Thesis Title Effect of Nimodipine on Attenuation of Neuronal Damage in Global Cerebral Ischemia.

Name Punnee Jitkhatonyu

Degree Master of Science (Physiology)

Thesis Supervisory Committee

Kanokwan Tilokskulchai, B.Sc.(Pharm.), Ph.D.

Niphon Poungvarin, M.D.,M.M.Sc.(Newcastle U), F.R.C.P.(Lond)

Tumptip Sangruchi, M.D.

Date of Graduation 23 May B.E. 2537(1994)

ABSTRACT

Background and Purpose: Ischemic insults to the brain in stroke or traumatic brain injury produce excessive entry of Ca^{2+} into ischemic cell. Increasing cytosolic Ca^{2+} in ischemic cells seem to play a central role in all of the mechanisms leading to ischemic cell deaths. Hence, the calcium entry blocker or calcium channel antagonist is recommended as potential therapeutic agent for treatment of acute cerebral ischemia. *Nimodipine*, a 1,4 dihydropyridine calcium entry blocker was tested in rats after global cerebral ischemia. The purpose of this experiment is to study the effect of nimodipine posttreatment on ischemic cell damage. **Methods:** Sprague Dawley rats were subjected to 30 minutes of forebrain ischemia by clamping both common carotid arteries and maintaining mean arterial blood pressure at 60-80 mmHg before occlusion. Rats were devided into five groups.

at 60-80 mmHg before occlusion. Rats were devided into five groups. Shamp-operated group I was only exposed by surgical procedures. Untreated ischemic group II was subjected to global cerebral ischemia with no medication. Animals in treated-ischemic group III received a single dose of nimodipine 1 mg/kg i.p.immediately after recirculation, in treated ischemic group IV received three doses of nimodipine 1 mg/kg intraperitoneally and subcutaneously at 0, 1, 24 hours after recirculation, and rats in treated ischemic group V were administered with nimodipine 1 mg/kg intraperitoneally and subcutaneously at 1, 3, 24 hours after recirculation. Histopathology of the brain was evaluated at 7 days after ischemia. The incidence of neuronal damage of all the brains were examined by light microscopy. Standardized histopathological examinations were performed by a examiner blinded to the animals therapy. **Results:** Estimation of the ischemic damaged cells in frontal and parietal areas were expressed as a percentage of the number of dead cells. There was significant reduction in the amount of ischemic dead cells in the frontal area of postischemic nimodipine-treatment groups(group III = 6.14±1.39, group IV = 6.78±1.42 and group V = 4.79±1.43 %) compared with the untreated group(group II = 27.62±8.33 %)(ANOVA;$p<0.05$). However, In parietal area, the percentage of cell deaths in the three nimodipine treated groups III-V(3.87±2.25, 3.22±0.73, 3.88±0.99 %) were less than the untreated ischemic group(8.05±3.91), but not statistically significant difference. These results demonstrate no difference in efficacy of the reduction of ischemic cell death between one dose and repeated doses of nimodipine given after cerebral ischemia. Indeed, examination of mortality among three treated-ischemic groups, the lowest mortality was found in group V. This

result may indicate the beneficial effect of nimodipine given at 1 hour after brain reperfusion. **Conclusion:** The observation that nimodipine could improve ischemic brain damage and mortality outcome was, therefore, of great interest. First, this suggests that nimodipine may be a useful therapeutic agent in situation of global cerebral ischemia when administered with optimal dose and at proper time in relation to the stage of recirculation. Second, this also suggests that the delayed post-ischemic hypoperfusion state does cause further neurologic damage. Since, an improve cerebral blood flow during this period was the only apparent effect of nimodipine in the present study. Although, other effects that were not looked for cannot be excluded.