FDA Alert for Healthcare Professionals

Clarithromycin (in the CLARICOR Study)

FDA ALERT [12/2005]:

FDA has learned of a placebo controlled study of patients in Denmark with heart disease (the CLARICOR Study), reporting increased mortality in patients treated with clarithromycin (14 days) compared with patients who received a placebo (http://bmj.bmjjournals.com/cgi/rapidpdf/bmj.38666.653600.55v1**). The observed difference in mortality became apparent after patients had been followed for one year or longer after the study drug was given. A mechanism by which two-weeks of clarithromycin could cause increased mortality measured after one year or longer is not clear. Previous trials of antibacterial drugs to prevent heart disease and other trials of clarithromycin have not shown a statistically significant effect on mortality. Considering the results from the CLARICOR study and the results from previous studies of antibacterial drugs to prevent heart disease, the FDA is not recommending any specific changes to the use of clarithromycin at this time. FDA has discussed these findings with the Danish Medicines Agency (DMA) and the FDA recommendation is consistent with that of the DMA. The FDA is providing the summary below to physicians and patients so that they can be aware of the information currently available. The FDA is attempting to get more information regarding the CLARICOR study and its findings.**

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about this information. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

- Healthcare providers should be aware of the information summarized below regarding the CLARICOR study. This information may also be helpful in addressing questions from patients about the CLARICOR study and clarithromycin (an antibiotic marketed as BIAXIN® and BIAXIN® XL).
- No specific changes in the product labeling for clarithromycin are being recommended at this time.

Summary

The following provides a more detailed description of the available information about the CLARICOR study and other published trials of antibacterial drugs in patients with heart disease.

The CLARICOR Study

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An article published by the *British Medical Journal* (available online at http://bmj.bmjjournals.com/cgi/rapidpdf/bmj.38666.653600.55v1), describes the findings of the CLARICOR study,[1] a study of clarithromycin for the prevention of heart disease. The study, conducted by academic investigators in Denmark, was designed to evaluate whether treatment with clarithromycin could prevent another event ("heart attack", unstable angina, or death) in patients with stable coronary artery (heart) disease (CAD). In this study, over 4300 people with stable CAD received either clarithromycin (500 mg once daily) or a placebo for two weeks. The results for the primary endpoint ("heart attack", unstable angina or death, whichever occurred first) did not achieve statistical significance ($p = 0.08$). There were 344 primary endpoint events in the clarithromycin group (15.8%) and 307 events in the placebo group (13.8%). Analysis of all cause mortality found that there were 212 deaths in the clarithromycin group and 172 deaths in the placebo group. The hazard ratio and 95% confidence interval for all-cause mortality was 1.27 (1.03 to 1.54) ($p = 0.03$).

The observed differences in deaths became apparent about one year or longer after the study drug was given. The finding of a higher mortality rate occurring beyond one year of follow-up after a single two-week course of clarithromycin was an unexpected finding. Most of these deaths were attributed to heart disease. When the analysis was limited to cardiovascular deaths, the difference in mortality between treatment groups was still present. There is no clear explanation for how clarithromycin would lead to more deaths than placebo and no biological mechanism to account for deaths occurring one year or longer after a single two-week treatment course of clarithromycin in the CLARICOR study. The authors' conclusions regarding this study are that even a brief course of clarithromycin given to patients with stable CAD may be associated with more deaths compared to similar patients given a placebo. The authors recommend further study of the long term effects of clarithromycin (and other antibacterial agents) in patients with coronary artery disease to further investigate the results of the CLARICOR study.

At this point in time, the FDA has not had access to the primary data for the CLARICOR study to perform an independent review of the study and its results. It is possible that further evaluation of the study will help in understanding the observed results. We also cannot exclude the possibility that other factors or chance could have contributed to the observed mortality difference. For example, the authors note that they would like to know about New York Heart Association class, ejection fraction at baseline and medical treatment and lifestyle during the study period.

FDA has reviewed analyses prepared by Abbott Laboratories of their clarithromycin clinical trials database. The analyses evaluate the available clinical trial data for clarithromycin to

[1] Jespersen, CM, Als-Nielsen, B, Damgaard, M., et al. "Randomised placebo controlled multicenter trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial." *BMJ*, DOI 10.1136/bmj.38666.653600.55

examine whether there are differences in death rates or adverse events related to heart disease between clarithromycin and other antibacterial drug comparators. These analyses do not show significant differences in the adverse events or death rates, but most of these studies ended after a few weeks or months. They do not continue for long enough to be able to see whether the difference in deaths reported in the CLARICOR trial would occur.

Previous Studies of Antibacterial Drugs for Prevention of Heart Disease

Some investigators have reported the presence of *Chlamydophila pneumoniae* in atherosclerotic plaques and there is some evidence of an association between *C. pneumoniae* antibodies and CAD. These findings have led investigators to perform clinical trials with antibacterial drugs active against *C. pneumoniae* (such as clarithromycin) in patients with CAD. The hypothesis of these trials has been that antibacterial therapy against *C. pneumoniae* would prevent progression of coronary artery disease and subsequent coronary events (e.g., heart attacks).

Two studies of clarithromycin (prior to CLARICOR) for the prevention of heart disease have been published. In one of these studies,[2] 148 patients with stable CAD were given clarithromycin or placebo for three months. After a year, there were four deaths in the clarithromycin group and one death in the placebo group. The number of patients in the study was too small to draw any conclusions about the death rates in this study. A second study[3] involved 473 patients undergoing surgery for heart disease. Patients received clarithromycin or placebo until their surgery (an average of 16 days of treatment). After two years of follow-up, there were 10 deaths in the clarithromycin group and 9 deaths in the placebo group. These two smaller studies do not show the same statistically significant difference in death rates shown in the CLARICOR study.

Several other antibacterial drugs have been studied for the prevention of heart disease.[4, 5] Antibacterial drugs with activity against *Chlamydophila pneumoniae* did not prevent subsequent cardiac events in patients with coronary artery disease. None of these other studies have shown statistically significant differences, either beneficial or harmful, in the rates of death for antibacterial-treated compared with placebo-treated patients.

[2] Sinisalo J and the Clarithromycin in Acute Coronary Syndrome Patients in Finland (CLARIFY) Study Group. "Effect of 3 Months of Antimicrobial Treatment with Clarithromycin in Acute Non-Q-wave Coronary Syndrome" Circulation (April 2, 2002) 105(13): 1555-1560.
[3] Berg et al. "Treatment with Clarithromycin Prior to Coronary Artery Bypass Graft Surgery Does Not Prevent Subsequent Cardiac Events" CID 40: 358-65 (February 1, 2005).
[4] Andraws R et al., "Effects of Antibiotic Therapy on Outcomes of Patients With Coronary Artery Disease – A Meta-analysis of Randomized Controlled Trials" JAMA (June 1, 2005) 293(21): 2641-2647.
[5] O'Connor CM et al., "Azithromycin for the Secondary Prevention of Coronary Heart Disease Events – The WIZARD Study: A Randomized Controlled Trial" JAMA (September 17, 2003) 290(11): 1459-1466.

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What the FDA is Doing

The FDA is taking the following steps in response to the preliminary findings reported from the CLARICOR study:

- FDA is providing this information to healthcare providers and patients via this Alert.
- FDA has discussed these findings with the Danish Medicines Agency (DMA) and is working with the DMA to obtain additional information regarding the CLARICOR study and its results. Through these efforts, FDA hopes to further investigate the findings reported from the CLARICOR study.
- FDA's Office of New Drugs and Office of Drug Safety are collaborating to evaluate available sources of post-marketing data for patients receiving clarithromycin.
- As information becomes available from continued analysis of the CLARICOR study or other sources, appropriate further steps will be determined.

We are providing this statement regarding the results of the CLARICOR study so that physicians and patients are aware of this information. FDA is not recommending any specific changes in the product labeling for clarithromycin (marketed as BIAXIN® and BIAXIN® XL) at this time. Physicians and patients should weigh the benefits and risks of any drug treatment, including clarithromycin.

The FDA will continue to notify healthcare providers and patients as new information becomes available.

Additional information regarding the CLARICOR study is also available on the Danish Medicines Agency website. (http://www.dkma.dk/)
(http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=7597)

The FDA urges health care providers and patients to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at http://www.fda.gov/medwatch/index.html.