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Preliminary Study on the Effect of Acute Imipramine Treatment on Harmaline Induced Tremors in Rats

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Abstract: Recent experimental and clinical studies clearly suggest the role of neurotranmitters like serotonin, gamma amino butyric acid, norepinephrine, dopamine and glutamic acid in the pathogenesis of tremors. The present study was undertaken to investigate the effect of imipramine, a tricyclic anti depressant drug that inhibits the reuptake of serotonin and norepinephrine, on harmaline induced tremors in rats. Four groups of wistar albino rats weighing 100 +/- grams were injected with harmaline (10 mg kg^{-1}, intraperitoneally) for inducing experimental tremor. The animals in groups 2, 3 and 4 were orally administered imipramine in prophylactic form at doses of 30, 60 and 90 mg kg^{-1} respectively, half an hour before harmaline administration. The rats in the group 1, however, served as control and received only water. The latency of onset, intensity or amplitude and the duration of tremor were recorded. Random electromyography readings demonstrated the significant increase in amplitude of tremors in imipramine treated rats. Imipramine was found to have a significant exacerbating effect on the duration of tremor in a dose dependent manner. The amplitude of tremor also showed dose dependant augmentation. This study clearly suggests the harmful effects of imipramine on harmaline induced tremors and warrants the need for more clinical studies on the possibilities of administering imipramine in patients with essential tremor.

Key words: Essential tremor, imipramine, harmaline, serotonin, rats

INTRODUCTION

Essential Tremor (ET) is the most common and least understood neurological disorder in adults. The prevalence of ET is generally greater than that of stroke, Alzheimer's disease, migraine and lumbar-sacral pain syndromes (Kurtzke,1982). The incidence of ET increases with advancing age but it is fairly common in all age groups and almost equal in both genders (Rautakorpi *et al*., 1982). Although ET is viewed as a benign problem, almost all patients with ET are disabled to some extent (e.g., Difficulty with or inability to perform daily activities such as writing, feeding or dressing.) around 15% are sufficiently motorically impaired due to continuous high amplitude shaking that they are unable to continue to work (Bain *et al*., 1994). The path physiology of ET, unfortunately, is poorly understood, but there is strong evidence that tremors are caused by a disturbance in the concentration of various neurotransmitters in the brain. Calcium and potassium imbalances are also believed to play a role in tremor generation (Elbe,1998, 1996). Gamma Amino Butyric Acid (GABA) and serotonin (5HT) have also been implicated. Experimental studies using GABA receptor agonists have clearly suggested its role in tremor path physiology (Tariq *et al*., 2001). In spite of the availability of several drugs, only a few medications are currently used in the treatment of ET. Drugs acting on the central nervous system like ethanol, propranolol (a beta adrenergic blocker) and primidone (a sedative and anti convulsant of the barbiturate group) are the drugs of choice for the management of ET (Paul *et al*., 1998). Other drugs include benzodiazepines, ethanol, botulinum toxin, adenosine agonists etc. However, chronic use of these drugs is often restricted due to unacceptable side effects. Data on drug interactions of many drugs acting on the CNS is scarce and there is very little existing information in the form of both clinical and experimental studies on side effects of drugs acting on the CNS on patients with neurological complaints. Neuropharmacologic literature on contra-indications of tricyclic anti depressants (imipramine, amitryptiline, doxepine etc.) was very little. Limitations of concomitant or single use of certain drugs in patients with tremor remains a big challenge for neuroscientists and clinical neurologists, as toxicology

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and neuro-pharmacology research on the neurological side effects of imipramine is limited. Agonists and antagonists of the various neurotransmitters have different effects on tremors. Imipramine, a tricyclic antidepressant, is known to inhibit the reuptake of 5HT and NE. There is a growing interest in the role of 5HT in cerebellar tremor. Serotonin is a known neurotransmitter in the cerebellum and has been shown to have a modulatory effect on the Purkinje cells (Strahlendorf *et al*., 1986). Serotoninergic disturbances have been seen in the cerebrospinal fluids of Freidrich's ataxia. L-5 hydroxy tryptophan, a precursor of serotonin, was reported to have limited beneficial effects in cerebellar syndromes (Rascol *et al*., 1981). Anti tremor effects of serotoninergic reuptake inhibitor, trazodone was also reported (Guan and Peroutka, 1990). However, the notion that serotoninergic drugs possess anti tremor activity cannot be generalized (Tariq *et al*., 2001). The hypothesis for this study, was based on the following facts. 5HT and NE imbalance in the brain are responsible for generating essential tremors (Sugihara *et al*., 1995). 5HT and NE reuptake are both affected by imipramine. Imipramine reuptake inhibition for NE is moderate and 5HT is moderate compared to other tric cyclic antidepressants which have either high, low or none degrees of reuptake inhibition. So, it was hypothesized that imipramine must have an effect on tremors considering the common neurotransmitters it shares with those considered to be the ones responsible for generating ET. Harmaline was used to induce tremors in rats. Harmaline, is an alkoloid obtained from *Peganum harmala* L. (Zygophyllaceae) and is classified under the alkaloid class of β-carbolines (Mahmoudian *et al*., 2002). The toxicity produced by harmaline causes syndromes that predominate the nervous system; the first signs are excitability followed by muscular trembling and stiffness, an uneasy staggering gait and accelerated breathing (Mahmoudian *et al*., 2002).

MATERIALS AND METHODS

The acute study was carried out on Wistar albino rats weighing 100-120 g. Six rats were placed in 4 groups each. The rats were fed on Purina chow diet with free access to water under room temperature and standard lighting condition (12 h light and 12 h dark). The first group served as a control group where harmaline alone was injected intraperitoneally. In the next 3 groups imipramine was prophylactically given orally in the doses 30, 60 and 90 mg kg^{-1}. After 30 min of imipramine administration harmaline was injected in the last 3 groups. The time of onset of tremor was noted for each rat. The intensity or amplitude of tremor was also noted after every interval of 10 min. The tremor intensity was graded according to the score given by (Tariq *et al*., 2001, 2002). Score '1' indicates a very low intensity and intermitten tremor. Score '2' indicates a medium intensity and intermitten tremor. Score '3' indicates a low intensity and continuous tremor. Score '4' indicates a high intensity and continuous tremor. The duration of tremor in each animal was also noted. The results were statistically analyzed by student t test.

RESULTS

Tremor intensity (amplitude): Imipramine when administered prophylactically was found to increase the intensity or amplitude of the tremor (Fig. 1) in rats with a pre existing tremor that was experimentally induced. A dose dependent increase with reference to time elapsed was observed. Tremor intensity was graded as '4' ten min after harmaline was injected in all the 4 groups. After 60 min, the control group showed a tremor score between '2' and '3'. The group given 30 mg kg^{-1} of imipramine had a score between '3' and '4'.The other 2 groups each recorded '4'. After 120 min the control group showed average amplitude of less than '1'. The other 3 groups with Harmaline showed intensities of more than '2' until

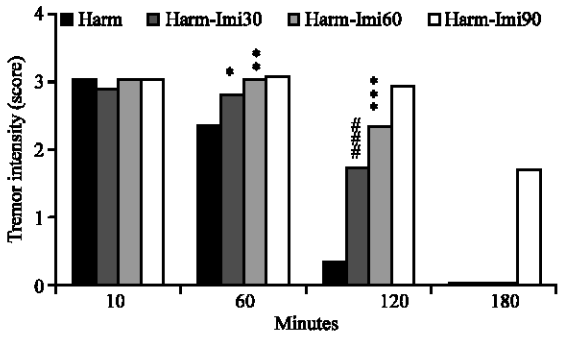

Fig. 1: The tremor intensity in the 4 groups with respect to time

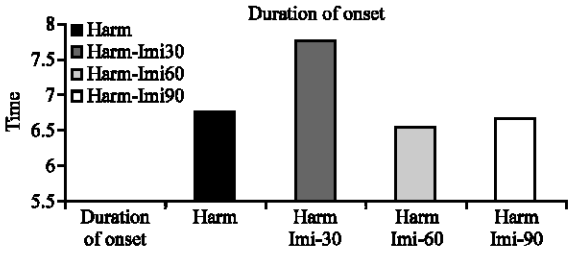

Fig. 2: The duration (in minutes) of the latency of onset of tremor after the administration of harmaline that was injected intra-peritoneally

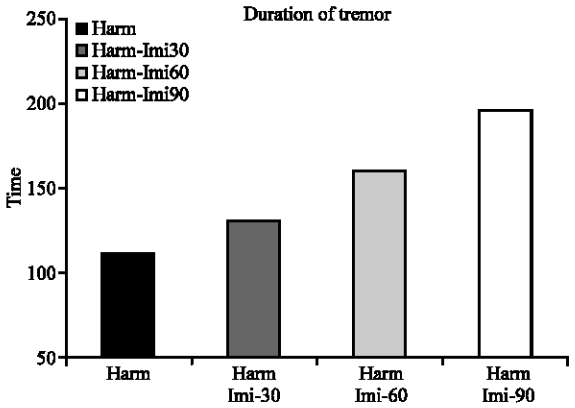

Fig. 3: The duration (in minutes) of tremor after administration of harmaline and imipramine and harmaline alone

'3.5'. After 180 min had elapsed the group 4 continued to show a tremor of score '2' while tremor had ceased in the control and groups 1 and 2. Random electro myographic recordings supported.

Duration and onset of tremor: In the onset of tremor (Fig. 2) there was no significant change in all groups though group 2 which was given 30 mg kg^{-1}, imipramine showed a slight increase in the duration of onset but no reasonable explanation was found to the unusual pattern that was seen with the increase in the duration of onset in the dosage of 30 mg kg^{-1}. The duration of tremor (Fig. 3) was an important aspect, which actually showed more precise results. The graph depicts us a dose dependent increase in the duration of tremor. The control group showed an average duration of 120 min. In rats given imipramine, 30 mg kg^{-1} tremor lasted for about 140 min. In rats that were given 60 mg kg^{-1} tremor lasted for nearly 170 min. In rats administered 90 mg kg^{-1} duration of tremor was about 200 min. We see a progressive rise in tremor duration as the dose was increased. This was the most significant data that the study provided.

DISCUSSION

Imipramine is a known inhibitor of the reuptake of serotonin in the brain. 5HT is a known neurotransmitter in the cerebellum. L-5-Hydroxytryptophan, a serotonin precursor, showed no improvement in tremor (Rascol *et al*., 1981). On the other hand, Odansetron, a 5HT antagonist, was effective in improving cerebellar tremor (Rice *et al*., 1997). This strongly suggests that 5HT concentration plays a very important role in tremor physiopathology. Therefore, we can consider that the greater the concentration of serotonin in the brain, the greater is the strength of the tremor. Imipramine showed a dose dependent augmentation of the harmaline-induced tremors. Group 2 and 3 showed a moderate exacerbation of tremor however Group 4 showed a steep rise in tremor duration and intensity. The frequency of tremor however remained similar for all 4 groups. Imipramine increases the serotonin concentration in the brain tissue. It was studied that olivary serotonin (5HT) plays an important role in harmaline induced tremor (Elbe, 1996). Transgenic mice with olivary 5HT deficiency were found to be tolerant to harmaline induced tremor (Welsh *et al*., 1998) whereas increase in olivary 5HT level was accompanied by enhanced responses to harmaline induced tremor, suggesting a direct association between olivary 5HT level and severity of harmaline induced tremor (Shuto *et al*., 1998). With all these factors in mind and the inference from the present study, we have strong evidence linking the association between ET and serotonin. We may also conclude that imipramine exacerbates pre-existing experimentally induced tremor in rats. The present study would entice us to clinically examine the effects of not only imipramine but the entire class of anti depressant drugs like tri cycylic antidepressant drugs, selective serotonin reuptake inhibitors like fluoxetine, MAO inhibitors, serotonin agonists etc. on their effects on patients with tremor and possibly other movement disorders. From the study we can also emphasize the need for a study in the toxicology and contraindication of imipramine administration in patients with known tremor such as in Parkinson's disease, thyrotoxicosis, chronic neuroleptic administration especially that of phenothiazines etc. This preliminary study serves as a prospect for further research on the role of serotonin and related drugs and compounds on the mechanisms and therapeutics of tremor. Imipramine needs to be further evaluated in chronic studies for its safety and toxicity in humans. The study is an indication for the need of further research in neuroscience for the study of tremor and drug interactions with motive of patient safety and better therapeutic strategies.

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