遺伝子的にクロピドグレルに耐性の人々に対し高用量クロピドグレルは有効である（Abstract＃18501）

ELEVATE-TIMI 56: CYP2C19遺伝子多型を有する人々において高用量クロピドグレルは有効である

ELEVATE-TIMI 56: Higher doses of clopidogrel effective in people with CYP2C19 gene variations

クロピドグレルの抗血小板作用の一部を阻害する遺伝子変異を有する患者において高用量クロピドグレルは標準用量よりも有効であるとのlate-breaking researchの結果が2011年American Heart Association学会で発表され、Journal of the American Medical Associationに掲載された。ELEVATE-TIMI 56は、特異的なCYP2C19遺伝子多型を有する患者において最高1日300mg（標準用量の4倍）のクロピドグレル維持用量を計画的に調査した初めてのスタディである。スタディには心筋梗塞既往者または血管形成術を施行された患者335人（平均年齢60歳、男性75%）を対象とした。一般集団と同様に、スタディ参加者のうち24%がCYP2C19遺伝子多型を1コピー有し、2%が2コピー有していた。クロピドグレル用量を増量することにより、CYP2C19遺伝子多型を1コピー有する患者においては抗血小板作用が改善した。クロピドグレルの用量を3倍または4倍に増加し血小板機能を評価したところ、有効性が最大でなかった患者はわずか10%であった。一方、CYP2C19遺伝子変異を有する患者の半分においては通常用量では望ましい抗血小板作用が達成できなかった。

Full Text

Higher doses of clopidogrel were more effective than standard dosing in patients with a gene variant that blocks some of the drug's platelet inhibition effects, according to late-breaking research presented at the American Heart Association's Scientific Sessions 2011.

The study is simultaneously published in the Journal of the American Medical Association.

Nearly one-third of patients don't respond optimally to the currently recommended dose of clopidogrel and remain at increased risk for these clots that can cause myocardial infarctions. Previous research has linked this unresponsiveness partially to a variation in the CYP2C19 gene, which prevents the drug from being converted into the effective form.

"We know that someone's genetic predisposition can affect their response to clopidogrel," said Jessica L. Mega, M.D., M.P.H., the study lead author and associate physician at Brigham & Women's Hospital at Harvard Medical School in Boston, Mass. "Because of this, giving this drug in the same dose to all people may not be the right approach."

ELEVATE-TIMI 56 is the first study to systematically examine high maintenance doses of clopidogrel up to 300 mg per day (four times the usual dose) in patients with particular CYP2C19 gene variations. The researchers found that boosting drug levels improved the anti-platelet effect in patients with one copy of the CYP2C19 gene variation. When doses were tripled and quadrupled, only 10 percent of patients didn't have the optimal response when platelet function was assessed. In contrast, the usual dose failed to achieve the desired anti-platelet effect in about half of patients who had a mutation in the CYP2C19 gene.

"These data provide a rational framework for how to start to approach alternative dosing of clopidogrel in the nearly one-third of the population who harbor a genetic roadblock to metabolizing clopidogrel appropriately," said Marc S. Sabatine, M.D., M.P.H., study senior author and chairman of the TIMI Study Group, Brigham & Women's Hospital. Researchers found on average:

- Fifty-two percent of patients with one copy of the CYP2C19 gene variation didn't respond optimally at the standard 75 milligrams (mg).
- Twenty-six percent didn't respond at 150 mg.
- Ten percent didn't respond at 225 and 300 mg.

"These data suggest that people with particular genetic modifications, especially those who have the CYP2C19 variation, may need a higher clopidogrel dose than the standard 75 milligrams daily," Mega said.

Patients without the gene mutation received either 75 or 150 milligrams. After an initial blood test to measure platelet function, patients underwent testing every two weeks for eight weeks. Researchers found no significant increase in side effects as dosage increased during the duration of the study.

The study, conducted October 2010 to September 2011, included 335 patients from 32 U.S. sites who suffered a heart attack or underwent procedures to open blocked heart vessels. Their average age was 60 years, 88 percent were Caucasian, and 75 percent were men.

Similar to the general population, 24 percent of study participants carried one copy and 2 percent had two copies of the CYP2C19 genetic variation. Among the small number of patients with two gene copies, even the higher drug doses were ineffective.

While the results do suggest that most patients with one copy of the relevant gene could achieve platelet inhibition with these higher doses of clopidogrel, this study was not designed to assess the clinical outcomes produced by the higher doses.

Co-authors are Willibald Hochholzer, M.D.; Andrew L. Frelinger III, Ph.D.; Michael J. Kluk, M.D., Ph.D.; Steven Isserman, M.D.; William J. Rogers, M.D.; Dominick J. Angiolillo, M.D.; Dean J. Kereiakes, M.D.; Christian T. Ruff, M.D., M.P.H.; David D. Berg, M.D.; John Cyr, P.A.; Benjamin M. Scirica, M.D., M.P.H.; Laura Grip, B.A.; Robert A. Mesa, B.S.; John F. Mattimore, B.A.; Janina A. Longtine, M.D., Ph.D.; Alan D. Michelson, M.D.; and Marc S. Sabatine, M.D., M.P.H.

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