CIRCADIAN VARIATIONS IN THE ACUTE TOXICITY OF AMITRIPTYLINE IN MICE

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SUMMARY : In this study, chronotoxicity of amitriptyline, a widely used antidepressant drug, was studied in mice. A significant circadian rhythm of acute toxicity was demonstrated when the drug administered at different times of day. The highest mortality was found when amitriptyline was injected at 23^{00}, and the lowest at 11^{00}. The results indicate that susceptibility and/or resistance to amitriptyline varies with the administration time.

Key Words : Circadian Rhythms, Acute Toxicity, Amitriptyline, Mice

INTRODUCTION

It is well known that many biochemical and physiological events within the organism, such as the activity of enzymes or the number of receptors, fluctuate regularly throughout the day(Wisser and Breuer,1981). As a result of this rhythmicity, the effects of many drugs, as well as toxic ones, can vary dramatically as a function of the time of day (Scheving et al.,1974; Smolensky and D'Alonzo,1988). Amitriptyline is an important and widely used antidepressant drug with prominent toxic effects due to its antimuscarinic and sedative properties. In clinical practice, it is usually given in single daily doses rather than divided doses. Therefore, the present study was undertaken to determine whether circadian variation in the acute toxicity occurred in mice.

MATERIALS AND METHODS

Animals : The experiments were performed on six groups of 10 local bred male mice(28-34 g). They were given food and water ad libitum , and were synchronized by maintaining under controlled environmental conditions at least two weeks prior to study. The lightening regimen was 12 hours of light and 12 hours of darkness (lights on 08^{00} - 20^{00}) with a light intensity of approximately 100 lux. This standardized light-dark cycle acts as an entraining agent of the circadian rhythmicity(Burns,1982). After two weeks of such synchronization, the biology of each animal is approximated to the biology of entire experimental group.

Experimental protocol : Animals were injected intraperitoneally in a volume of 5 ml/kg with a single 100 mg/kg dose of amitriptyline at one of the following hours : 03^{00}, 07^{00}, 11^{00}, 15^{00}, 19^{00} and 23^{00}. Amitriptyline was dissolved in %0.9 NaCl. A photosafe red bulb was used to allow visualization and injection of the mice during the dark. Animals were checked hourly for 24 hours after receiving amitriptyline and time of death was recorded. Most

deaths occurred within the first hour after treatment. Acute toxicity of amitriptyline was determined as mortality in 24 hours after injection. Results were analyzed statistically by chi-square test.

RESULTS

The 24-hour mortality rates after a single intraperitoneal injection of amitriptyline is shown in figure 1. The lowest mortality (20%) was found when amitriptyline injected at 11^{00} (three hours after lights on) and the highest (100%) at 23^{00} (15 hours after lights on). We have also found that there is a secondary peak in mortality at 07^{00}. Mice treated at 11^{00} were more resistant to amitriptyline than those of the other injection times. The highest and lowest mortality rates were found to be significantly different ($p<0.01$).

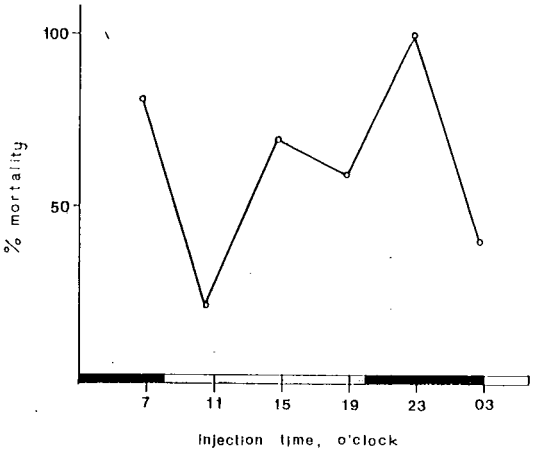

Fig 1 : The relationship between the administration time and 24-hour mortality rate in mice that have received 100 mg/kg amitriptyline.

DISCUSSION

Chronotoxicological investigations were usually performed in mice and rats of same strain, sex, and age after they had been synchronized in a standardized light-dark cycle usually consisting of an alternation of 12 hours of light and 12 hours of darkness. In contrast to man, rodents such as mice are active during darkness and rest during light. It is reported that there is good correlation between animal and human data of many drugs when this 12-hour difference in the activity pattern of rodents and humans is taken into consideration (Turek,1987).

Circadian variations in many of the biological and physiological functions have been demonstrated in mammalian organism. One of the expected results of this rhythmic phenomenon is the variations in the behavior of the organism to the same stimulus when applied at different times of day. In accordance with this biorhythmicity, circadian variations in toxicity have been demonstrated for several drugs, including phenylbutazone(Labrecque et al.1983), diazepam (Ross et al.1981), beta adrenoceptor blockers (Fujimura et al.1986), anticancer drugs (Mormont et al.1989), aminoglycosides and heavy metals (Cal et al.1989), and local anaesthetics (Lutsch and Morris,1967; Bruguerolle and Prat,1988).

Despite being an important antidepressant drug, no attention has been paid to the circadian rhythmic state of the patient when doses and protocols of amitriptyline are selected for therapy. Correlation of plasma concentration of amitriptyline with therapeutic response (Ziegler et al.1976) and time-dependent changes in its pharmacokinetics (Nakano and Hollister,1983) have also been reported. It is determined that in man, who were synchronized with diurnal activity and nocturnal rest; mean drug concentrations were higher when the same dose of the drug was administered in the morning (09^{00}) than in the evening (21^{00}) (Nakano and Hollister,1983). The results of the present study indicate that the acute toxicity of amitriptyline in mice varies with the administration time and is also more pronounced when the drug is applied a few hours after the beginning of the rest period.

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