Evaluation of efficacy and safety after replacement of methyl hydrogen with Deuterium at 7-position methyl formate of Clopidogrel

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Abstract

Background and Purpose: As a first-line clinical drug, thienopyridines still have many unsatisfactory aspects, such as the low bioavailability of clopidogrel and the high bleeding risk of prasugrel. Our team synthesized deuterium clopidogrel(the patent has been obtained in China) to mitigate the disadvantages of clopidogrel clinical application, including a slow onset, greater influence of gene polymorphism and drug-drug interaction. Experimental Approach: Molecular docking technology was used to analyze the affinity between deuterium clopidogrel and P2Y12 receptor; The levels of active metabolites of deuterium clopidogrel in vivo were detected by HPLC/MS-MS and the activities of main metabolic enzymes was analyzed; Subsequently, platelet aggregation function, thrombus model were used to evaluate the pharmacodynamics of deuterium clopidogrel; Finally, the safety of deuterium clopidogrel were evaluated by blood routine, PT, APTT, bleeding time, serological tests, liver pathological biopsy, liver cell apoptosis and apoptosis-related protein detection. Key Results: The introduction of deuterium makes the binding of clopidogrel to P2Y12 receptor more stable, improves the concentration of active metabolites, reduces the inhibition of major metabolic enzymes including CYP2B6, CYP2C9 and CYP2C19, leading to the better anti-platelet effect without increasing the risk of bleeding, and leads to the decrease in the degree of hepatocyte apoptosis. Conclusion and Implications: In terms of both efficacy and safety, deuterium clopidogrel has a better effect, the present findings render deuterium clopidogrel a promising candidate for clinical application in thromboembolism disease and provides a new idea for the development of this new antithrombotic drug.

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`Fig.1 Synthetic route+Molecular docking.docx` available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.2 Aggregation rate.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.3 Antithrombotic action.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.4 AM+CYP450.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.5 Routine blood.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.6 PT, APTT, BT.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.7 Liver function.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.8 Hematoxylin and eosin staining.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel

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Fig.9 Immunohistochemistry.doc available at https://authorea.com/users/727379/articles/709240-evaluation-of-efficacy-and-safety-after-replacement-of-methyl-hydrogen-with-deuterium-at-7-position-methyl-formate-of-clopidogrel