Drug Monitor

Clopidogrel: When Less is More

According to the Intracoronary Stenting and Antithrombotic Regimen: Choose Between Three High Oral Doses for Immediate Clopidogral Effect (ISAR-CHOICE) Trial, increasing the loading dose of clopidogrel doesn't correspondingly enhance the suppression of platelet function in patients who have undergone percutaneous coronary intervention (PCI). When trial researchers, from Deutsches Herzzentrum, Technische Universität München, Munich and Institut für Pharmakologie, Klinikum der Universität zu Köln, Cologne, both in Germany, investigated what the drug's effects would be if the loading dose were 900 mg, rather than the currently recommended 300 to 600 mg, they found that the body apparently reaches a saturation point.

In a double-blinded, randomized manner, researchers allocated one of three clopidogrel loading doses (300, 600, or 900 mg) to 60 patients with suspected or documented coronary artery disease, all of whom had been admitted for coronary angiography. The 600-mg dose significantly enhanced platelet inhibition compared to the 300-mg dose ($P \leq .03$). The 900-mg dose, however, did no more to increase plasma concentrations of active metabolite and clopidogrel or to further suppress adenosine diphosphate (ADP)-induced platelet aggregation four hours after administration.

These results suggest that a "bottleneck" result occurs in the intestinal absorption when doses exceed 600 mg. Researchers note that the vast majority of the antiplatelet effect of single doses (up to 600 mg) can be recorded within two hours. In this study, even in the group loaded with 900 mg of clopidogrel, the peak plasma concentration of the active metabolite was reached in less than one hour. The researchers cite results from a previous study that suggest splitting the 900-mg dose in two would allow for better absorption, though they acknowledge it might be impractical as a pre-PCI treatment.

Source: *Circulation.* 2005;112:2946–2950.

Who is Susceptible to DDS?

During treatment for Parkinson disease (PD), some patients develop a pattern of compulsive dopaminergic drug use, called the dopamine dysregulation syndrome (DDS). These patients express the need for increases in their medication early in the course of treatment and experience early tolerance to any observed benefits. They report feeling dysphoric and undertreated, despite the external appearance of adequate motor symptom control and increasingly severe peak-dose dyskinesias.

Researchers from Reta Lila Weston Institute of Neurological Studies and the National Hospital for Neurology and Neurosurgery, both in London, and MRC Cognition and Brain Sciences Unit, Cambridge, all in the United Kingdom, compared 25 patients with DDS to an outpatient sample of 100 patients with PD but without DDS. They investigated clinical features, impulsive sensation seeking (ISS) personality traits, past experimental drug use, alcohol consumption, smoking habits, and depressive symptoms in order to identify predisposing factors to DDS.

All participants were interviewed and subsequently given a series of questionnaires relating to temperament, character, and lifestyle. All 25 patients with DDS reported severe withdrawal dysphoria relieved by dopaminergic drug therapy, 23 had disabling dyskinesias, and more than half evidenced at least one of the following: aggression, psychosis, social breakdown, or behavioral compulsions. Researchers did not specifically examine other potential risk factors, such as impaired cognitive control; cognitive impulsivity; and environmental, social, genetic, and pharmacologic factors.

Compared to the patients without DDS, those with the syndrome had a significantly younger age of PD onset ($P < .01$). They also had higher levodopa equivalent unit dose, past experimental drug use, alcohol intake, and ISS ratings and lower reward-dependence trait scores. In addition, they tended to have higher novelty seeking scores and depressive symptoms than the PD control patients as well as a group of 25 healthy controls. Logistic regression analysis identified that novelty seeking personality traits, depressive symptoms, alcohol intake, and age at PD onset were significant predictors of DDS.

ISS traits are key in identifying patients at risk for DDS, the researchers say. In adolescence, ISS traits influence willingness to use and experiment with substances. In adults, they predict current drinking frequency. In general, the results showed that, despite the tendency of patients with PD to drink less alcohol than healthy controls, alcohol intake independently predicted DDS compared to the control group.

The researchers say that patients newly diagnosed with PD can be screened for novelty seeking traits and for the use of alcohol or drugs to identify those who may be more vulnerable to DDS throughout treatment. Subsequently, appropriate ways to cope can be addressed early on. ●

Source: *Neurology.* 2005;65:1570–1574.