Title: NIMODIPINE, PENTOBARBITAL AND SURVIVAL TIME IN HYPOXIC MICE

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Introduction: The human central nervous system utilizes 20% of resting body oxygen uptake, although it comprises less than 2% of body weight. A deficit in oxygen supply to the brain, or hypoxia, is one of the most hazardous conditions to proper functioning of cerebral tissue.

A variety of hypoxic models have been used to evaluate the protective effect of different pharmacologic agents (1,2,3,4). The aim of this study was to examine the influence of isopropyl (2 methoxyethyl, 1-methylethyl ester)1,4-dihydor-2,6-demethyl-4-(3-nitrophenyl)-3,5-pyridinedycarboxylate (nimodipine, Bay e 9736) alone and in combination with pentobarbital on survival time in hypoxic mice.

Methods: Male Swiss white mice (25-35g) were randomly divided into groups. Control animals were injected intraperitoneally with 0.9% saline. Treatment groups (N10-40) received injections with the following test agents: pentobarbital (50mg/kg), nimodipine (1mg/kg), and pentobarbital plus nimodipine. Nimodipine was dissolved using polyethylene glycol 400. Since nimodipine is sensitive to light, solution was prepared under light from sodium vapour lamps, placed in amber glass containers, and the infusing syringes were wrapped in aluminum foil. Twenty minutes after the injection, the mice were placed in one of two liter airtight flow-through double wall glass chambers (two mice per chamber) controlling temperature with water jacket circulation at 37 degrees Centigrade. A continuous flow of 4 liters/min. of a commercial mixture of 5% O_2 - 95% N_2 was used monitoring the O_2 concentrations with a Beckman oxygen analyzer. The survival time (ST) was defined as the interval between the introduction of the hypoxic mice mixture and the last respiratory effort. The data were subjected to analysis of variance and student's t-test.

Results: The oxygen concentration within the chambers was at 5.0 $\pm$ 0.1% in all experiments.

The mean survival time (± SEM) for control mice was 3.64 + 0.21 min. (Table 1). Survival time in pentobarbital treated mice and in nimodipine treated animals significantly increased as compared to controls receiving only saline (p 0.05). However, combined pentobarbital plus nimodipine injected mice do not live significantly longer than control mice.

Discussion: This study demonstrates that pentobarbital and nimodipine alone provide protection against lethal hypoxic hypoxia in intact normothermic mice. Our data confirms previous observations that pentobarbital improves cerebral energy balance and thus prolongs survival during hypoxia (3). A positive effect of a calcium antagonist, nimodipine, on cerebral blood flow in baboons, has been reported (5). The drug was also recommended for patients after subarachnoid hemorrhage as a preventive measure to reduce occurrance of cerebral arterial spasm (6). The results of our experiment seem to confirm the notion that nimodipine prolongs the survival of mice under hypoxic conditions possibly by improving cerebral blood flow. However, the combination of pentobarbital with nimodipine failed to provide a functional protection against severe hypoxic insult in the intact mice.

Table

Survival time in mice injected with saline, pentobarbital, nimodipine and nimodipine with pentobarbital

Treatment	Survival time mean ± (SEM) (min)
Saline	3.64 ± 0.21
Pentobarbital (50 mg/kg)	6.26 ± 0.43[1]
Nimodipine (1 mg/kg)	5.91 ± 0.38[1]
Nimodipine (1 mg/kg) and Pentobarbital (50 mg/kg)	4.09 ± 0.29[2]

[1]Significant from control ($p < 0.05$)
[2]Not significant from control

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