

MODULATION OF PAIN PERCEPTION BY RAMIPRIL AND LOSARTAN IN HUMAN VOLUNTEERS

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Abstract : The angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are a well known entity and have been used in therapeutics for various indications like hypertension, myocardial infarction and CHF. However, there is a renewed interest in these compounds in terms of their effects on pain perception in animals as well as in human beings. They have yielded contradictory results, showing hyperalgesia in some studies but analgesia in others. Hence this study was undertaken to evaluate the effect of Ramipril (an ACE-I) and Losartan (an ARB) on pain perception in human volunteers using cola caps and handcuff of sphygmomanometer. A total of 30 healthy, normotensive individuals with no previous history of intake of analgesics during or 4 weeks prior to the study were selected after an informed consent. The first group received a single dose of placebo, the second group received Ramipril (2.5 mg) & the third group received Losartan (50 mg). Pain perception threshold (the point at which an individual first experiences pain) and the maximum tolerated pain were assessed using the above method. The control group showed no significant changes in pain threshold, but the group receiving either Ramipril or Losartan showed a decline in threshold for maximum tolerated pain. Only Ramipril and not Losartan decreased the pain perception threshold. Our study revealed that single dose treatment of healthy volunteers with Ramipril and Losartan may cause algesia as early as after ingestion of the first dose and further studies are needed to study their long term effects on pain perception.

Key words : angiotensin receptor blockers pain ACE inhibitors

INTRODUCTION

Pain is a very subjective phenomenon, difficult to quantify in human beings but at the same time can be an incapacitating experience if left untreated. It may be a defensive mechanism in our body, protecting

us from harmful stimuli in day today life or an early warning symptom for life threatening situations like MI, hypertension or an underlying inflammatory condition (1, 2, 3, 4). Renin angiotensin system has recently been evaluated for its varied effects on pain and its modulation has carved a

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definite niche in therapeutics with angiotensin receptor blockers (ARBs) and Angiotensin converting enzyme inhibitors (ACEIs) being used treatment various pathological states like hypertension, congestive heart failure etc. (5, 6, 7). The ACEIs, but not the ARBs inhibit the enzyme dipeptidyl carboxypeptidase which is involved in the conversion of Angiotensin I to Angiotensin II and in the degradation of kinins (like substance P and Bradykinin and various other peptides). The ACEIs thus increase the level of pain producing peptides like the Bradykinin, substances P etc (8). These kinins are capable of inducing inflammatory changes like pain, vasodilatation, and increased vascular permeability, dry cough, swelling of lips, itching and urticaria. However, some recent-studies have shown that ACEIs and ARBs play a role in modifying pain perception (9) and the results have ranged from hyperalgesia to analgesia.

MATERIAL AND METHODS

Inspired by earlier findings of RAS modulation and its effects in pain perception, this study was conducted in our department after taking a written informed consent from volunteers.

Inclusion Criteria :

The subjects included were :

1. Normotensive healthy adults aged between 25–30 years with an average weight between 50–70 kg.
2. No history of hypertension, renal disease, peripheral neuropathy or recent use of analgesics were selected for the study.

Exclusion Criteria

1. Obese individuals
2. History of recent use (within 4 weeks of study) of analgesics, ACE inhibitors, ARBs or any other long term treatment.
3. Pregnant females.
4. Individuals with gout, arthritis.
5. Extremes of age (children and elderly were not included).

Material :

Tablets of Losartan (25 mg), Ramipril (2.5 mg) and a multivitamin (placebo), were obtained from a local commercial outlet.

Method :

A double blind randomized placebo controlled trial was done in 30 human volunteers. Based on above inclusion and exclusion criteria, the volunteers were divided into 3 groups of 10 each and allotted numbers between 1 to 30.

The pain perception threshold was assessed using blood pressure instrument (the sphygmomanometer) and a cola cap (26). Though each individual acted as its own control at 0h, but in order to exclude the placebo effect of consuming a tablet on pain perception over a period of time i.e., at 0h, 2h and 4h, we included the third group which received the multivitamin tablet in our study. The multivitamin tablet acted as the positive control. The tablets were packed in similar packets (same size and colour) which were coded as A, B and C. The volunteers were asked to pick up a packet, tell us the code and the number allotted to

him/her. The number allotted to each volunteer and their respective code was noted and the corresponding readings were tabulated against their codes at 0h, 2h and 4h.

A cola-cap with smooth serrated edges was placed on the ventral aspect of the left forearm and the blood pressure cuff was wrapped around it and inflated. The point at which an individual first perceived the pain (i.e. the pain perception threshold) and the point of maximum tolerated pain, were noted in terms of mm of mercury. The pain perception threshold and threshold for maximum tolerated pain was recorded for each individual at 0h (i.e. before giving drug) 2h and 4h.

Statistical analysis

All the data were expressed as mean \pm SE and were analysed using paired t-test.

P values < 0.05 were considered significant.

RESULTS

1. In the Ramipril group, there was a significant reduction ($P < 0.05$) in pain perception threshold at 4h but not at 2h when compared to 0h values. However in the Losartan group, there were no significant change in pain perception threshold either at 2h or 4h when compared to baseline value at 0h (Table I).
2. The maximum tolerated pain threshold reduced significantly in the Losartan as well as Ramipril group at 4h when compared with 0h values. However no significant reduction was found at 2h when compared with 0h values (Table II).
3. In the Placebo treated group, no significant change in pain perception

TABLE I: Effect of Losartan and Ramipril on pain perception threshold values at 0 hour, 2 hour and 4 hour after giving the drugs as evaluated by Sphygmomanometer (B.P. Cuff) and Cola Cap method.

Time in hours	Mean \pm S.E.		
	0 hour (mmHg)	2 hour (mmHg)	4 hour (mmHg)
Control	118.2 \pm 10.20	125.6 \pm 8.78	121.6 \pm 9.49
Losartan	120.6 \pm 7.26	109.6 \pm 6.26	103.2 \pm 8.94
Ramipril	116.2 \pm 6.29	105.0 \pm 4.84	93.60 \pm 3.42*

Significant values *P value < 0.05 .

TABLE II: Effect of Losartan and Ramipril on maximum pain threshold values at 0 hour, 2 hour and 4 hour after giving the drugs as evaluated by Sphygmomanometer (B.P. Cuff) and Cola Cap method.

Time in hours	Mean \pm S.E.		
	0 hour (mmHg)	2 hour (mmHg)	4 hour (mmHg)
Control	187.40 \pm 9.84	202.2 \pm 12.27	184.8 \pm 10.95
Losartan	223.8 \pm 13.72	219.00 \pm 10.75*	195 \pm 10.23*
Ramipril	213.0 \pm 12.49	198.60 \pm 13.4*	186.8 \pm 9.79*

Significant values *P value < 0.05 .

threshold or maximum tolerated pain threshold occurred at 0h, 2h or 4h (Table I and II).

DISCUSSION

The present study indicates that Ramipril but not Losartan lowered the threshold for pain perception at 4h, while both losartan and ramipril lowered the threshold for maximum tolerated pain at 4h.

The role of renin angiotensin system in pain perception has been reported in earlier studies (9). However, pain perception is in itself a complex phenomenon which has central and peripheral components and the two have been historically found to be linked differently in their sensitivity to pain in response to renin, renin substrates (21) and angiotensin. This inspired us to study the effect of single dose administration of Losartan and Ramipril on pain perception in human beings. It has been reported earlier that hypertension is associated with reduced pain sensitivity in men and this can be antagonized by ACEIs and ARBs (11, 12, 13). The facilitation of algescic peptides, bradykinin, substance P etc. by ACEIs was the presumed etiology in these patients because kinins are known to stimulate nerve endings and produce burning pain via bradykinin type 2 i.e. B₂ receptors (15). In our study, however, losartan which does not facilitate the algescic peptides also led to hyperalgesia which has been attributed to the unopposed action of angiotensin II on AT₂ receptors, AT₁ being blocked by ARBs. Not only Angiotensin II but for the first time a study has shown that renin substrates like angiotensin I, II, III have a well defined role in periaqueductal grey matter (PAG) region (21), the region which has been earlier

identified to produce antinociception in response to the RAS peptides injected here and this antinociceptive response was blocked by saralsin (23). These observations point towards complex pain mechanisms which not only involve neurotransmitters like serotonin, but also the endogenous opiodsystem, prostaglandins, substance P, bradykinin (10). The extent of involvement of these neurotransmitters in our study, however, could not be evaluated because it remains to be determined whether the central mechanisms are activated on single dose administration of losartan and ramipril or not. Various anatomical regions of brain like area postrema and nucleus tractus solitarius (8) have been involved in pain pathways and are modulated differently by RAS, and both AT₁ and AT₂ receptors were immunolocalized in neuronal cell bodies and in the ventrolateral PAG (22). Similar reasons could have been the contributory factors in our study where both the losartan and ramipril treated groups showed hyperalgesia. It has been postulated that bradykinin B₂ receptors and AT₁ receptors heterodimerise and this process enhances angiotensin II sensitivity in pre-eclampsia patients (16). Though the functional role of AT₂ receptors in pain has been documented earlier but whether such heterodimerization of B₂ receptors also occurs with AT₂ receptors is not known. In our study, increased pain sensitivity to pain can be attributed to preferential activation of AT₂ by losartan and subsequent heterodimerization with B₂ (bradykinin 2) receptors or by other unexplored mechanisms.

A recent study suggests that AT₁ receptor blockers can cause endogenous bradykinin induced hypotension via AT₂ mediated

increase in bradykinin and NO production and losartan has been shown to increase bradykinin concentration in hypertensives (18, 19, 20). A similar increase in algescic peptides even after a single dose of losartan and ramipril seems to be the probable cause of algescia in our study with both ramipril and losartan. However, more studies with single dose of ACEIs and ARBs are needed to confirm whether hyperalgescia occurs on a single dose only or also after chronic administration of these drugs.

A further enigmatic finding associated with RAS manipulation is the difference in terms of peripheral and central stimulation of RAS. Peripheral as well as central RAS stimulation can lead to either algescia or analgesia (23).

The role of renin angiotensin system if further explored can open an entirely new field of research and perhaps an alternative way of stimulating the endogenous opioid

system without the risk of addiction or exposing an individual to pinpricks of the conventional accupuncture therapy of the Chinese origin. Both long and short term studies are needed at various stages of use of both ACEIs and ARBs. The production of algescia in an early phase of treatment can be rather beneficial in diabetics with previous history of angina or cardiovascular risk, where warning signs of an impending MI may save a patients life by converting a painless silent MI into a painful one (24, 25). Algescic effect, however, may warrant a cautious use of ACEIs in painful conditions which may worsen in presence of increased algescic peptides like in patients with cancer pain, herpes zoster and bone secondaries.

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