Effect Of Co-Administration Of Venlafaxine And Perindopril To Uninephrectomized DOCA-Salt-Treated Albino Rats.

S Kamal

Citation

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Abstract

The present study investigates the effect of combination of the antidepressant venlafaxine (serotonin/noradrenaline reuptake inhibitor, SNRI) with the angiotensin converting enzyme inhibitor perindopril on the immobility time in the forced swimming test (FST) as well as on systolic blood pressure (SBP) in uninephroctemized DOCA salt-treated rats as a model of experimental hypertension. The FST is a behavioral test used to predict the efficacy of antidepressant treatments. It has a good predictive value for antidepressant potency in humans . This is to try to provide an experimental study about the benefit of the use of perindopril as a better antihypertensive in hypertensive patients with co-morbidity like depression or anxiety.Albino rats were divided into 4 groups; Group 1 (control) uninephrectomized without DOCA injection; Group 2 was uninephrectomized and received DOCA without any treatment. Group 3 were uninephrectomized and received DOCA then venlafaxine only in a dose of 8 mg/kg i. p. 30 min. before FST; Group 4 was uninephrectomized and received DOCA then the interacting drugs before FST. SBP measurements were conducted in all groups over a period of 8 hours post-injection at 30 min. intervals. Results revealed that perindopril potentiates the anti-immobility effect of venlafaxine. Additionally, venlafaxine did not affect the anti-hypertensive effect of perindopril. Venlafaxine did not change the SBP of non-hypertensive albino rats as showed in a pilot study.These results could provide a support for the effective use of venlafaxine in association with perindopril in hypertension and depression co-morbidity.

INTRODUCTION

Despite the high prevalence of depression and hypertension, the co-administration of drugs used in treatment of the two diseases has received little attention. Depression can negatively affect the course of hypertensive illness. Additionally, the use of antidepressive agents can interfere with blood pressure control of patients with hypertension by inducing changes in blood pressure and orthostatic hypotension (Scalco et al., 2005).

Pharmacotherapy plays an important part in management of hypertension and depression--two disorders that are often concomitant and have high rates of morbidity and mortality. However, simultaneous use of agents to treat these conditions may cause serious drug interactions. Additionally, development of hypertension is one of the known complications of venlafaxine which is a serotonin/noradrenaline reuptake inhibitor, SNRI. Shrivastava and Kochar (2002) revealed that the positive blood pressure lowering effects of a concomitantly administered antihypertensive drug is mandatory to be independent from changes in the antidepressant effect of venlafaxine. Siever and Davis (1985) noted that depression seems to be characterized by a dysregulation of the noradrenergic and serotoninergic systems, which has a key role in maintenance of blood pressure. The unique mechanism of action of venlafaxine is to be a selective reuptake inhibitor of norepinephrine besides blockade of serotonin uptake (Szot et al., 1999). On the other hand, the vasoprotective effect of perindopril might be explained on the basis that the RAS plays an important role in the elevation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase and this can be effectively reversed upon perindopril treatment (Ito et al., 2002)

A review of literature demonstrated important data concerning psychotropic effects of angiotensin converting enzyme inhibitors [ACEIs]. Pharmacologic data confirm that the most lipophilic ACEIs penetrate the central nervous system and argue in favor of the role of these molecules in activating central opioides. As these data provide evidence of mood elevating effect in some patients, but also of an overall benefit in hypertensive populations. The clinical

importance of the antidepressant-like effect of ACEIs needs further investigations. Accordingly, the present study was performed to evaluate (a) the possible anti-immobility effect of perindopril, as an ACEI, and its influence when combined with venlafaxine as an antidepressant drug, (b) to elucidate the effect of venlafaxine on the hypotensive effect provoked by perindopril in hypertensive rats. The results of the present study could help in the proper selection of this ACEI as a better antihypertensive in hypertensive patients with depression as a co-morbidity.

MATERIALS AND METHODS

MATERIALS

ANIMALS

Male Albino rats, 180–200 g,.The animals were housed in standard laboratory conditions under a 12 h light/dark cycle, light on at 6 a.m., in a temperature controlled room at 21 ± 2°C, , with free access to standard food and tap water. The rats were kept four per cage.

DRUGS

Deoxycorticosterone acetate (DOCA) (Sigma chemicals co. available as powder suspended in corn oil), urethane (Sigma chemicals co.). Perindopril (Servier Laboratories, Paris, France), Venlafaxine HCl (Wyeth-Ayerst, USA). Drugs were dissolved in saline .

METHODS

DOCA-Salt Hypertension (Matsumura et al., 1999) Sixty rats were anesthetized with urethane (1 mg/kg ip), and the right kidney was removed via a right flank incision. After a 1-week recovery period, these rats were treated twice weekly with DOCA and administered subcutaneously (15 mg/kg), and 1% NaCl was added to their tap water for drinking. Two weeks after the start of DOCA-salt treatment, these rats were randomly divided into 5 groups (each group, n=12).

ANIMAL GROUPING

Group 1 (control) uninephrectomized without DOCA injection (Sham-operated group) received standard volume of 5 mL/kg body weight of saline.

Group 2 were uninephrectomized and received DOCA without any treatment.

Group 3 were uninephrectomized and received DOCA then venlafaxine only in a dose of 8 mg/kg ip 1 hour before the forced swimming test (FST) (Dawson et al., 1999). Plasma T_{max} is around 1 hour in rodents (Howell et al., 1994)

Group 4 were uninephrectomized and received DOCA then the interacting drugs. Perindopril was injected intraperitoneally, in a standard volume of 5 mL//kg body weight, 45 min. before the forced swimming test (FST) at a dose of 3 mg/kg and plasma T_{max} is in the range of 30 min to 1.5 hours (Wong et al., 1997).

Group 5 were uninephrectomized and received DOCA then the interacting drugs. The drugs were injected intraperitoneally, in a standard volume of 5 mL//kg body weight, 1 hour (for venlafaxine) and 45 minutes (for the interacting agent perindopril) before the forced swimming test (FST). Doses of both drugs are the same as used in either group 3 for venlafaxine or group 4 for perindopril.

MEASUREMENT OF IMMOBILITY IN RATS BY THE FORCED SWIMMING TEST (FST)

The FST used here was essentially the same as described in detail elsewhere (Detke et al., 1997). Swimming sessions were conducted by placing rats into individual glass cylinders (46 cm height & 20 cm diameter) containing 23-25°C water 30 cm deep, so that rats could not support themselves by touching the bottom with their paws. ,

Two training swimming sessions were conducted: an initial 15-min pretest followed 24 h later by a 5-min test. Following each swimming session, the rats were removed from the cylinders, dried with paper towels and returned to their home cages. A single observer, who was blind to the treatment conditions, did all the behavioral scoring.

The immobility is defined as floating in water without struggling, and doing only those necessary movements to keep the head above water; For each rat,the immobility time is calculated in sec. over a period of 5 minutes.

ASSESSMENT OF SYSTOLIC BLOOD PRESSURE (SBP) CHANGES

SBP was measured by a tail-cuff sphygmomanometer (UR-5000, Ueda Co, Ltd, Japan). SBP measurements were conducted in all groups over a period of 8 hours post-injection at 30 min. intervals. For each animal an average of at least three consecutive measurements was taken to reduce variability (Bunag, 1973).

ETHICS

All procedures were in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals, as well as the guidelines of the Animal

Welfare Act.

STATISTICS

For each group of rats, the mean period of immobility in sec. and the standard deviation (SD) were calculated. The effects of venlafaxine alone and in combination with perindopril on rat's behaviour in the FST and on SBP were determined by a one-way analysis of variance (ANOVA) and Dunnett's comparison test between different groups.

RESULTS

I. Effects of venlafaxine alone and in combination with perindopril on immobility time

Co-administration of venlafaxine and perindopril resulted in additive anti-immobility effects ($p<0.05$ compared to different groups). The period of immobility was significantly lesser for the combination of perindopril and venlafaxine than for the different groups ($p < 0.05$) (Figure 1).

NB. Administration of perindopril alone to this model of hypertensive albino rats in the present study did not affect their immobility time. The duration of immobility was comparable to that reported with group 2. Perindopril potentiated the anti-immobility effect in hypertensive rats only when concomitantly administered with venlafaxine.

Figure (1): Changes in the immobility time in male albino rats of the different groups: control sham-operated, uninephroctomized DOCA-salt hypertensive rats with and without treatment. Data are mean±SD from 12 animals per group.

* $p<0.05$ significant reduction in the immobility time in group 3 & 5 versus other groups.

II. Effect of venlafaxine alone and in combination with perindopril on systolic blood pressure (SBP)

The increase in SBP in uninephrocetomized DOCA-salt treated albino rats was significantly ($P< 0.05$) lowered by co-administration of perindopril and venlafaxine compared to non-treated or venlafaxine-treated hypertensive rats (group 2 & 3). The reduction in SBP in group 5 was comparable to that reduced in group 4, meaning that venlafaxine did not alter the anti-hypertensive effect of perindopril.

The mean±SD of SBP for each group remained constant all over the 8-hours period of measurement of SBP

N.B. A pilot study, done before the start of this present study, showed that no effect of venlafaxine on SBP of a control non-hypertensive group of albino rats [not exposed to uninephrectomy nor to DOCA salt treatment nor to both together]. The design of the present study is based upon the use of a model of hypertension in albino rats to demonstrate the possible interaction between both venlafaxine and perindopril when concomitantly administered to them without a possibility of induction of hypertension by the antidepressant drug.

Figure (2): Effect of venlafaxine alone and in combination with perindopril on systolic blood pressure (SBP) in different groups.

* significant ($p<0.05$) reduction in SBP in treated groups 4 & 5 with either perindopril alone or both venlafaxine and perindopril compared to hypertensive non-treated or only venlafaxine treated rats (group 2, 3).

DISCUSSION

A functional deficiency of noradrenaline or 5-hydroxytryptamine (5-HT) in the synaptic cleft was proposed as the neuronal basis of depression (Bourin et al., 2002).

Redrobe and Bourin (1998) reported that the FST has been described as particularly sensitive to drugs that enhance noradrenergic transmission. The present study revealed that venlafaxine, a SNRI, when administered alone, produced significant anti-immobility effects in the FST. On the other hand, when perindopril, an ACEI, was administered at a dose of (3 mg/kg ip), it potentiates the behavioural effect of venlafaxine.

This finding could be explained on the basis of serotonergic and adrenergic neurotransmission secondary to their re-uptake inhibition by venlafaxine, As it is a dual serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline uptake inhibitor, it has been claimed to have an onset of antidepressant action which is faster than for other comparable drugs. Acute administration of venlafaxine to rats by i.p. injection resulted in dose-dependent increases in cortical and hippocampal 5-HT levels, as measured by in vivo microdialysis, over the range 5–20 mg/kg. The effect of venlafaxine (10 mg/kg ip) was potentiated by prior administration of pindolol (10 mg/kg sc) in hippocampus but not in frontal cortex. This means that acute administration of venlafaxine at this dose, exerted a reduction in sensitivity of

presynaptic 5-HT_{1A} autoreceptors and hence it resulted in an enhancement of the release of 5-HT in selected brain areas (Gur et al., 1999). On the other hand, the present study showed a significant increase of SBP of already uninephrectomized hypertensive rats, either as control or treated with venlafaxine, although the pilot study showed no effect of venlafaxine on SBP of non-hypertensive albino rats. However, rats treated with both venlafaxine and perindopril showed significant lowering of blood pressure most probably owing to the anti-hypertensive effect of perindopril without any interference from venlafaxine. Indeed, the action of perindopril was evaluated in an experimental study using the learned helplessness paradigm. Doses of perindopril were in a range of 0.06–8 mg/kg per day and induced a reversal of escape deficits. The results support the hypothesis that ACE inhibition is a key factor in the behavioral antidepressant-like activity of perindopril (Martin et al., 1990).

Studies on the mood or the quality of life of treated hypertensive patients show ACEIs to have an euphoric-type positive effect compared to other anti-hypertensive treatments. Captopril and perindopril also act like potential antidepressants in experimental models of antidepression. Furthermore, pharmacologic data confirm that the most lipophilic ACEIs penetrate the central nervous system and argue in favor of the role of these molecules in activating central opioides (Mesure et al., 1995).

The present study showed that perindopril potentiated the anti-immobility effect of venlafaxine in the studied hypertensive albino rats. However, when administered alone to a separate group of this model, it did not show any reduction in the immobility time. This could be explained by the findings of Reardon et al (2000) that perindopril crosses the blood brain barrier and increases striatal dopamine synthesis and release and modifies the clinical features of parkinson's disease in human, which could be the same mechansim of its anti-immobility effect in albino rats. The additional serotonin and norepinephrine reuptake inhibition by venlafaxine could help in expression of an antidepressant like action of perindopril via accumulation of the biogenic amines in relevant brain areas. This possibility raises the need of a further experimental studies using the in-vivo microdialysis on these brain areas during the co-administration of venlafaxine and perindopril.

Kayak and Patil (2008) demonstrated that ACEIs as fosinopril and ramipril showed significant antidepressant activity as evidenced by a significant decrease in the duration of immobility in an experimental study using the tail suspension test (TST) in albino rats and mice while losartan showed a significant antidepressant and even an anxiolytic activity. These findings suggest that these drugs could be better antihypertensives in hypertensive patients with co-morbidity like depression or anxiety.

In conclusion, perindopril potentiates the anti-immobility effect of venlafaxine in DOCA salt induced hypertensive rats. On the other hand venlafaxine did not alter the reduction in SBP of hypertensive rats treated with perindopril. These observations can provide a suggestion that perindopril can have beneficial effect in hypertension associated with depressed mood without interference with the mechanism of action of venlafaxine as an example of SNRIs. An overall benefit in hypertensive populations could be applied if the clinical importance of the antidepressant effect of ACEIs undergoes further investigations.

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Author Information

S M Kamal
Associate professor, Pharmacology laboratory, Ain Shams University