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322 *Current Neuropharmacology*, **2016**, *14*, 322-325

Current Drug Managements of Wilson's Disease: From West to East

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Abstract: Wilson's disease (WD), also called hepatolenticular degeneration, is an autosomal recessive inheritance disorder of copper metabolism characterized by the multiple mutations in the ATP-ase 7B gene of chromosome 13q. About half of the WD patients have neurological or psychiatric symptoms. As WD is a kind of medicable or nearly curable neurodegenerative disease in the field of medicine, early consideration/examination and without delay/ life-long treatment usually lead to better prognoses. The drugs, also named as anticopper agents, are commonly used in clinics including D-penicillamine, trientine, sodium dimercaptosuccinate, dimercaptosuccinic acid, zinc and tetrathiomolybdate. This provides detailed reviews about these medicines.

Keywords: D-penicillamine, dimercaptosuccinic acid, hepatolenticular degeneration, sodium dimercaptosuccinate, tetrathiomolybdate, trientine, Wilson's disease, zinc.

INTRODUCTION

Wilson's disease (WD), also called hepatolenticular degeneration, is a kind of genetically neurodegenerative disorder characterized with abnormal copper metabolism caused by an autosomal recessive inheritance of ATP7B gene mutation, and its clinical representations can be usually classified mainly as: cerebral type, hepatic type, presymptomatic (or asymptomatic) type, and the others [1, 2]. The dysfunction of ATP7B enzyme can result in disorders of copper-protein and paraeccrisis of biliary/intestinal copper, so free copper ion increases and abnormally deposits in various tissues and organs such as liver, brain and cornea by binding with protein, which causes the toxic damage to those organs. The diagnostic criteria of Wilson's disease are as follows: 1. clinical manifestations of liver damage or neurological symptoms; 2. decrease of ceruloplasmin (<0.2g/L); 3. adultly 24-hour urinary copper >100μg; and 4. visible corneal-pigmented ring (K-F ring) under the slit lamp [1, 3, 4].

WD often occurs in teenagers, with a world-wide prevalence of 1:30 000 and an incidence rate of 15-25 per million. As WD is one of the medicable or nearly curable genetic diseases by the drugs in the field of neuro-degenerative disorders, early diagnosis and early and life-long treatment lead to better prognoses. Although WD is a relatively rare disease, ten thousands of WD in-patients have already been institutioned in Hefei, Shanghai, Guangzhou of China [2, 5]. The drugs commonly used in clinic for Wilson's Disease are elaborated as follows.

COPPER CHELATING AGENTS

Copper chelating agents, orally or intravenously, excrete copper out of the various WD tissues from liver to skin, by combining Cu^{++} to form water-soluble copper complex, which can be excreted by the stool and urine.

D-penicillamine (D-PCA)

As the conventional anticopper, found by a great Englishman Walshe JM (1956), earliest first choice for WD, D-PCA has worldly been of the advantage of high excretion amount of urine copper, as it has recently been considered the disadvantage of relatively slow excretion speed of copper out of the brain, and especially re-contribution effort of copper, resulting in Cu^{++} from liver to brain. Therefore, it should not be applied to severe cases or advanced stage cases,particularly cerebral type. Studies have confirmed that D-PCA had a better curative effect on WD patients with liver damage, but negative influences on neurologic function impacted 10% -50% of WD patients with cerebral damage in the initial treatment, and about half of those patients suffered from irreversible damage [2, 3]. So some WD experts believe that D-PCA is not the drug of first choice for WD with neurological damage [4], even nothing but D-penicillamine list as first position in most of standard textbooks of Neurology and/or Medicine for 60 years. The deterioration phenomenon may be due to the transferring of a large number of copper from liver to blood, which can result in the increasing of blood free copper level, and some of those free copper metastasize to brain, rising to the aggravation of neurological symptoms [5]. D-PCA, also named as half-

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immunosuppressor, may cause series of adverse reactions such as: gastrointestinal symptoms and anaphylactic reaction at the early stage, leukocytopenia, thrombocytopenia, hemolytic anemia and autoimmune systemic diseases in the long-term usage [6, 7]. It is basically knowledgeable that D-PCA is prohibited to treat pregnant WD patients. About 30% of the patients finally stopped using D-PCA because of the serious adverse reactions [7]. Gradually increasing the amount of D-PCA could improve the drug tolerance, the initial dosage is 250-500 mg/d, with an increase of 250 mg every 4-7 days until reaching the maximum dosage 1000-1500 mg/d in 2-4 doses [2]. The recommended maintenance dosage is 750-1000 mg/d [8]. For children, the dosage is 20 mg/(kg·d), or about 250 mg/d [2]. The best medicine-taken time recommended is 1 hour before meals or 2 hours after meals because food can restrict the absorption of D-PCA. Daily added 25-50 mg vitamin B_6 is recommended because D-PCA can affect the metabolism of vitamin B_6 [9]. The amount of urinary copper , content of plasmatic free Cu^{++}, and level of non-ceruloplasmin need to be monitored in order to determine the efficacy and adjust the dosage.

Triethylene Tetramine, Trientine

Trientine (TETA) is a multi-amine metal chelating agent, which has a similar mechanism and treatment effect as D-PCA. Walshe first reported the application of trientine to WD patients in 1982 [10], which was recommended by the U.S Food and Drug Administration (FDA) as a D-PCA substitute or a second-line drug for patients who could not tolerate D-PCA in the same year [11]. For the patients treated by trientine, the proportion with worsened neurological symptom was significantly less than D-PCA, therefore it was recommended as the first choice for patients with neurological involvement. But in recent years, the double-blind study of Brewer *et al.* [12] on trientine and tetrathiomolybdate showed that when trientine was used for initial treatment of neurological WD, about 24% of patients had worsened neurological symptoms, half of whom died because the neurological symptom continued to worsen. Therefore, it might be considered that trientine was similar to D-PCA, inappropriate for the initial treatment of neurological WD. Trientine has a few adverse reactions, mainly pancytopenia. Its general dosage is 750-l,500 mg/d in 2-3 doses, and the maintenance dosage is 750-1,000mg/d. For children, there is no dosage standard by weight, usually 20mg/ (kg•d), namely about 250mg/d in 2-3 doses. Trientine and D-PCA should be dosed 1 hour before or 2 hours after a meal. Similar to D-PCA, for the patients treated by trientine, the amount of urinary copper and non-ceruloplasmin level needs to be monitored in order to determine the efficacy and adjust the dosage [2]. Trientine chelates iron preparation, and they should not be taken at the same time, because the compound formed is toxic [13].

Sodium Dimercaptosuccinate (Na-DMS), Dimercaptosuccinic Acid (DMSA), Sodium Dimercaptosulphonate (DMPS), and Captopril

Sodium dimercaptosuccinate (Na-DMS) is considered as a dominant intravenous medicine for Chinese WD, especially for the severe and advanced inpatients, as it has high urine copper excretion and minor side effects. DMPS invented by Russian, has been successfully used to the WD patients for 50 years in mainland China, usually 5-10mg / (kg•d) [14]. Dimercaptosuccinic acid (DMSA) invented by two Chinese: Ding GS and Liang Y in 1950'. It is an oral drug. It can enhance its effect on excretion of copper of WD. It is possibly the first choice for the outpatients in China by taking DMSA capsule, whose predecessor: Sodium dimercaptosulphonate (Na-DMPS) has intravenously low toxicity and minor side effects. The disadvantage is that it has little effect on severe or advanced stage of WD cases [14]. Captopril used in the treatment of hypertension, is a strong and competitive inhibitor of angiotensin-converting enzyme (ACE). The authors found that Captopril may decopper mildly and reduce the hepatic portal hypertension in cirrhosis of WD patients [14].

DRUGS PREVENTING INTESTINAL ABSORPTION OF COPPER AND PROMOTING EXCRETION OF COPPER

Zinc Preparation

Zinc preparations include zinc gluconate, zinc sulfate, zinc acetate, licorzinc and so on. By interfering with gastrointestinal copper absorption, the zinc preparation plays a therapeutic role with relatively slow effect. Yang RM and his Colleagues treated the patients orally by zinc sulfate or zinc gluconate, as a result, WD patients' urinary copper excretion all significantly increased [6]. Brewer JL *et al.* showed that in the asymptomatic stage or early stage with clinical symptoms of WD patients or in the maintenance treatment stage after copper chelating agent was used, zinc had better clinical effects, and at present zinc has become an cheap and important therapeutic agent for WD [11]. Taly *et al.* [15] found that the efficacy of zinc preparation was similar to penicillamine but had significantly superior tolerance. The zinc preparation has not caused worst early symptom in the initial treatment of neurological WD [14, 16]. To this end, European and American neurologists unanimously recommended the zinc preparation for the treatment of WD patients with early symptoms and pregnant WD patients, the initial treatment of neurological WD and the maintenance treatment of various types of WD [17-19]. At present, the combined and phased use of complexing agent and zinc preparation is largely advocated for therapy, but Sinha *et al.* [20] and Hoogenraad [16] argued recently that the gradually reduced dosage of complexing agent and final pure zinc preparation for maintenance treatment were economic, safe and effective for most WD patients. Gastrointestinal irritation is the main adverse reaction of zinc preparation, and zinc acetate and zinc gluconate [14, 16-18] have significantly lighter gastric irritation than zinc sulfate. Therefore, zinc acetate or zinc gluconate has substituted zinc sulfate for WD treatment. The dosage of Zinc preparation depends on the content of zinc, that is, for adult, 150mg/d in 3 doses; for children less than 50kg, 75mg/d in 3 doses; and for children younger than 5, it is difficult to determine the dosage. If the zinc preparation is orally taken with meal, the absorption and efficacy of zinc may be affected, so patients are generally recommended to take it 2 hours before the meal or on an empty stomach. With significant gastrointestinal reactions, a higher dose of zinc preparation can be taken with meal to

enhance the treatment compliance [2], which can be monitored by frequent reexaminations of urinary zinc. Zinc could integrate with penicillamine in the intestinal tract, so the dosing interval between zinc preparation and penicillamine should be more than 2 hours.

Tetrathiomolybdate

Tetrathiomolybdate (TM) is a potent decoppering agent, which interferes with intestinal copper absorption (taken with meal) or combines with plasma copper (taken before meal). Phase III clinical trial results have confirmed that tetrathiomolybdate itself does not worsen neurological functions, so it is particularly applicable to WD patients with neurological involvement [12, 21]. Brewer GJ, *et al.* [22] treated 55 cerebral-type WD patients, only 2 of them had aggravated neurological symptoms. Those patients' clinical symptoms were significantly improved at the 3rd year follow-up visit, when zinc sulfate was used in the maintenance therapy. Therefore, some specialists may consider that, treatment with PCA should be avoided for patients with cerebral type WD, TM associate with zinc can be used as the preferred treatment for the neuropsychiatrical WD [23]. For WD patients with neurological deficits, tetrathiomolybdate is proven to be more effective than trientine with fewer side effects [12], but there is no experimental study on the application of tetrathiomolybdate for WD patients with liver disease. Despite the initial treatment with tetrathiomolybdate for various types of WD patients [24], FDA has not yet approved it. Its adverse effects include bone marrow suppression, liver toxicity as well as neurological dysfunction induced by excessive decoppering. However, an excess of molybdenum is toxic, so TM should not be used in maintenance therapy [25].

ANTIOXIDANT

Mainly vitamin E, which can be used for adjuvant therapy. Clinical observations showed that WD patients had reduced vitamin E in plasma and liver [26, 27]. There are a few reports on improved symptoms due to vitamin E, but its efficacy remains to be proven [2]. Reduced Glutathione has been used in China to protect the related tissues [9].

TRADITIONAL CHINESE MEDICINE

Traditional Chinese Medicines with functions of cholagogue and promoting dieresis, such as: Radix et Rhizoma Rhei, Rhizoma coptidis, Rhizoma Curcumae Longae, Herba Lysimachiae, Rhizoma Alismatis, may be used to ameliorate the excretion of copper by means of bile, feces and urine are used to promote the excretion of bile copper, fecal copper and urinary copper. Gandou Decoction created by Yang RM had been proved to be effective for WD [6]. Currently by the authors' clinical experience, the total treatment scheme integrated Chinese and Western medicine is recommended for WD, especially for early stage patients and in the maintenance therapy stage.

HOW TO MAKE THE AGENT CHOICES FOR VARIED WD FACETS?

For asymptomatic or pre-clinical patients, zinc preparations are recommended to be used singly. The treatment recommended for hepatic type WD patients is zinc integrated with trientine, and for patients with cerebral type WD, initial treatment with PCA and trientine should be avoided, and zinc or zinc in combination with Tetrathiomolybdate or DMSA can be used as the treatment of first choice [5, 28]. Patients, who cannot use the above drugs due to limited conditions, can use penicillamine for treatment, but their conditions should be observed closely. In case of worse symptoms and PCA intolerance, the PCA should be withdrawn in time. In China DMPS is intravenously used as the routine management for a few weeks in one year for the in-patients after the initial treatment [5]. At the maintenance treatment stage, the dose of copper chelating drugs should be reduced, or zinc or traditional Chinese Medicine could be chosen instead [29]. The amount of urinary copper, plasma copper, especially free copper ion without ceruloplasmin level need to be monitored in order to determine the efficacy and adjust the dosage. All patients are generally not allowed to stop medicines, since the treatment interruption is very likely to result in the irreversible injuries of CNS tissues and the decompensated liver diseases [30], except for the specific stages: pre-pregnancy, pregnancy and lactation, especially for D-PCA painful experience.

In conclusion, we are supposed to develop individualized treatment plan according to the different types and different stages of WD, and in the predicting the future of ATP 7B gene mutation subtypes, which could help to decide the drug combination, even for essentially urgent liver transplantation of the abdominal Wilsonian type WD that is basically non-responsive to any type of anticopper drugs [30]. Besides the anticopper efficiency, the attentions should be paid to the neuroprotective and hepatoprotective agents in the future, as well as according to the genetic mutation and gene types [14, 31-37].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported by grants from the National Natural Science Foundation of China (81071065).

REFERENCES

[1] Roberts, E.A.; Schilsky, M.L. Diagnosis and Treatment of Wilson Disease: An Update. *Hepatology*, **2008**, *47*(6), 2089-2111. http://dx.doi.org/10.1002/hep.22261

[2] Wang, X.P. Wilson disease: asymptomatic or late-onset type? *Acta Neurol. Scand*., **1996**, *94*(6), 421-422.http://dx.doi.org/10.1111/j.1600-0404.1996.tb00056.x

[3] Merle, U.; Schaefer, M.; Ferenci, P.; Stremmel, W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut*, **2007**, *56*(1), 115-120.http://dx.doi.org/10.1136/gut.2005.087262

[4] Ala, A.; Walker, A.P.; Ashkan, K.; Dooley, J.S.; Schilsky, M.L. Wilson's disease. *Lancet*, **2007**, *369*, 397-408.http://dx.doi.org/10.1016/S0140-6736(07)60196-2

[5] Yang, R.M. Update on decopper treatment in patients with hepatolenticular degeneration. *World Clin. Drugs (Chin)*, **2010**, *31*(5), 257-260.

[6] Yang, R.M. Treatment of Wilson disease integrated Traditional Chinese and Western medicine. *Chin. J. Integr. Tradit. West. Med. (Chin)*, **2007**, *27*, 773-775.

[7] Medici, V.; Trevisan, C.P.; D'Inca, R.; Barollo, M.; Zancan, L.; Fagiuoli, S.; Martines, D.; Irato, P.; Sturniolo, G.C. Diagnosis and management of Wilson's disease: results of a single center experience. *J. Clin. Gastroenterol*., **2006**, *40*(10), 936-941.http://dx.doi.org/10.1097/01.mcg.0000225670.91722.59

[8] Prashanth, L.K.; Taly, A.B.; Sinha, S.; Factors that influence prognosis in severe forms of Wilson Disease. *Q. J. Med*., **2005**, *98*(1), 557-563. http://dx.doi.org/10.1093/qjmed/hci095

[9] Zhai, Y.F.; Wang, H.Q.; Wu, H.Q. Hepatolenticular degeneration pathogenesis and the diagnosis and treatment progress. *Med. Recapitulate*, **2012**, *18*(23), 3986-3988.

[10] Walshe, J.M. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. *Lancet*, **1982**, *319*(8273), 643-647.http://dx.doi.org/10.1016/S0140-6736(82)92201-2

[11] Brewer, G.J.; Terry, C.A.; Aisen, A.M.; Hill, G.M. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. *Arch. Neurol*., **1987**, *44*(5), 490-492. http://dx.doi.org/10.1001/archneur.1987.00520170020016

[12] Brewer, G.J.; Askari, F.; Lorincz, M.T.; Carlson, M.; Schilsky, M.; Kluin, K.J.; Hedera, P.; Moretti, P.; Fink, J.K.; Tankanow, R.; Dick, R.B.; Sitterly, J. Treatment of Wilson's disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson's disease. *Arch. Neurol*., **2006**, *63*(4), 521-527.http://dx.doi.org/10.1001/archneur.63.4.521

[13] Bandmann, O.; Weiss, K.H.; Kaler, S.G. Wilson's disease and other neurological copper disorders. *Lancet Neurol*., **2015**, *14*(1), 103-113.http://dx.doi.org/10.1016/S1474-4422(14)70190-5

[14] Wang, X.P.; Yang, R.M.; Ren, M.S.; Sun, B.M. Anticopper efficacy of captopril and sodium dimercaptosulphonate in patients with Wilson's disease. *Funct. Neurol.*, **2003**, *18*(3), 149-153.

[15] Taly, A.B.; Meenakshi-Sundaram, S.; Sinha, S.; Wilson disease: description of 282 patients evaluated over three decades. *Medicine*, **2007**, *86*(2), 112-121.http://dx.doi.org/10.1097/MD.0b013e318045a00e

[16] Hoogenraad, T.U. Paradigm shift in treatment of Wilson's disease: zinc therapy now treatment of choice. *Brain Dev*., **2006**, *28*(3), 141-146.http://dx.doi.org/10.1016/j.braindev.2005.08.008

[17] Brewer, G.J.; Yuzbasiyan-Gurkan, V.; Johnson, V. The treatment of Wilson's disease with zinc: IX: Response of serum lipids. *J. Lab. Clin. Med*., **1991**, *118*(5), 466-470.

[18] Lorincz, M.T. Neurologic Wilson's disease. *Ann. N.Y. Acad. Sci*., **2009**, *77*(1), 1-15.

[19] Marcellin, M.; Di Ciommov, V.; Callea F.; Devito, R.; Comparcola, D.; Sartorelli, M.R.; Carelli, G.; Nobili, V. Treatment of Wilson's disease with zinc from the time of diagnosis in pediatric patients: a single-hospital, 10 year follow-up study. *J. Lab. Clin. Med*., **2005**, *145*(3), 139-143.http://dx.doi.org/10.1016/j.lab.2005.01.007

[20] Sinha, S.; Taly, A.B. Withdrawal of penicillamine from zinc sulphate- penicillamine maintenance therapy in Wilson's disease: Promising, safe and cheap. *J. Neurol. Sci*., **2008**, *264*(1-2), 129-132.http://dx.doi.org/10.1016/j.jns.2007.08.006

[21] Medici, V.; Sturniolo, G.C. Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. *Drugs*, **2008**, *11*(8), 592-606.

[22] Brewer, G.J.; Hedera, P.; Kluin, K.J.; Carlson, M.; Askari, F.; Dick, R.B.; Treatment of Wilson disease with Ammonium tetrathiomolybdate: III. Initial therapy in a total 0f 55 neurologically affected patients and follow-up with zinc therapy. *Arch. Neurol*., **2003**, *60*, 379-385.

[23] Brewer, G.J. Neurologically presenting Wilson's disease: epidemiology , pathophysiology and treatment. *CNS Drugs*, **2005**, *19*, 185-192. http://dx.doi.org/10.2165/00023210-200519030-00001

[24] Brewer, G.J. Recognition, diagnosis, and management of Wilson's disease. *Proc. Soc. Exp. Bio. Med*., **2000**, *223*(1), 39-46.http://dx.doi.org/10.1046/j.1525-1373.2000.22305.x

[25] Brewer, G.J. Tetrathiomolybdate anticopper therapy for Wilson's disease inhibits angiogenesis, fibrosis and inflammation. *J. Cell Mol. Med*., **2003**, *7*, 11-20.

[26] Sinha, S.; Christopher, R.; Arunodaya, G.R.; Prashanth, L.K.; Gopinath, G.; Swamy, H.S.; Taly, A.B. Is low serum tocopherol in Wilson's disease a significant symptom? *J. Neurol. Sci*., **2005**, *228*(2), 121-123.http://dx.doi.org/10.1016/j.jns.2004.10.017

[27] Nagasaka, H.; Inoue, I.; Inui, A.; Komatsu, H.; Sogo, T.; Murayama, K.; Murakami, T.; Yorifuji, T.; Asayama, K.; Katayama, S.; Uemoto, S.; Kobayashi, K.; Takayanagi, M.; Fujisawa, T.; Tsukahara, H. Relationship between oxidative stress and antioxidant systems in the liver of patients with Wilson disease: hepatic manifestation in Wilson disease as a consequence of augmented oxidative stress. *Pediatr. Res*., **2006**, *60*(4), 472-477.http://dx.doi.org/10.1203/01.pdr.0000238341.12229.d3

[28] Brewer, G.J.; Askari, F.; Lorincz, M.T. Tetrathiomolybdate versus trientine in the initial treatment of neurologic Wilson's disease. *Prog. Neurotherap. Neuropsychopharmac*., **2008**, *3*(1), 153-165. http://dx.doi.org/10.1017/CBO9780511666971.010

[29] Ala, A.; Walker, A.P.; Ashkan, K.; Dooley, J.S.; Schilsky, M.L. Wilson' disease. *Lancet*, **2007**, *369*(9559), 397-408.http://dx.doi.org/10.1016/S0140-6736(07)60196-2

[30] Li, X.H.; Zhang, X.X. Update on diagnosis and treatment of Wilson's disease - a report of guideline made by AASLD. *J. Diagn. Concepts Pract.*, **2009**, *8*(2), 222-229.

[31] Li, W.J.; Wang, J.F.; Wang, X.P. Wilson's disease: update on integrated Chinese and Western medicine. *Chin. J. Integr. Med*., **2013**, *19*(3), 233-240. http://dx.doi.org/10.1007/s11655-012-1089-8

[32] Weiss, K.H.; Stremmel, W. Clinical considerations for an effective medical therapy in Wilson's disease. *Ann. N.Y. Acad. Sci*., **2014**, *1315*, 81-85. doi: 10.1111/nyas.12437.

[33] No authors listed. Copper rewired. *Nature*, **2014**, *508*(7495), 150.

[34] Wang, X.P.; Wang, X.H.; Bao, Y.C.; Zhou, J.N. Apolipoprotien E genotypes in Chinese patients with Wilson's disease. *Q. J. Med.,* **2003**, *96*, 566-567.http://dx.doi.org/10.1093/qjmed/hcg093

[35] Xiao, J.J.; Yin, M.; Wang, Z.J.; Wang, X.P. Transplanted Neural Stem Cells: Playing a Neuroprotective Role by Ceruloplasmin in the *Substantia Nigra* of PD Model Rats? *Oxid. Med. Cell Longev*., **2015**, *2015*,618631. doi: 10.1155/2015/618631.

[36] Chen, C.; Shen, B.; Xiao, J.J.; Wu, R.; Duff Canning, S.J.; Wang, X.P. Currently Clinical Views on Genetics of Wilson's Disease. *Chin. Med. J. (Engl)*., **2015**,*128*(13), 1826-1830. doi: 10.4103/0366-6999.159361.

[37] Montana, V.; Verkhratsky, A.; Parpura, V. Pathological role for exocytotic glutamate release from astrocytes in hepatic encephalopathy. *Curr. Neuropharmacol*., **2014**, *12*(4), 324-433. http://dx.doi.org/10.2174/1570159X12666140903094700

Received: May 15, 2015 Revised: July 16, 2015 Accepted: October 09, 2015