Effects of combined treatment with cognitive enhancer memantine and antidepressant fluoxetine on CYP2D2 metabolic activity in rats

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ORIGINAL ARTICLE

Abstract

OBJECTIVES: The drug-drug interactions can result in alterations of the therapeutical responses. The present study was designed to investigate possible pharmacokinetic interactions between the cognitive agent memantine and the antidepressant fluoxetine combined often in treatments of cognitive disorders including Alzheimer disease. The attention was focused on changes of the cytochrome P450 2D2 isoenzyme activity in two animal models.

METHODS AND DESIGN: The tested drugs were administered alone or in a combination to rat males and their effects on the 2D2 isoenzyme activity was determined after *in vivo* administration. The levels of marker dextromethorphan, its 2D2 specific metabolite dextrorphan were analyzed in plasma of rats and using the model of isolated perfused rat liver in the perfusion medium. The dextromethorphan/dextrorphan (DEM/DEX) metabolic ratios were determined as a sign of inhibitory influences on CYP2D2.

RESULTS: The analyses showed elevation of DEM/DEX metabolic ratio after all treatments: a) memantine, b) fluoxetine and c) memantine+fluoxetine, however the results were not completely identical. The intensity of inhibitory effects on the CYP2D2 activity were: memantine < memantine + fluoxetine < fluoxetine.

CONCLUSION: The results presented suggest that the clinical pharmacotherapeutical approach to combine memantine with fluoxetine is from the point of view of pharmacokinetic drug-drug interaction on the level of CYP2D2 isoenzyme safe and even of benefit as memantine could elicit a suppression of the inhibitory influence of fluoxetine.

Abbreviations:
AD	- Alzeimer's disease
DEM	- dextromethorphan
DEX	- dextrorphan
FLU	- fluoxetine
HPLC	- high-performance liquid chromatography
MEM	- memantine
MR	- metabolic ratio
NMDA	- N-methyl-D-aspartic acid

INTRODUCTION

Alzheimer disease and other neuropsychiatric disorders leading to dementia or cognitive deficits are supposed to be the major health concern of the coming decades (McDonald *et al.* 2010). The incidence of cognitive impairment is rapidly rising as the life expectancy is remarkably increasing over the last 50 years

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and the exponential risk of age-related dementias is described (Rocca 2000). Although dementia is the problem of high importance, only few substances are approved and used in the therapy of this illness. Apart from the inhibitors of acetylcholinesterase, memantine (MEM) is still the only drug acting on glutamatergic NMDA receptors. It was originally synthesized in Eli Lilly Research Laboratories as an agent lowering hyperglycemia, but it was completely devoid of such effect and it was introduced into the therapy of cerebral ischemia and Alzheimer's dementia (AD) later on (Parsons *et al.* 1999). Memantine is believed to be a safe drug with a minimum of adverse effects in comparison to other NMDA blockers such as MK-801 or phencyclidine. The difference between these substances and MEM lays probably in the pathway of influencing the glutamate channels. Molecules with lower affinity, faster blocking/unblocking kinetics and weaker voltage-dependency (MEM, dextromethorphan, amantadine) are not burdened with negative psychotropic effects which are known to be associated with administration of high affinity NMDA receptor blockers with slow action (MK-801, phencyclidine) (Parsons *et al.* 1999). The most frequent side effect of memantine are psychomimetic responses, which appear in the case that a recommended starting dosing titration (5–20 mg over 3–4 weeks) is skipped or if MEM is co-administered with dopaminergic agents (Parsons *et al.* 1999). The same expectations were reviewed recently (Repantis *et al.* 2010) on the basis of some stimulant-like effect reports. Those reports on negative effects of MEM were not a cause for treatment discontinuation as described in the meta-analysis containing 6 trials in 2312 subjects (Doody *et al.* 2007).

The most frequent MEM prescription can be found in elderly with high probability of commorbidities requiring other pharmacotherapeutical intervention. Rather often with some other psychotropics, due to apathy (Wuwongse *et al.* 2010) or depression (the incidence from 3.2 up to 27% patients with AD) (Newman 1999, Castilla-Puentes & Habeych 2010). MEM is also reported to enhance effects of antipsychotics on negative symptoms (Krivoy *et al.* 2008), positively influence treatment of substance abuse (alcohol, heroin) (Zdanys & Tampi 2008) and it also showed the synergic effect with fluoxetine (FLU) in the combined treatment of obsessive compulsive disorder (Wald *et al.* 2009). The proposed combination either with psychotropics or with other drugs of other classes brings out the problem of drug-drug interaction. MEM is believed to be a safe drug. It is not metabolized via cytochrome P450 (CYP) system and it is believed to produce irrelevant changes in the activity of these enzymes, thus no pharmacokinetic interactions on that level are expected (Nameda). Nevertheless some discrepant reports can be found (Keltner & Williams 2004, Micuda *et al.* 2003). There was investigated in the present study the activity of rat CYP2D2, which is an orthologue of human CYP2D6 (Zahradnikova *et al.* 2007), one of the most clinically relevant CYP isoenzymes. The influences of MEM, CYP2D2 inhibitor FLU, and MEM+FLU were analysed in rats in vivo and in the isolated liver.

MATERIAL AND METHODS

Animals

The experiment was carried out on male Wistar albino rats weighing 200 ± 20 g (Biotest, Czech Republic) at the beginning of experiment. Animals were housed under controlled conditions (temperature: 22 ± 2°C; air humidity 50–60%; light regime 12 h light/12 h dark, lights on 6:00–18:00) in standard plastic cages with free access to water and pellet diet and underwent a 7 day long acclimatization before the start of the experiment. Rats were randomly subdivided into 5 groups per 10 animals for the isolated liver experiment. Tested substances were dissolved in saline and administered intraperitoneally, 1 bolus/day for 10 days according to the following design: M5 (MEM 5 mg/kg/day); FLU5 and FLU20 (FLU 5 or 20 mg/kg/day), MF5 (MEM+FLU 5 mg/kg/day both) and C (saline in adequate volume of 1 ml/kg/day as a control). Another 4 groups per 18 animals served for the pharmacokinetic experiment *in vivo*. These groups were administered identically as the M5, MF5, F20 and C. All procedures of animal care were approved by the Czech Central Commission for Animal Welfare.

The model of perfused rat liver

The activity of CYP2D2 was assessed in the model of isolated perfused rat liver as described elsewhere (Zendulka *et al.* 2008). The animal was anesthetized with the mixture of ketamine (100 mg/kg) and xylazine (16 mg/kg), *vena portae* was cannulated and the liver was isolated from the abdominal cavity. The liver was perfused with tempered saline during the isolation. Then, saline was changed for Williams medium E (120 ml) and liver was perfused in the modified recirculating apparatus described by Miller (Miller *et al.* 1951) for 120 minutes from the start time: the addition of DEM (1.2 mg) into the perfusion medium. The perfusion medium samples were collected in the 30th, 60th and 120th minute of perfusion.

The in vivo rat pharmacokinetic model

Animals were anesthetized with the same anesthetic mixture of ketamine and xylazine as described in the previous model. DEM was injected into the tail vein at the dose of 10 mg/kg. Experimental groups were subdivided into three subunits per 6 animals. Three samples were withdrawn from each animal to obtain nine sampling intervals for each group at all. Blood was withdrawn from *plexus retrobulbaris* by a heparinized glass capillary tube in the following intervals after the DEM injection: 10th; 20th; 40th; 60th; 90th; 120th; 180th; 240th

and 300th minute. Coagulated blood was then centrifuged to obtain serum samples.

Sample analyses

Analyses of plasmatic and perfusion medium samples were performed after the incubation with β-glucuronidase and a liquid/liquid extraction using HPLC methods described by Zimova (Zimova *et al.* 2001). Metabolic ratios (MRs) were calculated using equation MR = conc. DEM / conc. DEX.
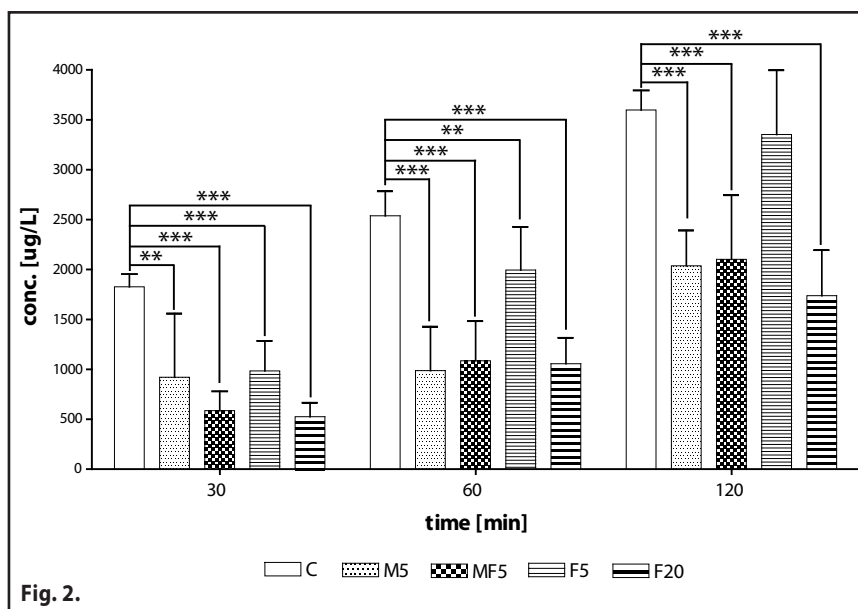
Statistical analyses

Values of measured DEM and DEX concentration were tested for outliners with Dixon's Q-test and outliners were rejected (95% confidence level). Remaining values were statistically analyzed with the F-test and Student's t-test (Microsoft Excel 2000). The level $p \leq 0.05$ was considered to be a statistically significant difference.

Fig. 1. Levels of dextromethorphan in the perfusion medium in animals administered with memantine 5 mg/kg/day (M), fluoxetine 5 or 20 mg/kg/day (F5 and F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C). Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.
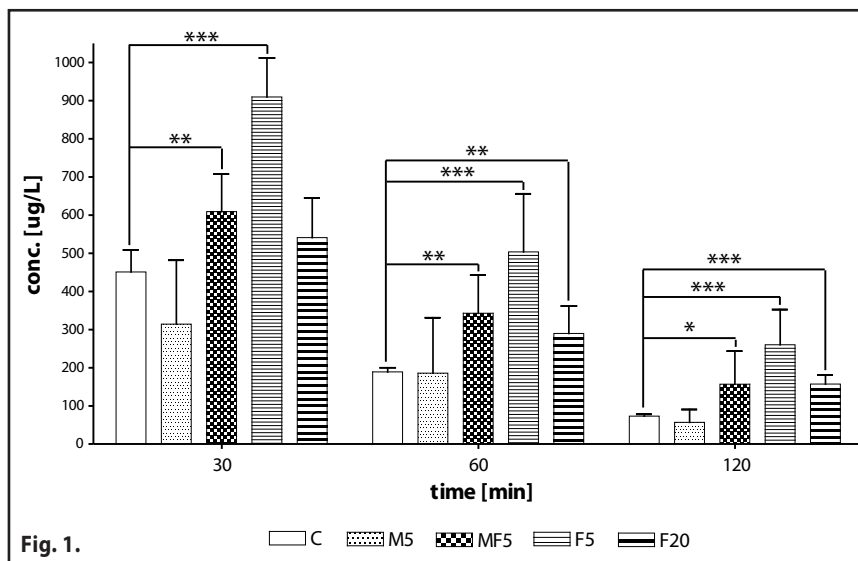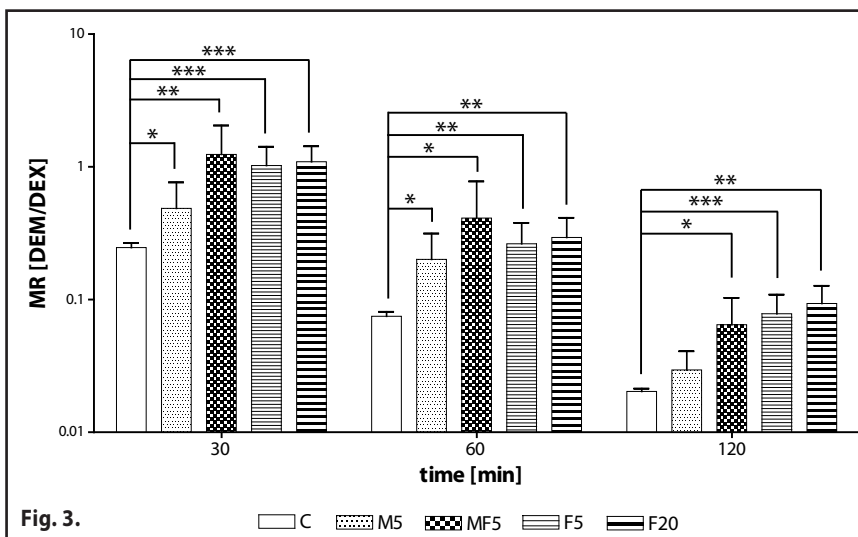
Fig. 2. Levels of dextrorphan in the perfusion medium in animals administered with memantine 5 mg/kg/day (M), fluoxetine 5 or 20 mg/kg/day (F5 and F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C). Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.

Fig. 3. Metabolic ratios of dextromethorphan/dextrorphan in animals administered with memantine 5 mg/kg/day (M), fluoxetine 5 or 20 mg/kg/day (F5 and F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C). Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.

Fig. 1.

Fig. 2.

Fig. 3.

Tab. 1. Plasmatic levels of dextromethorphan [μg/L] in animals administered with memantine 5 mg/kg/day (M), fluoxetine 20 mg/kg/day (F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C), in the pharmacokinetic experiment *in vivo*. Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.

Time [min]	Group			
	C	M5	MF5	F20
10	2089.0 ± 424.2	530.0 ± 20.1***	285.9 ± 103.4***	1017.0 ±123.0**
20	1746.3 ± 194.7	333.1 ± 41.4***	176.6 ± 92.4***	822.2 ± 57.3***
40	273.0 ± 34.1	217.1 ± 110.8	110.9 ± 19.2***	535.5 ±96.6***
60	161.9 ± 27.2	130.4 ± 36.4	82.4 ± 20.6***	440.3 ± 39.9***
90	91.8 ± 6.8	88.7 ± 35.3	60.4 ± 6.6***	332.8 ± 72.7***
120	91.9 ± 41.3	66.1 ± 18.2	38.0 ± 7.3**	222.0 ± 83.3***
180	104.9 ± 45.0	25.4 ± 3.8**	31.7 ± 7.2**	191.4 ± 46.8***
240	69.5 ± 38.7	42.7 ± 24.2	12.8 ± 1.7**	122.6 ± 32.7**
300	25.2 ± 10.8	22.6 ± 7.3	20.5 ± 8.4	119.1 ± 46.2***

Tab. 2. Plasmatic levels of dextrorphan [μg/L] in animals administered with memantine 5 mg/kg/day (M), fluoxetine 20 mg/kg/day (F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C), in the pharmacokinetic experiment *in vivo*. Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.

Time [min]	Group			
	C	M5	MF5	F20
10	1281.5 ± 486.6	142.7 ± 24.7**	37.4 ± 9.7**	442.7 ± 262.7**
20	2100,8 ± 373.1	160.6 ± 40.7***	67.4 ± 41.2***	841.1 ± 366.1***
40	546.5 ± 47.0	198.3 ± 105.0***	87.8 ± 16.0***	920.8 ± 401.5*
60	514.6 ± 161.8	169.4 ± 70.7**	83.7 ± 31.4***	710.1 ±74.3*
90	328.0 ± 93.5	104.1 ± 32.0***	78.5 ± 15.2***	819.1 ± 466.9
120	424.1 ± 146.3	288.2 ± 216.6	59.7 ± 13.1***	611.5 ± 160.0
180	1405.0 ± 608.7	104.2 ± 60.8***	114.4 ± 68.7***	1110.5 ± 425.6*
240	1483.1 ± 434.6	272.6 ± 103.8***	389.4 ± 87.0***	1071.1 ± 313.3
300	1550.3 ± 408.2	657.4 ± 196.2***	327.1 ± 87.0	1241.3 ± 502.3

Tab. 3. Dextromethorphan/dextrorphan metabolic ratios in animals administered with memantine 5 mg/kg/day (M), fluoxetine 20 mg/kg/day (F20), memantine+fluoxetine both 5 mg/kg/day (MF5) and in control animals (C), in the pharmacokinetic experiment *in vivo*. Experimental conditions are described in Material and Methods. Data represent mean ± S.E.M. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ versus C group.

Time [min]	Group			
	C	M5	MF5	F20
10	1.80 ± 0.64	3.79 ± 0.54***	8.12 ± 3.78**	3.02 ± 1.64
20	0.85 ± 0.20	2.18 ± 0.54***	2.87 ± 0.72**	1.30 ± 0.61
40	0.51 ± 0.03	1.19 ± 0.37**	1.30 ± 0.30***	0.55 ± 0.15
60	0.34 ± 0.11	0.83 ± 0.19***	1.04 ± 0.22***	0.61 ± 0.08***
90	0.14 ± 0. 13	0.87 ± 0.06***	0.85 ± 0.11***	0.40 ± 0.14*
120	0.26 ± 0.13	0.38 ± 0.26	0.66 ± 0.16***	0.43 ± 0.24
180	0.09 ± 0.06	0.34 ± 0.22**	0.44 ± 0.29*	0.20 ± 0.07**
240	0.05 ± 0.03	0.22 ± 0.22	0.04 ± 0.01	0.12 ± 0. 04**
300	0.02 ± 0.01	0.03 ±0.01**	0.06 ± 0.01***	0.11 ± 0.05***

RESULTS

The model of isolated perfused rat liver

Levels of DEM measured in the perfusion medium were elevated during the whole perfusion in the F5 and MF5 and in the 60th and 120th min in F20 animals (Figure 1). The administration of MEM did not influence levels of DEM (M5) as they resembled those in the control (C) group. In opposite DEX concentrations were lower than in controls in all groups studied, independently on the treatment regimen (Figure 2). The only insignificant difference was measured in the F5 group in the 120th minute (Figure 2). MRs were elevated in all groups at all intervals with the exception of the 120th min in the group M5, but a trend close to the level of significance ($p=0.077$) was still present (Figure 3). The MRs increase in the MF5, F5 and F20 was similar with no significant differences between groups monitored.

The in vivo rat pharmacokinetic model

The influence of administered drugs on the levels of DEM varied. In the MF5 group the amounts of DEM were decreased. In opposite, FLU elicited in the F20 elevation of DEM and MEM (M5) showed practically no influence (Table 1). Concentrations of DEX were also altered, but did not reflected changes in DEM levels. DEX levels were lowered in the M5 animals and this effect was enhanced by FLU co-administration in the MF5 group (Table 2). Amounts of DEX similar to controls were found in the F20, where differences were present mainly in the first 90 minutes. In all experimental groups elevated values of MRs were found (Table 3). The significant difference between the M5, MF5 animals and controls lasted for the whole experiment with the exception of the MR in the 240th min interval. The F20 experimental group also showed elevation of MRs with later upset (after 180 minutes). All three experimental groups had elevated MRs in the end of experiment and the groups differ among each other. The highest MRs were calculated for the F20 and it was higher compared to the MF5 value, which was still more elevated than MRs of the M5.

DISCUSSION

The present study proved MEM as an inhibitor of the rat CYP2D2 enzyme. This correlates with human liver microsomes study (Micuda *et al.* 2004) which described inhibition of CYP 2B6 ($K_i=76.7\,\mu M$) and 2D6 ($K_i=94.9\,\mu M$). The other published data available report no drug-drug interactions on CYP level caused by MEM (Sonkusare *et al.* 2005; Nameda 2010).

The results obtained from both our experimental models are similar but not identical. On the contrary to *in vivo* testing there was registered a time dependent effect of MEM on CYP2D2 in the model of isolated perfused rat liver. The inhibition caused by MEM was detected only in the first two sampling intervals while it was not present in the 120th min (the *p*-value (0.07) was close to the level of significance – *p*=0.05). This effect was more pronounced in the *in vivo* experiment when MEM inhibited CYP2D2 activity even longer (up to the 300th min). One could speculate that the higher DEM concentration available at the beginning of the *in vivo* experiment is the factor modulating the inhibition capacity of MEM. Thus the similar DEM levels during sampling in both models found could be a sign of higher inhibition caused by MEM *in vivo*. (The relatively high variability in DEM levels measured *in vitro* could probably result in non-significant differences calculated.)

There was documented in our study an interesting interaction between MEM and FLU changing the inhibitory effect on the CYP2D2 activity. Despite both drugs suppressed the enzyme activity with lower impact of MEM the combined treatment MEM+FLU showed milder effect than FLU alone. FLU is described as a moderate competitive inhibitor of human CYP2D6 with K_i value $0.6\,\mu M$ (Pelkonen *et al.* 2008) and its major metabolite norfluoxetine showed the same activity (Otton *et al.* 1993, Crewe *et al.* 2004). The inhibition of CYP2D after FLU treatment is observed even after a single dose, is dose-dependent (Jeppesen *et al.* 1996) and can vary among different tissues and organs (Haduch *et al.* 2011). The mechanisms of the interaction between FLU and MEM as modifiers of CYP2D2 activity can be competitive, uncompetitive or mixed-type according to binding to the enzyme target. However the antagonism between enzyme modifiers MEM and FLU desribed in our study belongs to effects classified as rare and possible to be predicted only under very particular circumstances (Schenker & Baici 2009). Furthermore, the principles of interaction between two enzyme inhibitors can depend on the type of inhibition caused as well as on their concentrations (Schenker & Baici 2009). In our case, comparable amounts of MEM and FLU were administered ($28\,\mu M$/kg/day and 16μ M/kg/day respectively) while K_i was different. Additional experiments with various other MEM and FLU doses applied can help to clarify this drug-drug interaction.

There are six CYP2D isoenzymes that have been genetically identified in rats compared to only one in humans (Hiroi *et al.* 2002). The sequential similarity between rat CYP2D2 and human CYP2D6 is over 70% (Soucek & Gut 1992). DEM is biotransformed into DEX exclusively via CYP2D2 enzyme in rats (Kobayashi *et al.* 2002) and there are two more metabolites present (Zendulka *et al.* 2009). The CYP2D2 catalyzes other reactions specific for the human 2D6 isoenzyme, too (Hiroi *et al.* 2002). Thus, the correlation between results obtained in CYP2D2 rat models and in CYP2D6 human studies is usually high. The dose of 5 mg/kg/day in our study was selected on the basis of MEM pharmacokinetic properties to simulate drug plasmatic levels in rats similar to those reached in humans treated with the therapeutic doses of the drug. The MEM dose used in

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our work is likely to be sufficient to reach peak serum concentrations at 20–30 min at the upper limit of doses seen in serum of healthy volunteers and patients with well tolerated doses of MEM (Parsons *et al.* 1999).

CONCLUSION

We conclude that the co-administration of therapeutically relevant doses of MEM with CYP2D6 drug substrates or even inhibitors of this enzyme would not be rated as a risk of possible clinical drug-drug interaction occurrence. The combination of MEM with CYP2D6 inhibitor could even be profitable, because MEM can moderate FLU inhibitory influence as was documented in the present study.

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