Nigerian Journal of Pharmaceutical Research
Vol. 5 No. 1 pp 1-4 (September, 2006)

A COMPARATIVE EVALUATION OF PENTAZOCINE AND DIPYRONE ON DIAZEPAM-INDUCED SLEEP IN MICE

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Abstract
This work reports on the evaluation of pentazocine and dipyrone analgesics on diazepam-induced sleep in mice. Diazepam (10 mg/kg) administered intraperitoneally (ip) was used to determine the onset and duration of sleep in mice and the mean of both set values were calculated and recorded. Pentazocine 20, 30 and 50 mg/kg administered (ip) was found to significantly decrease the onset of diazepam (10 mg/kg) induced sleep dose dependently (P<0.001) while lower doses of 5, 10 and 15 mg/kg had no significant effect on the onset of sleep. Doses ranging from 15-50 mg/kg were found to significantly increase the duration of sleep dose dependently (P<0.001). However, 5 and 10 mg/kg produced no significant effect on duration of sleep. On the other hand, dipyrone (5-50 mg/kg) significantly increased the onset of diazepam-induced sleep (P<0.002, P<0.001). A15-50 mg/kg of dipyrone significantly decreased duration of sleep with increase in dose (P<0.001). Lower doses (5 and 10 mg/kg) of this drug did not produce any significant effect on sleep duration in mice. It is concluded that pentazocine potentiates diazepam-induced sleep while dipyrone antagonizes diazepam-induced sleep in mice dose dependently by decreasing its duration.

Keywords: *Pentazocine; dipyrone; diazepam; sleep*

INTRODUCTION

Sleep is a recurrent, reversible condition of muscular inertia and reduced sensory activity to the environment (Bowman and Rand, 1984). It is characterized by cyclical electroencephalographic (EEG) and eye movement changes. Measures of these characteristics are used to describe sleep stages because they are convenient and seem to correlate with the fundamental physiological changes in neurotransmitters (noradrenaline, dopamine serotonin, acetylcholine) functions that are inaccessible to measurement in clinical situations (Bowman and Rand, 1984).

Drugs which affet sleep include sedatives and hypnotics. Sedative drugs (for example diazepam) decrease activity, moderates excitement and calm an individual while a hypnotic (e.g phenobarbitone) produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep in EEG character and from which the recipient may easily be aroused. With most of the current drugs, both sedative and hypnotic actions occur (Gennaoro *et al.*,

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ISSN 0189-8434 © 2006 NAPA

1995).

Pain is a subjective and multidimensional experience comprising several components, sensory, affective and cognitive. Analgesics are agents that relieve pain threshold (i.e point at which individual begins to perceive a stimulus as painful) without disturbing consciousness or altering other sensory modalities. They are broadly classified as:

a. Opioid analgesics,(e.g morphine, pentazocine) and
b. Non-opioid analgesics(e.g aspirin and dipyrone).

The present study is aimed at evaluating the effect of pentazocine, (an opioid analgesic) and dipyrone (a non-opioid analgesic) on diazepam induced sleep in mice.

MATERIALS AND METHOD

Animals

Swiss albino mice of either sex (19-23 g) were obtained from the Animal House, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, where they were inbred locally. They were kept in the laboratory at room temperature ($27\pm1^{o}C$) and fed on balanced diet and portable water *ad libitum*.

Drugs

Pentazocine and diazepam were obtained from Ranbaxy (Thailand) and Roche Pharmaceutical (England) respectively.

Methods

The mice were divided into three group: A, B, C.

Group A: Treatment with diazepam

Four mice (two of either sex) were used in this group. Each mouse received 10 mg/kg of diazepam intraperitoneally (i.p). They were placed in separate cages for observation.

Group B: Treatment of pentazocine and diazepam

The mice were divided into six subgroups of four mice each (two of either sex). Each mouse in subgroups I, II, III, IV, V and VI received 5, 10, 15, 20, 30 and 50 mg/kg pentazocine (ip) respectively. Thirty minutes after pentazocine administraion the mice were injected with 10mg/kg of diazepam (ip) and placed in separate cages for observation.

Group C: Treatment with dipyrone and diazepam

In this group, mice were also divided into six subgroups I, II, III, IV, V and VI of four mice each (two of either sex). Each mouse in the subgroups was injected with 5, 10, 15, 20, 30 and 50 mg/kg dipyrone (ip) respectively. Thirty minutes after dipyrone administration, the mice were injected with 10 mg/kg diazepam (ip) and placed in separate cages for observation.

In all the groups (A, B and C), the onset and duration of sleep for each animal were recorded by means of stop-clock. The criteria for sleep were loss of righting reflex (Miya *et al*., 1973). The interval between loss and recovery of righting reflex was used as the index of hypnotic effect (duration of sleep) (Fujimori and Cobb, 1965).

Statistical analysis

The onset and duration of sleep were expressed as Mean±SEM.The mean value of control groups were compared to the mean value of groups treated with drugs using student *t*-test. Results were considered significant at $P<0.05$.

RESULTS AND DISCUSSION

Effect of Diazepam in Mice

The results showed that (diazepam 10 mg/kg) produced sleep in all the mice used (Figs. 1, 2, 3 and 4), due to depressant effect of the drug on the central nervous system (CNS) as a benzodiazepine. Benzodiazepines are believed to exert at least some of their actions via GABA, which is the main inhibitory neurotransmitter in the mammalian brain. The benzodiazepines are reported to potentiate GABA-mediated, inhibitory

neurotransmission. Neurophysiological and biochemical evidence indicates that a GABA-benzodiazepine-chloride ionophore comprises a supramolecular structure. Therefore, an interaction between a benzodiazepine and its receptors stimulates GABA-receptor, activates chloride channels and increases inhibition of neurotransmission (Gennarn *et al*., 1995). This effect is responsible for the loss of righting reflex. Thus, diazepam decreases sleep latency, increases total sleep time and also decrease the number of awakenings by increasing the awakening threshold.

Effect of pentazocine on diazepam induced Sleep in Mice

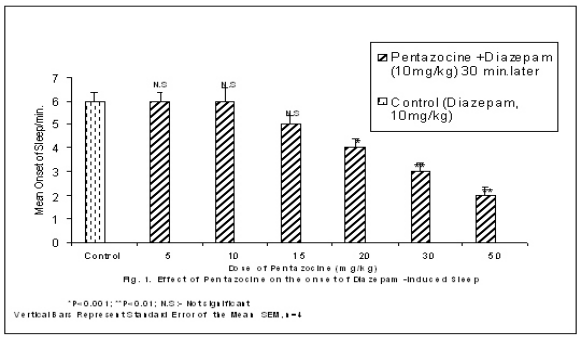
Results showed that 5-15 mg/kg pentazocine produced insignificant effect on the onset of diazepam-induced sleep while 5 and 10 mg/kg of pentazocine produced insignificant effect on the duration of diazepam-induced sleep. However, 20-50 mg/kg of this drug produced significant decrease ($P<0.01$, $P<0.001$) in the onset of diazepam-induced sleep, while 15-50 mg/kg petazocine produced significant increase ($P<0.01$, $P<0.001$) in duration of diazepam induced sleep (Fig. 1 and 3). Pentazocine appears to decrease the onset and increase the duration of diazepam-induced sleep dose-dependently. This effect could be due to additive sedative effect of pentazocine with diazepam.

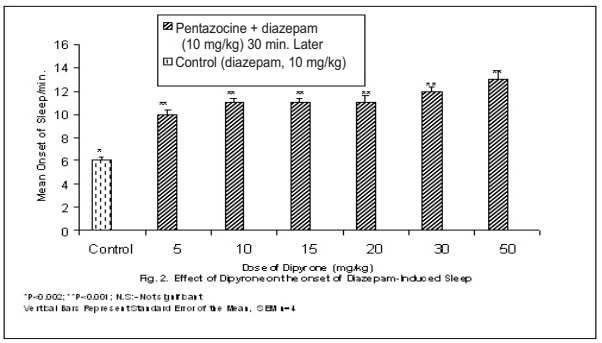
Pentazocine an opioid analgesic is a *kappa* agonist with weak *mu* antagonist or partial agonist properties. The principal effects of the opioid analgesics which have affinity for *mu* receptors are on the CNS. More important effects include; sedation, euphoria, analgesic and respiratory depression (Katzung, 1998). The opioid analgesics (e,g pentazocine) interact with other CNS depressants based on their pharmacological and kinetic mechanisms, thus, when used with sedative-hypnotic drugs such as diazepam, there may be intensification of their overlapping actions, i.e. additive CNS depressant effect (Corrigan,, 1976). Drowsiness and clouding of mentality are frequent concomitants of opioid actions. Sleep is induced by opiates more frequently in erderly than the young healthy individuals. Ordinarily, the patient can be easily aroused from sleep. However, the combination of morphine-like opioids (e.g pentazocine) with other CNS depressant drugs(e.g diazepam) may result in very deep sleep (Katzung, 1998). This was confirmed in the present work.

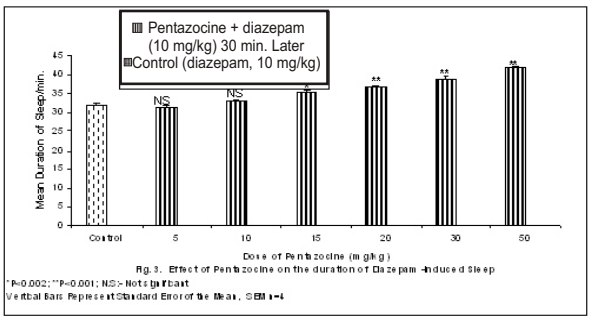
Effect of Dipyrone on Diazepam-induced Sleep in Mice

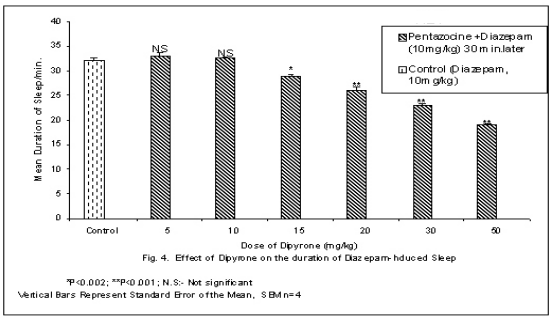
Results showed that 5-50 mg/kg dipyrone produced significant increase ($P<0.002$, $P<0.001$) in the onset of diazepam-induced sleep, while 5 and 10 mg/kg of dipyrone produced insignificant effect on the duration of diazepam-induced sleep. However, 15, 20, 30 and 50 mg/kg of dipyrone produced significant increase ($P<0.01$, $P<0.001$) in the duration of diazepam-induced sleep. Dipyrone appears to increase the onset and decrease the duration of diazepam-induced sleep dose dependently (Fig 2 and 4). This effect could be due to intense pain at the site of injection of dipyrone which antagonizes the sedative effect of diazepam.

Dipyrone, a non-opioid analgesic is reported to induce intense pain, local tissue necrosis and thromboplebitis at the site of injection (Bapna and Dandiya, 1977). Pain results in continual activation of the ascending reticular formation by the collaterals from the second-order neurones carrying the pain impulses to the thalamus causing insomnia (Bowman and Rand, 1984). The activity of the ascending reticular formation (the wake system) is increased by strong sensory stimuli such as pain passing to it by way of collaterals from the second-order sensory neurones and by this, it alerts the cortex and maintain wakefulness (Bowman and Rand, 1984). Thus, pain can be considered as a strong stimulant and may counteract the persisting effect of sedative drugs. This is the case observed in this work with dipyrone in diazepam- induced sleep.









Conclusion

From the results obtained in this work, it can be concluded that pentazocine potentiates diazepam-induced sleep in mice dose-dependently. The interaction between pentazocine and diazepam could be be an additive pharmacodynamic phenomena, since both drugs have CNS depressant properties. On the other hand, it is concluded that dipyrone antagonizes diazepam-induced sleep in mice dose-dependently. The interaction between dipyrone and diazepam is an antagonistic pharmacodynamic phenomenon, since dipyrone may produce pain at the site of injection which can be considered as a strong stimulant and this antagonized the CNS-depressant effect of diazepam.

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