paresis=5, unable to walk but able to stand=10, unable to stand=15, absent of purposeful movement=20

NRS = 80 − sum of above score / 80 × 100
(0 = death, 100 = normal)

effect of NC on global cerebral ischemia has not been reported.

We, therefore, evaluated the efficacy of NC as a drug for cerebral resuscitation by examining neurologic recovery after 10-min of complete global cerebral ischemia in dogs.

Methods and Materials

Eighteen mongrel dogs of either sex (10.6 ± 1.5 Kg: SDM) were divided into two groups, 9 in the control group (C group) and 9 in the nicardipine group (NC group). Dogs were intubated following intravenous injection of thiopental (25 mg·kg^{-1}) and ventilated by a volume limited animal ventilator (R60, AIKA) with 100% oxygen to maintain Pa_{CO_2} at 35–40 mmHg, with continuous monitoring of endoexpiratory CO_2 (Hewllet Packard 78356A). Following this, anesthesia was maintained by 1% halothane with pancuronium bromide for muscle paralysis.

Following left thoracotomy, tapes were placed around the inferior and superior caval veins, and the ascending aorta for occlusion of these vessels. A femoral artery was cannulated for direct measurement of systemic blood pressure with a pressure transducer (Statham P23ID). Lactated Ringer's solution was infused at a speed of 8 ml·kg^{-1}·hr^{-1} before resuscitation and 10 ml·kg^{-1}·hr^{-1} after resuscitation through a cannulated femoral vein. After completion of this procedure the concentration of halothane was lowered to and maintained at 0.3% throughout the study. Esophageal temperature was kept around 37°C using a warming blanket as necessary.

Complete global cerebral ischemia for 10 min was achieved by occluding the inferior caval vein, the ascending aorta and the superior caval vein in this order by tightening of the tapes. During occlusion of the great vessels, the heart was protected by cooling with ice water placed in the pericardial cavity. The heart beat continuously during the 10 min of occlusion, but at a slow rate. By drawing out ice water and loosening the tapes, systemic circulation was re-established. Immediately after untightening the tapes, 1 mg of ethyl phenylephrine (Effortil®) and 1 ml·kg^{-1} of $NaHCO_3$ were injected. Systemic blood pressure rose quickly due to this procedure. This rise followed by transient hypertension over 180 mmHg of systolic pressure and then gradually returned to and remained at the

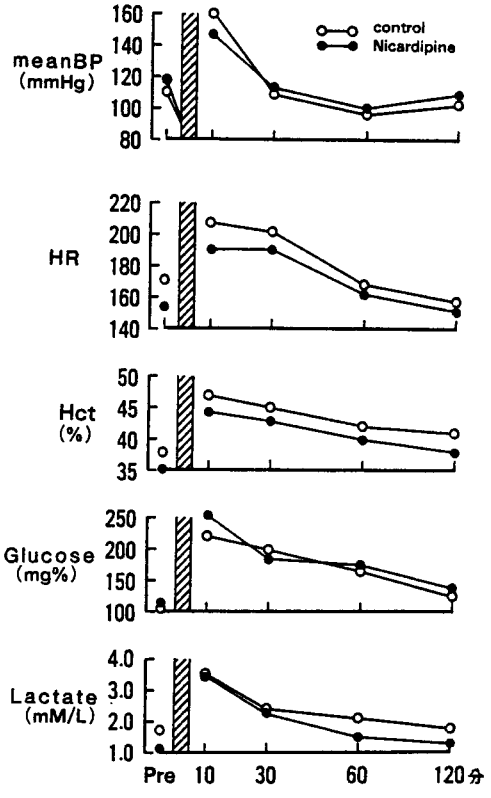

Fig. 1. Changes in mean blood pressure (mean Bp), heart rate (HR), hematocrit (Hct) and serum glucose and lactate concentrations following 10-minutes global cerebral ischemia.

pre-ischemic level.

Nicardipine (NC) was injected in bolus at a dose of 10 $\mu g \cdot kg^{-1}$ after re-establishment of circulation, usually during the hypertensive period, and then infused continuously at a rate of 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the next 2 hr in the NC group. In the control group, NC was not administered.

Blood pressure, heart rate, hematocrit, and serum glucose and lactate concentrations were measured before ischemia, 10, 30, 60 and 120 min after re-establishment of circulation. Two hours after re-establishment of circulation, the opened chest was closed and the dog was allowed to recover from anesthesia by discontinuation of halothane-inhalation and by administration of neostigmine. Two grams of sodium fosfomycin was injected as an antibiotic. When blood gas showed a normal respiratory state under spontaneous respiration, the dogs were extubated.

The dogs were brought to a special observation cage and observed for 7 days. Electrolyte solution (a half concentration of lactated Ringer's solution with 5% glucose) was continuously infused (4 $ml \cdot kg^{-1} \cdot hr^{-1}$) with an infusion pump until the dogs could drink and eat. Neurologic recovery was evaluated by examination of scores (neurologic recovery score: NRS) (table 1) every day at about 5 p.m.

Statistical analysis was made by Student's t test or X^2 test. P values less than 0.05 were assumed to be a significant difference.

Results

Esophageal temperature before cerebral ischemia was 37.3 ± 0.3°C in the control group (C group) and 37.4 ± 0.3°C (SDM) in the nicardipine group (NC group). There were no significant differences between the two groups.

Mean blood pressure (mBP) rose quickly to over 150 mmHg immediately after re-establishment of circulation, then gradually decreased and was remained at over 100 mmHg for the next 120 min (fig. 1). Increased heart rate (HR) after ischemia returned to the pre-ischemic level within 60 min (fig. 1). The hematocrit (Hct) increased after ischemia and remained at a higher level for the next 120 min. There were no significant differences in mBP, HR and Hct between the C and NC groups (fig. 1). Serum glucose concentration increased to 218 ± 20.3 mg% (SEM) at 10 min after ischemia from the value of 103.8 ± 5.3 mg% during the pre-ischemic period in the C group ($P < 0.01$), and to 252.0 ± 28.5 mg% from 113.6 ± 10.6 mg% in the NC group ($P < 0.01$) (fig. 1). Serum lactate concentration also increased to 3.48 ± 0.37 mM at 10 min from the pre-ischemic value of 1.73 ± 0.22 mM (SEM) in the C group ($P < 0.001$), and to 3.37 ± 0.30 from 1.13 ± 0.33 in the NC group ($P < 0.001$). Glucose and lactate concentrations returned to the pre-ischemic level within 90 min after ischemia in both groups

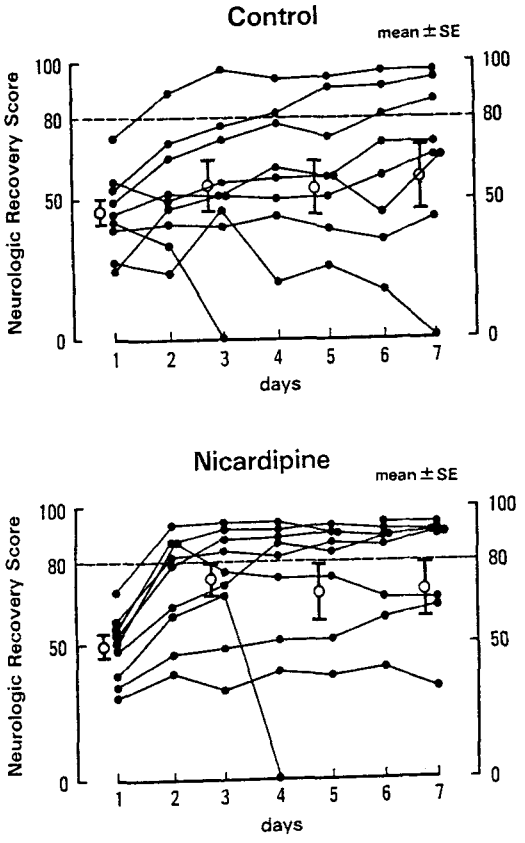

Fig. 2. Changes in neurologic recovery score for 7 days in the control and nicardipine groups. Open circles are mean ± SE.

(fig. 1). There were no significant differences between the C and NC groups in changes in glucose and lactate concentrations.

The mortality of the C group and the NC group at 7th day were 2/9 and 1/9, respectively, with no significant differences between the two groups. Changes in neurologic recovery score (NRS) are illustrated in figure 2. There were no significant differences in mean values of NRS between the two groups, except on the 2nd day at which time NRS was 52.3 ± 6.8 (SEM) in the C group and 70.6 ± 6.5 in the NC group ($P < 0.05$). The numbers of dogs which had recovered in NRS value to over 80 on the 2nd day in the C group was 1/9, while the number in the NC group was 5/9 ($P < 0.05$). On the 7th day, however, the number of dogs which had recovered to over 80 was 3/9 in the C

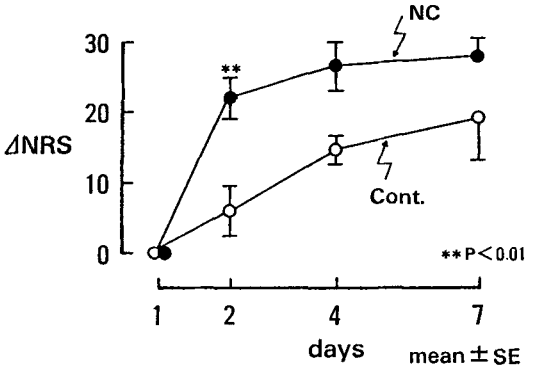

Fig. 3. Changes in neurologic recovery score (NRS) from the first day to the second, the 4th and the 7th day.

NC = the nicardipine group, Cont = the control group. **: $P < 0.01$ vs the control group.

group and 5/9 in the NC group; there was no significant difference between the two groups. The slope of mean NRS from the first day to the 2nd day in the NC group (22.0 ± 3.0: SEM) was steeper than that in the C group (5.9 ± 3.4) ($P < 0.01$) (fig. 3).

Discussion

Nicardipine (NC) given for 2 hr after recovery from complete cerebral ischemia accelerated neurological recovery during the early period after ischemia, namely, the 2nd and the 3rd day, as demonstrated by the better neurologic recovery score (NRS), the higher number of dogs which had recovered to over 80 in NRS, and the steeper slope of NRS during the early period in the NC group. The mortality and NRS on the 7th day after ischemia, however, did not differ between the two groups. These results suggest that NC treatment affects the speed of neurologic recovery from ischemic insult, but that it does not influence the final outcome.

We have reported that NC given after ischemia prevents the development of post-ischemic cerebral hypoperfusion[10]. The contribution of cerebral blood flow (CBF) to the recovery from neurologic damage produced by ischemic insult has been controversial. Beneficial effects of nimodipine (NM)[4] and lidoflazine (LF)[12] on neurological recovery were accompanied by an improvement of

CBF after ischemia, but the effect of flunarizine (FL) on CBF was various[6,13].

In experimental animals including a dog, a rat and a primate, NM, LF and FL have been reported to improve the mortality and the neurological outcome when given after complete cerebral ischemia, although the improvement was not dramatic[4–7]. Verapamil had no positive effect[14]. Recently two clinical trials have been carried out using NM on patients after cardiac arrest. The open clinical trial by Roines et al. suggested the efficacy of NM on cerebral resuscitation[8]. The blind and randomized trial by Forsman et al., however, did not demonstrate any amelioration in neurologic recovery and mortality by NM, although CBF was two times higher and incidences of arrhythmia were less in the NM-treated group[9]. These authors stated their intention to continue the trial employing increasing trial numbers and higher dose of NM.

The use of CCBs for purposes of cerebral resuscitation after ischemia is based upon the hypothesis that excessively increased intracellular Ca^{2+} ischemia may be the main trigger inducing cellular damage or death after ischemia[1–3,15]. The increase in Ca^{2+} in cells activates phospholipase A, which in turn accelerates the production of thromboxine (TX) and leukotriene (LT) through an arachidonic acid cascade accompanied by a release of oxygen free radicals (FR). Proteolytic enzymes are also activated by the increased Ca^{2+}. The extensively accumulated Ca^{2+} in mitochondria (MTC) inhibits ATP production in MTC, and MTC in a hypoxic state releases FR through the electron transport system. These products and changes destroy cellular structures and deteriorate their functions, then induce cell death. Furthermore, the increased Ca^{2+}, TX and LT may mediate cerebral vasospasm, which further precipitates cerebral ischemia. Therefore, the prevention of Ca^{2+} accumulation in cells may be essential for the treatment of cerebral ischemia. Intracellular Ca^{2+} concentration is regulated by a calcium channel, a calcium pump and a Na^{+}-Ca^{2+} exchange system. If ischemia induced intracellular Ca^{2+} accumulation is attributed mainly to the dysfunction of the latter two systems, the blocking of a calcium channel by CCB may not be effective in preventing Ca^{2+} accumulation. Hodani et al., however, demonstrated that NC treatment after ischemia reduced Ca^{2+} accumulation in cells of the ischemic area[16], suggesting some contributions of calcium channels to the ischemia mediated these changes.

Factors which may influence neurologic recovery after ischemia, such as body temperature, blood pressure, hematocrit, serum glucose and lactate concentrations, did not differ between the treated and the untreated groups at pre- and post-ischemic periods in this study. Thus, the acceleration of early recovery mediated by NC may be due to the direct effect of NC on ischemic cells, not to any indirect effects through these factors. The improvement of CBF may be the another factor which contributes to the beneficial effects.

One possible reason why there was no distinct difference in the final neurologic outcome between the two groups may be the better neurologic recovery in the C group, which makes the difference insignificant between the two groups. The other possibility may simply be that NC is ineffective when administered in this manner. We, therefore, are now carrying out further study in which more severe ischemic insult is employed, i.e., 15-minute ischemia, and in which NC is administered for a longer period, i.e., 3 days.

In conclusion, NC given after ischemia accelerated early recovery of neurologic damage induced by 10-minute ischemia, but did not influence the final neurologic outcome in dogs.

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References

1. White BC, Winegar CD, Wilson RF, Hoehner PJ, Tromboley JH: Possible role of calcium blockers in cerebral resuscitation: A review of the literature and synthesis of future studies. Crit Care Med 11:202–207, 1983
2. Siesji BK: Cerebral circulation and metabolism. J Neurosurg 60:883–908, 1984

3. Baethmann A, Jansen M: Possible role of calcium entry blockers in brain protection. Eur Neurol 25:suppl. 1, 102–114, 1986
4. Steen PA, Newberg LA, Milde JH, Michenfelder JD: Cerebral blood flow and neurologic outcome when nimodipine is given after complete cerebral ischemia in the dog. J Cereb Blood Flow Metab 4:82–87, 1984
5. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL, Michenfelder JD: Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 62:406–414, 1985
6. Desphande JK, Wieloch T: Flunarizine, a calcium entry blocker, ameliorates ischemic brain damage in the rat. Anesthesiology 64:214–224, 1986
7. Vaagenes P, Cantadore R, Safar P, Moossy J, Rao G, Diven W, Alexander H, Stezoski W: Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. Crit Care Med 12:846–855, 1984
8. Roine R, Kaste M, Kinnunen A, Nikki P: Safety and efficacy of nimodipine in resuscitation of patients outside hospital. Brit Med J 294:20, 1987
9. Forsman M, Aarseth HP, Nordby HK, Skulberg A, Steen PA: Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: Correlation with neurologic outcome. Anesth Analg 68:436–443, 1989
10. Iwatsuki N, Ono K, Koga Y, Amaha K: Prevention of postischemic hypoperfusion after canine cardiac arrest by nicardipine. Crit Care Med 15:313–317, 1987
11. Grotta J, Spydell J, Pettigrew C, Ostrow P, Hunter D: The effect of nicardipine on neuronal function following ischemia. Stroke 17:213–219, 1986
12. White BC, Winegar CD, Wilson RF, Krause GS: Calcium blockers in cerebral resuscitation. J Trauma 23:788–794, 1983
13. White BC, Gadzinski DS, Hoehner PJ, Krome C, Hoehner T, White JD, Trombley JH: Effect of flunarizine on canine cerebral cortical blood flow and vascular resistance post cardiac arrest. Ann Emerg Med 11:119–126, 1982
14. Vaagenes P, Cantadore R, Safar P, Alexander H: The effect of lidoflazine and verapamil on neurological outcome after 10 minutes ventricular fibrillation. Crit Care Med 12:228, 1984
15. Siesjo BK: Calcium and ischemic brain damage. Eur Neurol 25:suppl. 1, 45–56, 1986