Original Article

Anticonvulsant activity of Nebivolol in MES induced seizures in mice

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Abstract

Background: Epilepsy is a common neurological disorder affecting a significant number of adults and children around the world. Among the commonly used drugs for epilepsy are phenytoin, phenobarbitone, sodium valproate etc. These anticonvulsants need to be taken for a long duration and most of these produce side effects, which may affect the treatment of patients with epilepsy. Hence there is a need for other drugs with fewer side effects. Beta blocker Nebivololhas been studied by few researchers for its anticonvulsant activity but there is stilla paucity of data on the effect of nebivolol as an anticonvulsant. **Objective:** The present study was undertaken to evaluate the anticonvulsant potential of nebivolol alone and in combination with phenytoin and phenobarbitone in the Maximal electroshock seizure (MES) model in mice. **Methods:** The study was conducted in the Department of Pharmacology, Topiwala National Medical College, Mumbaiover a 2 year period. Swiss Albino mice weighing between 18-30 grams and of either sex (n=36) were used for the study. Animals were randomly divided into six groups (Control, Phenytoin, Phenobarbitone, Nebivolol (NBV), NBV + Phenytoin and NBV + Phenobarbitone) according to the treatment given to each group. Maximal Electro Shock induced seizures (MES) model was used for giving the shock using electroconvulsiometer. Parameters calculated were Duration of Tonic Hind limb Extension (THE), percentage Abolition of Tonic Hind limb Extension and death incidence. One Way ANOVA with Tukey's post HOC test were used for data analysis. **Result(s)**: As compared to the control group (1% Tween 80), nebivolol (1 mg/kg), nebivolol (1 mg/kg) + phenytoin (12.5 mg/kg) and nebivolol (1 mg/kg) + phenobarbitone (5 mg/kg) caused a significant reduction in the duration of tonic hindlimb extension. In the combination groups, this effect was comparable to that obtained with phenytoin (25 mg/kg) and phenobarbitone (10 mg/kg). Standard doses of Phenytoin (25 mg/kg) and phenobarbitone (10 mg/kg) caused abolition of the tonic hindlimb extension in 50 per cent and 33.33 per cent of the animals respectively, whereas nebivolol (1 mg/kg) + sub therapeutic dose of phenytoin (12.5 mg/kg) caused abolition in 16.66 per cent of the animals. **Conclusion:** The study concludes that nebivolol possesses anticonvulsant action alone and in combination with sub therapeutic doses of phenytoin and phenobarbitone when evaluated by the maximal electroshock seizures method in mice. More research is required to ascertain the mechanism of action of nebivolol and to detect the effects of nebivolol on the cognitive and motor functions.

Keywords: Epilepsy, Anticonvulsant, MES, Nebivolol, Phenytoin, Phenobarbitone.

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INTRODUCTION

Epilepsy is a common neurological disorder affecting a significant number of adults and children around the world. It is characterized by abnormal synchronization of neurons, and the hallmarks of a seizure are hyper-excitability of neurons and hyper-synchrony of neuronal networks (Stafstrom, 2006). Different neurotransmitters and neuromodulators are known to play a significant role in the system of excitation of neurons in epilepsy (Fisher and Coyle, 1991). The most commonly believed mechanism behind the development of epilepsy is repetitive firing of neurons due to activation of the

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voltage gated sodium channels in the cerebral cortex. GABA inhibits synaptic transmission through its receptor, which when affected may lead to seizures. (McNamara, 2011). Among the commonly used drugs for epilepsy are phenytoin and phenobarbitone. Phenytoin blocks the sodium channels and has a membrane stabilizing action on the neurons while phenobarbitone causes GABA receptor mediated synaptic inhibition. But these anticonvulsants have to be taken usually for a long duration and produce side effects, which may affect the treatment of patients with epilepsy. Although a number of drugs are available seizures remain uncontrolled in more than 20% of the patients (Liao, 2005). Hence there is a need for additional anticonvulsant drugs with a fewer side effects. Also if some other drugs with anticonvulsant activity can be combined with the conventional anticonvulsants it would help in reducing their dose thus minimizing their side effects. It has been a common practice to combine anticonvulsant drugs for more effective seizure control or equivalent control with milder side effects than could be obtained from larger doses of a single drug (Guelen *et al*, 1975). Various beta-adrenergic receptor antagonists like propranolol, acebutolol, betaxolol, metoprolol and pindolol have been shown to have anticonvulsant action due to blockade of beta-1 adrenergic receptors in the brain (Luchowska *et al*, 2001). Nebivolol (NBV) a third generation Beta-1-adrenoceptor blocking agent is a racemic mixture of equal amounts of D-NBV and L-NBV (Schneider *et al*, 1990). The D isomer is a potent, highly selective and long acting Beta-1-adrenoceptor blocking agent. NBV has nitric oxide (NO) releasing property, antioxidative effect and is a highly lipophilic drug (de Groot *et al*, 2004). Because of these properties in addition to selective beta-1-adrenoceptor blocking action, it may be useful as a potential anticonvulsant. Goel *et al*, 2009 and 2011have shown that nebivolol has anticonvulsant effect when evaluated individually and in combination with lamotrigine in an experimental model of convulsions in mice. RadhaGoel *et al* 2015 report a similar beneficial effect of Nebivolol in combination with Gabapentin in increasing current electroshock seizures (ICES) and Pentylene Tetrazole (PTZ) induced seizures. However, there is still a paucity of data regarding the anticonvulsant effects of NBV and its potential to be used in supplement to standard antiepileptic agents This study was conducted to test anticonvulsant effects of nebivololalone and in combination with phenytoin and phenobarbitone by using the maximal electroshock seizures (MES) method in mice. Taking into consideration the high prevalence of epilepsy, this study may have significant clinical implications. It may also be a good treatment option for patients having comorbidities like hypertension.

MATERIAL AND METHODS

This experimental multiple dose study was conducted in Department of Pharmacology, Topiwala National Medical College and B.Y.L. Nair Hospital, Mumbai during a 2 year period. This study was approved by the Institutional Animal Ethics Committee.

Animals

Thirty six Swiss Albino mice weighing between 18-30 grams, of either sex were used for the study. They were randomly divided into six groups (n=6) and were accommodated in polypropylene cages with grill on its top. Identification was done by cage tag. Bedding of clean paddy husk was provided. Animals were fed on standard pellet diet with food and water given *ad libitum*. Water was provided in glass bottles with stainless steel sipper tubes. One week period of acclimatization was given in the Central animal house situated in the Medical College at temperature 25 º C, humidity 60 % and 12 hours light and dark cycle. Body weight of all the animals was recorded on the first day of the study and everyday thereafter for calculation of dosage to be given.

Source and dosage of chemicals and drugs

Phenytoin: Pure powder form of phenytoin sodium was obtained from ZydusCadila Pharmaceuticals Limited, Ahmedabad. It was administered in a therapeutic dos e of 25 mg per kg intraperitoneally (i.p.) in mice. It was suspended in 1 % tween 80 and administered in a volume of 0.01 ml/g body weight. Dose used was extrapolated from human dose (200-400 mg/day) and standard doses used in previous studies (Galani and Patel, 2010; McNamara, 2011). A pilot study was conducted to find the sub therapeutic dose of phenytoin sodium in which half of the therapeutic dose (12.5 mg / kg) was tested, which did not provide protection against Maximal electroshock seizure (Data not shown). This sub therapeutic dose of 12.5 mg per kg based on pilot study was used in the actual experiment.

Phenobarbitone

Pure powder form of phenobarbitone procured from Piramal healthcare Ltd, Mumbai was used. Phenobarbitone was administered in dose of 10 mg per kg intraperitoneally in mice. It was suspended in 1 % tween 80 and administered in a volume of 0.01 ml/g body weight. Dose used was extrapolated from human dose (60-180 mg/day) and standard dose used in previous studies (Hosseinzadeh and Khosravan, 2002 and McNamara, 2011). A pilot study was conducted to find the sub therapeutic dose of phenobarbitone in which half of the therapeutic dose (5 mg / kg) was tested, which did not provide protection against Maximal electroshock seizure (Data not shown). This sub therapeutic dose of 5 mg per kg based on pilot study was used in the actual experiment.

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Nebivolol: Pure powder form of nebivolol procured from Cipla Pharmaceuticals Ltd, Mumbai was used. Nebivolol was administered in dose of 1 mg per kg intraperitoneally in mice which was extrapolated from human dose (5-40 mg/day) and was also based on standard dose used in previous studies (Goel *et al*, 2009 and 2011). It was suspended in 1 % tween 80 and administered in a volume of 0.01 ml/g body weight.

Tween 80: Tween 80 was purchased from Amrutlal Bhurabhai Vora Chemical Company, Mumbai. Solution containing 1% tween 80 was freshly prepared using distilled water on the day of administration of the drug. This 1 % solution was used for suspending the drugs phenytoin, phenobarbitone and nebivolol.

Electroconvulsiometer: Electroconvulsiometer manufactured by **Bhushan electronics** was used to induce convulsions in mice. The current was delivered with the help of dial adjustments. Bilateral ear clip electrodes were used to deliver the current to mice. Current of 50 mA strength for 0.2 seconds was used to induce convulsions in mice(Pathak *et al*, 2010).The electroconvulsiometer was calibrated and its output checked.

Maximal Electro Shock induced seizures (MES) model was used for giving the shock. In this model, electrical stimulation was applied via ear electrodes with a stimulator that delivers constant current. The animals were acclimatized to the feel of the ear-clip electrodes and getting used to the new environment so that they did not resist unduly at the time of administering the electric shock. Animals were screened twenty four hours before the study for convulsion. The ears were cleaned with spirit to remove any oil film due to sebaceous gland secretions in the skin of the ear and then with saline for electric contact. Only those mice which showed positive hind limb extension response during the screening with convulsive dose (50 mA for 0.2 seconds) were selected for the study (Mittal, 2006).

Procedure: Study was done as a multiple dose study for 7 days. The drugs were administered daily for seven days intraperitoneally and then the animals in each group were checked for convulsions on the seventh day one hour after the final dose (Singh *et al*, 2010).

Groups and Drug administration: A 1 % solution of Tween 80 was prepared daily using distilled water. All the drugs (Phenytoin, Phenobarbitone and Nebivolol) were suspended in freshly prepared 1 % Tween 80 solution before administration (Lukawski *et al*, 2010). 36 animals randomly divided into six groups, were subdivided as follows.

Group 1: A 1 % solution of Tween 80 was used as the control and was administered intraperitoneally (I.P.) in a volume of 0.01 ml/gm body weight every 24 hours for 7 days.

Group 2: Phenytoin (25 mg/kg) was used as standard and was administered in a volume of 0.01 ml/gm body weight every 24 hours as a single intraperitoneal injection for 7 days.

Group 3: Phenobarbitone (10 mg/kg) was also used as standard and was administered in a volume of 0.01 ml/gm body weight every 24 hours as a single intraperitoneal injection for 7 days.

Group 4: Nebivolol (1 mg/kg) was administered in a volume of 0.01 ml/gm body weight every 24 hours as a single intraperitoneal injection for 7 days.

Group 5: Nebivolol (1mg/kg) followed by phenytoin (12.5 mg/kg) (each in a volume of 0.01ml/gm body weight) in two different quadrants of the abdomen were administered every 24 hours as two intraperitoneal injections for 7 days.

Group 6: Nebivolol (1mg/kg) followed by phenobarbitone (5 mg/kg) (each in a volume of 0.01ml/gm body weight) in two different quadrants of the abdomen were administered every 24 hours as two intraperitoneal injections for 7 days.

Experiment

The experiment was conducted on a wooden table so as to clearly observe the reactions in the mice. After applying the current the mice were observed for convulsions in the form of tonic hind limb extension (THE) i.e. the hind limbs of animals outstretched 180° to the plane of the body axis. Duration of tonic convulsions (Tonic hindlimb extension) in seconds using a stopwatch and the abolition of tonic hindlimb extension and mortality in each group were recorded. The primary endpoint for anticonvulsant activity and protection against MES induced seizure was decrease in the duration of Tonic hind limb extension (THE) compared to control and the secondary endpoint was abolition of THE (Dhande *et al*, 2009).

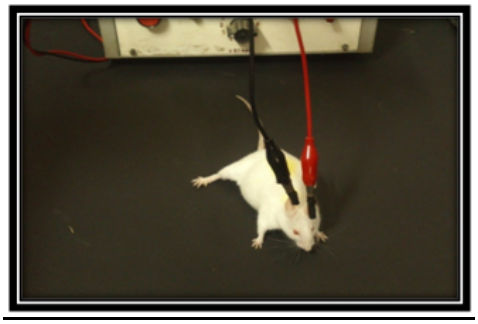

Figure 1: Mice being given electroconvulsions through ear electrodes

STATISTICAL ANALYSIS

The numerical data were presented as mean and standard error of mean (SEM).The duration of tonic hindlimb extension (seconds + SEM) in each group was compared

with the control. The effect of nebivolol (Group 2) on duration of tonic hindlimb extension was compared with that of the standard therapeutic doses of phenytoin and phenobarbitone (Group 2 and 3). The effect of the combinations i.e. Nebivolol+ Phenytoin and Nebivolol + Phenobarbitone (Group 4 and 5) was compared with the effect of phenytoin and phenobarbitone (Group 2 and 3) respectively. Analysis of quantitative data for a qualitative variable among more than 2 subgroups was done using One way ANOVA and Tukeys post-HOC test was used for pair wise group comparison. A p value of < 0.05 was considered statistically significant.

RESULTS

Table 1: Duration of THE in various treatment groups as compared with Control

Group No.	Groups	Duration of THE (in seconds)
1	Control - Tween 80 (1%)	15.94 ± 1.11
2	Phenytoin (25 mg/kg)	3.212 ± 1.444***
3	Phenobarbitone (10 mg/kg)	3.805 ± 1.225***
4	Nebivolol (1 mg/kg)	9.905 ± 0.694**
5	NBV (1 mg/kg) + Phenytoin (12.5 mg/kg)	5.327 ± 1.086***
6	NBV(1mg/kg)+ Phenobarbitone (5 mg/kg)	7.555 ± 0.164***

***: p < 0.001; **: p < 0.01; *: p < 0.05; NS: Not significant (p > 0.05)

Table 2: Duration of THE in Nebivololgroups as compared with Positive Controls

Group No.	Groups	Duration of THE (in seconds)
2	Phenytoin (25 mg/kg)	3.212 ± 1.444**
3	Phenobarbitone (10 mg/kg)	3.805 ± 1.225**
4	Nebivolol (1 mg/kg)	9.905 ± 0.694

***: p < 0.001; **: p < 0.01; *: p < 0.05; NS: Not significant (p > 0.05)

Table 3: Duration of THE in Nebivolol + Phenytoin group as compared with Phenytoin

Group No.	Groups	Duration of THE (in seconds)
2	Phenytoin (25 mg/kg)	3.212 + 1.444
5	Nebivolol (1 mg/kg) + Phenytoin (12.5 mg/kg)	5.327 + 1.086 ^{NS}

***: p < 0.001; **: p < 0.01; *: p < 0.05; NS: Not significant (p > 0.05)

Table 4: Duration of THE in Nebivolol + Phenobarbitone group as compared with Phenobarbitone

Group No.	Groups	Duration of THE (in seconds)
3	Phenobarbitone (10 mg/kg)	3.805 ± 1.225
6	Nebivolol (1mg/kg) + Phenobarbitone (5 mg/kg)	7.555 ± 0.1644 ^{NS}

***: p < 0.001; **: p < 0.01; *: p < 0.05; NS: Not significant (p > 0.05)

ABOLITION of Tonic Hind limb Extension (THE)

The tonic hindlimb extension was not abolished in any of the animals in Group 1 (1% Tween 80), Group 4 (Nebivolol 1mg/kg) and Group 6 (Nebivolol 1mg/kg + Phenobarbitone 5mg/kg).Whereas in Group 2 (Phenytoin 25 mg/kg) and Group 3 (Phenobarbitone 10 mg/kg) there was abolition of tonic hindlimb extension in 3 out of 6 animals (50 per cent) and 2 out of 6 animals (33.33 per cent) respectively. In the combination test drug group i.e. Group 5 (Nebivolol 1 mg/kg + Phenytoin 12.5 mg/kg) the tonic hind limb extension was abolished in 1 out of 6 (16.66 %) of the animals (Figure-2).

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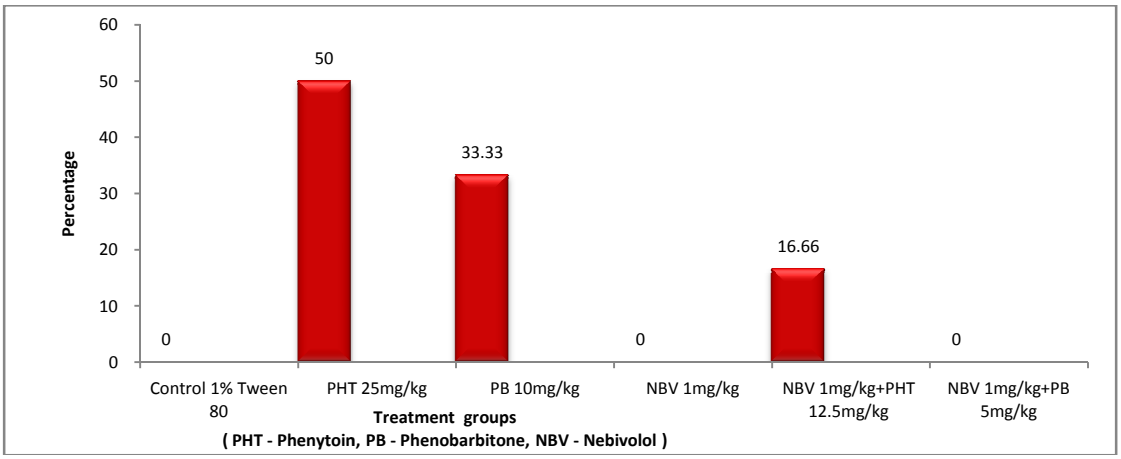

Figure 2: Percentage Abolition of Tonic Hind limb Extension (THE)

Incidence of death

One out of the 6 mice in the control group (1% Tween 80) died due to convulsion induced by the MES method. There was no death reported in any of the other groups due to convulsions induced by MES.

DISCUSSION

The present study was undertaken to evaluate the anticonvulsant effect of nebivolol and its combination with phenytoin and phenobarbitone in an experimental model of mice. The study evidences the anticonvulsant effect of nebivolol with some novel findings of its combinations with traditional anticonvulsant drugs. Significant reduction in THE observed on comparison of NBV group (Group 4 – Nebivolol) with control group ($p < 0.01$) and the highly significant reduction in THE observed in the combination groups (Groups 5 and 6), indicate that nebivolol has anticonvulsant property which is in accordance with anticonvulsant action of nebivolol proved by Goel *et al*. In that study two doses of nebivolol were used i.e.0.25 and 0.50 mg/kg which were one twentieth and one tenth of the human dose andnebivolol produced a dose dependent increase in seizure threshold as well as the latency of the seizures. Also two models of epilepsy i.e. increasing current electroshock (ICES) and Pentylenetetrazole (PTZ) – induced seizures in mice were used. Whereas in our study we used a single higher dose i.e. 1 mg/kg which is one fifth of human dose and a single model i.e. maximal electroshock seizures. This was because we wanted to evaluate a higher dose of nebivolol for its anticonvulsant action so that it provides definitive anticonvulsant action and so can be combined with other drugs. Also we used the MES method as it is the standard method which simulates grandmal seizures against which phenytoin and phenobarbitone are effective as against Pentylenetetrazole which produces absence seizures against which these drugs are not effective. Hence we have evaluated the anticonvulsant action of nebivolol against the more common grandmal seizures and with the standard effective drugs phenytoin and phenobarbitone. In this study, The was abolished in 50 % and 33.33 % of the animals in Phenytoin and Phenobarbitone groups respectively. This reconfirmed the protective effects of the standard drugs phenytoin and phenobarbitone. In the combination test drug group i.e. group 5 (Nebivolol + Phenytoin), THE was abolished in 16.66 % of the animals. In comparison to this The was not abolished in any of the animals in the control group, nebivolol group and nebivolol + Phenobarbitone group. In our study, nebivolol in combination with sub therapeutic doses of phenytoin and phenobarbitone also provided significant anticonvulsant action. This offers an exciting prospect which will help in reducing the doses of these standard anticonvulsant drugs thereby reducing their side effects. The combined anticonvulsant activity may be due to action of both the drugs through different mechanisms or drug interactions which may be either pharmacodynamic or pharmacokinetic needing elucidation. Further studies are required to confirm these effects both experimentally and clinically. We used two parameters to assess the anticonvulsant action of various groups i.e. duration of tonic hind limb extension in seconds and abolition of tonic hind limb extension. Tonic hind limb extension may not be abolished in all cases as some compounds may provide submaximal protection, whereas certain compounds may only control the spread of seizures which is evident by reduction in the duration of convulsions (Sonavane *et al*, 2002 and Dhande *et al*, 2009). Hence we recorded the duration of the THE in each group and it was used as a parameter to assess the anticonvulsant action of the groups in which there was no abolition of the tonic hind limb extension. Except one death in the control group, all the other groups did not show any mortality due

to convulsions induced by MES. This also suggests an anticonvulsant action provided in the rest of the groups. Nebivolol was also found to potentiate the anticonvulsant action of lamotrigine in experimental model of convulsions in mice (Goel *et al*, 2009). A similar study done in male albino mice where convulsions were induced chemically with pentylenetetrazole (PTZ) at a dose of 60mg/kg intraperitoneally, Dr Muthukavitha *et al* (2015) have also observed a significant anticonvulsant effect of Nebivolol indicated by the increased latency to clonic jerks. As mentioned earlier, RadhaGoel *et al* 2015 have also reported a beneficial effect of Nebivolol in combination with Gabapentin in increasing current electroshock seizures (ICES) and PTZ induced seizures. The anticonvulsant action of nebivolol thus opens up an interesting perspective in the treatment of epilepsy. It is a selective Beta-1 receptor antagonist, thus the anticonvulsant action may be due to blockade of beta-1 receptors in the brain as nebivolol is highly lipophilic. There is evidence to suggest that beta adrenoceptor activation may progress epileptic phenomena by increasing the rate of spontanaeousepileptiform discharge in hippocampal slices. A high density of β- adrenoceptors occurs in all the subfields of the hippocampus known for its dominant role in the propagation of seizures (McNamara JO, 2011). β agonists potentiated the epileptiform abnormalities occurring in slices of pyriform cortex obtained from kindled animals.Moreover, β receptor antagonists have revealed anticonvulsant actions under experimental conditions (Janssens WJ *et al*, 1991 andMcIntyre DC *et al*, 1986). Hence contribution of noradrenergic neurotransmission to seizure susceptibility and epileptogenesis is gaining momentum. Nebivolol, although devoid of intrinsic sympathomimetic activity, causes release of endothelial derived nitric oxide (NO) which is responsible for its vasodilatory effect. Nebivolol also has significant antioxidant properties. The exact mechanism by which nebivolol exerts its anticonvulsant action is not known. However hypotheses have been suggested linking beta-1 adrenoceptor blocking action in the brain, antioxidative action and nitric oxide releasing property to its anticonvulsant property (Goel *et al*, 2009, 2011). It is also noteworthy that Hypertension itself can lead to seizures through vascular brain damage which may or may not involve manifest stroke. Hypertension is also the most prevalent modifiable risk factor for both ischemic and haemorrhagic stroke, which is often associated with epilepsy. Severe and uncontrolled hypertension might increase the risk of epilepsy in the absence of prior clinically detected stroke. (Hesdorffer DC *et al*, 1996) So it can be suggested that use of combination of Nebivolol with a standard antiepileptic drug provides an excellent opportunity of reducing standard antiepileptic drug dosesandthus decrease their side effects significantly. This strategy could be more fruitful in hypertensive patients.

CONCLUSION

In conclusion, our results suggest that nebivolol possesses anticonvulsant action alone and in combination with sub therapeutic doses of phenytoin and phenobarbitone when evaluated by the maximal electroshock seizures method in mice. More research is required to ascertain the mechanism of action of nebivolol and to detect the effect of nebivolol on the cognitive and motor functions. Further studies are required to establish the exact basis for anticonvulsant activity of nebivolol, and to extrapolate animal data to human situations.

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