AMIODARONE IN PATIENTS WITH HEART FAILURE

TWO recent studies have suggested that amiodarone, a potent antiarrhythmic agent, is a promising drug for the treatment of ventricular tachyarrhythmias after myocardial infarction.[1,2] The results of two additional studies of the use of amiodarone after myocardial infarction (the European Myocardial Infarct Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) will soon be reported.[3,4]

In this issue of the *Journal,* Singh and his coworkers report the results of the Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure.[5] This trial examined the effect of amiodarone on mortality in patients with chronic congestive heart failure and 10 or more ventricular premature beats.[6] Such patients have a particularly high risk of dying from ventricular arrhythmias. Unexpectedly, amiodarone had no significant effect on survival at two years. In a subgroup analysis, amiodarone also had no effect on overall mortality among patients with ischemic cardiomyopathy, but there was a trend in favor of amiodarone among patients with idiopathic (nonischemic) cardiomyopathy.

Previous studies have included too few patients for investigators to be able to detect an effect of amiodarone on mortality among patients with heart failure.[7] The results of two trials in Argentina were recently reported.[8,9] The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) study[8] was a multicenter, prospective, randomized (but not blinded) trial of amiodarone as compared with placebo in 516 patients with severe heart failure; the study population was stratified according to the presence or absence of nonsustained ventricular tachycardia. The trial was terminated prematurely because there were 106 deaths in the control group but only 87 in the amiodarone group (risk reduction with amiodarone, 28 percent; 95 percent confidence interval, 4 to 45 percent; $P = 0.024$). Furthermore, amiodarone was associated with slightly (but not significantly) lower rates of sudden death and death from progressive heart failure.

What are the reasons for the different results of the Veterans Affairs trial reported in this issue and the GESICA trial? Patients enrolled in the Veterans Affairs trial were an average of six years older than those in the GESICA trial. Thus, other diseases might have affected the clinical outcome. A difference in sex distribution may also have played a part. In the Veterans Affairs trial, 99 percent of the patients were men, as compared with only 81 percent of those in the GESICA trial. Despite the greater number of male than female patients in the GESICA trial, the reduction in overall mortality was small and not statistically significant among the men (26 percent, $P = 0.10$) but was more pronounced among the women (48 percent, $P = 0.076$). The unexpected results reported by Singh et al. may therefore reflect the lack of an effect of amiodarone in men. However, similar differences between men and women have not been reported in other postinfarction trials of amiodarone.[1,2] Thus, although age and sex may have played a part, these differences may well have occurred by chance. Whether other factors, such as differences in the cause, severity, or duration of heart failure between the male and female patients, may have influenced the outcome cannot be determined from the study's first report.[6]

The severity of heart failure may also explain the discrepancy in results. Patients in the GESICA trial had more advanced heart failure and lower ejection fractions than those in the Veterans Affairs trial. Survival at two years was lower in the placebo group in the GESICA trial (45 percent) than in the comparable group in the Veterans Affairs trial (71 percent). The fact that the GESICA trial, which included patients with more advanced heart failure, demonstrated a greater benefit of amiodarone therapy than did the Veterans Affairs trial may suggest that as heart failure becomes more severe, there is a greater chance for amiodarone to have a beneficial effect. That is, there may be a more favorable balance between the risk of the underlying disorder and the risk–benefit profile of the drug. Unfortunately, this notion is not consistent with a subgroup analysis in the GESICA trial that showed a trend toward a greater reduction in risk among patients with functional class II disease than among those with class III or IV disease. Furthermore, the Basel Antiarrhythmic Study of Infarct Survival[10] found a risk reduction with amiodarone only in patients with an ejection fraction of at least 40 percent.

The reasons for these discrepancies remain conjectural. With more severe heart failure, death may be due to pump failure, whereas with less severe heart failure, death from arrhythmia may be more common. Amiodarone has an antiarrhythmic effect on the heart, but it has other important actions, too. For example, in the Veterans Affairs trial, amiodarone significantly increased the ejection fraction. However, this improvement was not accompanied by a reduction in mortality. Furthermore, when the data were analyzed according to the initial ejection fraction (<30 percent or 30 to 40 percent), the overall mortality did not differ significantly between the amiodarone and placebo groups. Amiodarone also significantly reduced the frequency of ventricular arrhythmias in the Veterans Affairs trial, but this reduction did not result in improved survival.

The report by Singh et al. suggests that the cause of heart failure may influence the efficacy of amiodarone, since only patients with heart failure not due to myocardial ischemia seemed to derive a benefit from the drug. Only 29 percent of the patients in the Veterans Affairs trial had nonischemic heart disease, as compared with 60 percent of those in the GESICA trial. Thus, if we accept the finding of a beneficial effect of amiodarone in patients with nonischemic heart failure in the Veterans Affairs trial, the overall positive results of the GESICA trial may be due in part to the larger proportion of patients with nonischemic heart failure.

In other studies, patients were not stratified accord-

ing to the cause of heart failure. One example is the recent retrospective Cardiac Insufficiency Bisoprolol Study,[11] which found no significant risk reduction with the beta-blocker bisoprolol in patients with ischemic heart failure, but did find a benefit in those with nonischemic heart failure. In the recent Prospective Randomized Amlodipine Survival Evaluation,[12] in which patients with severe symptomatic heart failure were stratified according to the cause of the heart failure, survival was improved by the calcium-channel blocker amlodipine among patients with idiopathic dilated cardiomyopathy but not among those with ischemic cardiomyopathy. These findings suggest that the underlying cause of heart failure may play an important part in determining the efficacy of the drug.

With regard to adverse reactions to amiodarone, in the Veterans Affairs trial treatment was stopped in 32 percent of the placebo group and in 41 percent of the amiodarone group, but severe adverse reactions were rare. Whether the characteristics of the patients in whom treatment was discontinued were similar to those of the patients who continued to take the medication is not known. A secondary analysis according to the treatment actually received might have been helpful. The high rate of interruption of treatment raises a serious question about the validity of the trial. In contrast, the medication was stopped in only about 3 percent of the patients in the GESICA trial. The incidence of amiodarone-induced torsade de pointes (i.e., disorganized ventricular tachycardia) seems to have been very low. In some patients, however, these arrhythmias might have been missed because of their infrequent occurrence and because there was no systematic search for them.

The results of the Veterans Affairs trial are important for the assessment of antiarrhythmic drugs. However, the discrepancies between these findings and those of the GESICA trial need to be resolved, and the results of the European Myocardial Infarct Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial are eagerly awaited. In addition, the role of amiodarone in patients who have documented sustained ventricular tachycardia or in patients after aborted sudden death needs to be reevaluated, especially with the availability of implantable cardioverter–defibrillator devices. Despite the lack of a beneficial effect of amiodarone on mortality in the Veterans Affairs trial, the results of this study are important, because they show that amiodarone is safe (with no associated increase in mortality and probably no tendency to cause proarrhythmia) and can be given with a low frequency of side effects in a heterogeneous population of patients with congestive heart failure. In this sense, the Veterans Affairs trial has proved to be less an efficacy trial than a safety trial.

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REFERENCES

1. Burkart F, Pfisterer M, Kiowski W, Follath F, Burckhardt D. Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias: Basel Antiarrhythmic Study of Infarct Survival (BASIS). J Am Coll Cardiol 1990;16:1711-8.
2. Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, et al. Effect of amiodarone on mortality after myocardial infarction: a double-blind, placebo-controlled, pilot study. J Am Coll Cardiol 1992;20:1056-62.
3. Camm AJ, Julian D, Janse G, et al. The European Myocardial Infarct Amiodarone Trial (EMIAT). Am J Cardiol 1993;72:95F-98F.
4. Cairns JA, Connolly SJ, Roberts R, Gent M. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT): rationale and protocol. Am J Cardiol 1993;72:87F-94F.
5. Singh SN, Fletcher RD, Gross Fisher S, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. N Engl J Med 1995;333:77-82.
6. Singh SN, Fletcher RD, Fisher S, et al. Veterans Affairs congestive heart failure antiarrhythmic trial. Am J Cardiol 1993;72:99F-102F.
7. Nicklas JM, McKenna WJ, Stewart RA, et al. Prospective, double-blind, placebo-controlled trial of low-dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy. Am Heart J 1991;122:1016-21.
8. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Lancet 1994;344:493-8.
9. Garguichevich J, Ramos J, Gambarte A, et al. Argentine pilot study of sudden death and amiodarone: E.P.A.M.S.A. final report. Circulation 1993;88: Suppl:I-447. abstract.
10. Pfisterer M, Kiowski W, Burckhardt D, Follath F, Burkart F. Beneficial effect of amiodarone on cardiac mortality in patients with asymptomatic complex ventricular arrhythmias after acute myocardial infarction and preserved but not impaired left ventricular function. Am J Cardiol 1992;69:1399-402.
11. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765-73.
12. Packer M. Prospective randomized amlodipine survival evaluation. Presented at the Annual Meeting of the American College of Cardiology, New Orleans, March 19-22, 1995.

WHAT CAUSES WASTING IN AIDS?

THE wasting syndrome, defined as the unintentional loss of more than 10 percent of body weight, is a devastating complication of AIDS, other infections, and cancer.[1] Because weight loss is an independent contributor to death,[2,3] reversing it could theoretically both extend life and improve its quality.

Unfortunately, nutritional supplementation is not uniformly effective in patients with the wasting syndrome.[1] Such supplementation does improve the nitrogen balance in patients with carcinoma of the esophagus and stomach in whom food intake is decreased. In patients with lymphoma or patients with AIDS who have active infections, hyperalimentation increases fat mass but not lean body mass. However, in critically ill patients with sepsis, total parenteral nutrition does not reverse the negative nitrogen balance and may not even prevent the loss of weight.[1]

Many efforts have been made to understand the wasting syndrome.[1] Although it is at one extreme of the spectrum of wasting, sepsis has served as the model for studying the mechanisms involved. Sepsis is a markedly hypermetabolic state characterized by increased resting energy expenditure, negative nitrogen balance, and disturbances in metabolism that waste energy. For example, futile cycling occurs when fatty acids are mobilized from fat and, rather than being oxidized, are re-esterified into triglyceride, secreted from the liver, and stored again in fat. Inappropriate use of substrate occurs when glucose is converted to fatty acid and ultimately stored as fat, a normal event when energy intake is excessive but an inappropriate one when it is not.

Human immunodeficiency virus (HIV) infection causes an increase in resting energy expenditure and disturbances in metabolism similar to those in sepsis.[1,4-7] Given the difficulty of reversing the wasting syndrome with alimentation, it has been tempting to attribute wasting in patients with AIDS to hypermetabolism. However, the quantitative contribution of these metabolic pathways to the increase in resting energy expenditure is small. Indeed, the role of increased resting energy expenditure in wasting is unknown, and theoretically, increased intake of calories could replenish any energy expended.

Recent studies of HIV-infected patients indicate that these disturbances in lipid metabolism and even the increase in resting energy expenditure do not suffice to cause wasting, for several reasons. First, such patients can usually sustain their weight and lean body mass for prolonged periods.[4] Second, resting energy expenditure is increased in patients at all stages of HIV infection,[5-7] even asymptomatic patients with normal CD4 cell counts.[5] (It should be noted that since the metabolic changes are due to the host response, these studies indicated that HIV infection was not latent but contained.) Yet increased resting energy expenditure was not enough to cause wasting.[5-7] Instead, the change in weight in patients with HIV infection was proportional to their caloric intake.[7] Patients who were losing weight had anorexia induced by secondary infection. Thus, it seemed unlikely that hypermetabolism in itself was the driving force behind their wasting.

The true measure of hypermetabolism, however, is total energy expenditure, which consists of resting energy expenditure plus diet-induced thermogenesis plus energy expended in activity. Until total energy expenditure was measured, the relative roles of hypermetabolism and decreased caloric intake remained uncertain. In this issue of the *Journal,* Macallan et al. report the results of a study of the wasting syndrome in patients with HIV infection in which total energy expenditure was measured by the doubly-labeled–water technique.[8] These investigators studied patients who were losing weight, had stable weight, or were gaining weight. None of these groups had an increase in total energy expenditure, and indeed, this value decreased in the group with the most rapid weight loss. Thus, even in terms of total energy expenditure, hypermetabolism does not cause wasting. Instead, as in the earlier study,[7] caloric intake was the chief determinant of weight change.[8]

What, therefore, is the role of energy expenditure in the wasting process of AIDS? Increased resting energy expenditure is not sufficient to cause wasting in AIDS; the body has mechanisms to compensate for this small increase. In uninfected persons, caloric restriction causes a decrease in resting energy expenditure that blunts the loss of weight, preserving lean body mass. During HIV infection, in contrast, the elevation in resting energy expenditure persists despite decreased caloric intake.[7,8] Thus, failure to compensate with a decrease in resting energy expenditure during decreased caloric intake accelerates the negative energy balance.

Macallan et al. present evidence for another compensatory response: patients with rapid weight loss had a decrease in physical activity, which decreased their total energy expenditure, in turn reducing the energy deficit.[8] Thus, the lethargy and fatigue that accompany infection help maintain energy balance and weight. Yet physical activity is important for maintaining lean body mass. Furthermore, the HIV-infected men with stable weight had normal total energy expenditure and caloric intake, despite their increased resting energy expenditure. To retain stable weight, such patients too must decrease the amount of energy they expend in activity; maintaining normal activity may lead to more subtle defects in energy balance, as the data of Macallan et al. suggest.[8]

If metabolic disturbances are not enough to cause wasting and decreased caloric intake does cause it, what is the role of increasing energy intake to reverse the wasting syndrome, and why is increased intake of calories stored mostly as fat? Rapid weight loss due to decreased caloric intake is usually caused by secondary infection, whereas weight gain resulting from increased caloric intake usually occurs during a recovery from such infection.[7,9] The recovery of weight is often incomplete, however, and lean body mass may not be re-

gained as efficiently as fat.[1,2] The decrease in physical activity due to lethargy and fatigue from illness that Macallan et al. describe[8] may contribute to the failure to rebuild lean body mass. Whether increasing caloric intake during wasting can blunt the loss of lean body mass remains unknown.

The clinical implications of these studies are important. Despite metabolic disturbances and increased resting energy expenditure, most HIV-infected patients maintain their weight. Wasting predicts impending complications. Rapid weight loss (more than 4 kg in less than four months) accompanied by anorexia is a sign of secondary infection.[7,9] Slower weight loss (more than 4 kg in more than four months) is often due to gastrointestinal disease with diarrhea,[9] with less marked decreases in caloric intake.[8] Because successful treatment of secondary infection is the best way to increase weight and lean body mass, early diagnosis is critical. Thus, keeping a graphic record of the weight of each patient with AIDS will provide an early warning of infections.[10]

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REFERENCES

1. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. N Engl J Med 1992;327:329-37.
2. Kotler DP, Tierney AR, Wang J, Pierson RN Jr. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr 1989;50:444-7.
3. Guenter P, Muurahainen N, Simons G, et al. Relationships among nutritional status, disease progression and survival in HIV infection. J Acquir Immune Defic Syndr 1993;6:1130-8.
4. Hommes MJ, Romijn JA, Endert E, Sauerwein HP. Resting energy expenditure and substrate oxidation in human immunodeficiency virus (HIV)-infected asymptomatic men: HIV affects host metabolism in the early asymptomatic stage. Am J Clin Nutr 1991;54:311-5.
5. Melchior JC, Salmon D, Rigaud D, et al. Resting energy expenditure is increased in stable, malnourished HIV-infected patients. Am J Clin Nutr 1991; 53:437-41.
6. Grunfeld C, Pang M, Shimizu L, Shigenaga JK, Jensen P, Feingold KR. Resting energy expenditure, caloric intake, and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Am J Clin Nutr 1992;55:455-60.
7. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1989;86:27-31.
8. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. N Engl J Med 1995;333:83-8.
9. Macallan DC, Noble C, Baldwin C, Foskett M, McManus T, Griffin GE. Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. Am J Clin Nutr 1993;58:417-24.
10. Grunfeld C, Feingold KR. Body weight as essential data in the management of patients with human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Am J Clin Nutr 1993;58:317-8.

PROTECTING THE EMBRYO FROM X-RATED DRUGS

NO one who attended the hearings on isotretinoin at the Maryland headquarters of the Food and Drug Administration (FDA) in April 1988 could have failed to notice that the physicians present were split into two camps. On one side sat the dermatologists. They showed slides of patients with disfiguring acne, some of whom had threatened to commit suicide. On the other side sat the pediatricians. They showed slides of patients ravaged by prenatal exposure to isotretinoin, now profoundly handicapped physically and mentally. The first group pleaded that isotretinoin be allowed to remain on the market, and the second group that it be taken off.

The FDA decided to allow isotretinoin (already labeled "X" to indicate that it should not be used during pregnancy) to remain on the market but to require stronger warnings against its use during pregnancy. The agency now requires a negative pregnancy test before treatment with the drug, labels warning against becoming pregnant while taking it, the use of contraceptives during therapy, and an informed-consent form, with both written and oral sections warning of isotretinoin's potent teratogenic effects. Have these measures been effective?

In this issue of the *Journal,* Mitchell and colleagues[1] report on the effect of these measures in over 120,000 women 12 to 59 years of age who used isotretinoin. This remarkable effort provides some encouraging news. Virtually all the women (99 percent) reported having been told by their doctors that they should not become pregnant while taking the drug, and nearly all those who were sexually active used some form of contraception. One disturbing finding was that one third of the women reported not having had any type of pregnancy test before starting therapy. Fortunately, only 402 pregnancies were reported during isotretinoin treatment.

Do these results mean that we can now breathe a sigh of relief? Not quite. Participation in this study was voluntary; roughly half the exposed women chose not to participate. Thus, the results might be considered a best case. That is, women who are sufficiently motivated to participate in a research study are also sufficiently motivated to avoid becoming pregnant while taking isotretinoin. In the worst case, the women who chose not to participate in the study may have been less responsible and have failed to use effective contraception. This worst case would result in many more exposed and malformed offspring.

Because we cannot be sure that all the women taking isotretinoin are avoiding pregnancy, we must ask some critical questions. Are the current recommendations concerning contraceptive use strong enough? Some women reported using condoms or the rhythm method — methods with high failure rates. It would be safer to require women to use more reliable methods. Intrauterine devices and injectable or implantable hormonal contraceptives have low failure rates and do not depend on a woman's or her partner's remembering to use them.

We must also ask whether too many women are be-

ing treated with isotretinoin. Isotretinoin is indicated as a drug of last resort for severe, disfiguring, nodular acne, to be prescribed only after other drugs, including systemic antibiotics, have failed.[2] The FDA has argued that the number of women who receive isotretinoin far exceeds the number who meet these criteria.[3]

Clearly, it behooves physicians to restrict isotretinoin use to women for whom all other therapy has failed and to be sure a woman is not pregnant before starting therapy. Asking adolescents who deny being sexually active to use contraceptives may be awkward, but because more than 1 million 15-to-19-year-olds become pregnant each year (95 percent of them unintentionally),[4] it may not be a bad idea. A woman should be advised to stop using isotretinoin immediately if her menstrual period is late,[5] because many malformations are still avoidable at that time. With sufficient effort, it should be possible to reduce the number of embryos exposed to isotretinoin even further; however, embryos will continue to be exposed to other possible and established teratogens.

Disturbingly little is known about the teratogenic potential of most drugs. Although the FDA has developed classes (A, B, C, D, and X) to define the safety of drugs during pregnancy, most drugs have not been given a rating by their manufacturers.[6] Pharmaceutical companies are appropriately reluctant to test drugs in pregnant women. Studies in animals help little. Of approximately 1200 known animal teratogens, only about 30 are known to be teratogenic in humans.[7] Fortunately, these 1200 animal teratogens include chemicals and other agents that pregnant women are unlikely to encounter. Unfortunately, they also include drugs for which there are insufficient data to prove that they are safe for humans. Paradoxically, it can be more difficult to prove that a drug is not a teratogen than to prove that it is one. In addition to needing to know more about which drugs are teratogens, we need to investigate the issue of individual susceptibility. For example, recent work on neural-tube defects suggests that it may be possible to identify women at risk by studying how they metabolize homocysteine.[8]

Unavoidable exposure continues to present a dilemma to the treating physician. What can one do when a woman using a teratogenic drug — for example, an anticonvulsant agent — is at risk for becoming pregnant? Any woman of childbearing age who is taking a teratogenic drug should be informed of the risk, the need to consult her physician before becoming pregnant, and the need for reliable contraception if she is sexually active. The feasibility of changing to a nonteratogenic drug should be explored when she desires to become pregnant, or sooner, if an equally effective alternative is available. If there is no safe alternative, she must be alerted to the danger of having a malformed infant. Simply discontinuing therapy would certainly be better for the embryo, but it would be good for neither the embryo nor the mother if she were to have recurrent problems — seizures, for example. The possibility of prenatal diagnosis of drug-related defects should be discussed, but not all drug-related defects can be identified before delivery.

Mitchell and coworkers have shown how successful a well-educated, motivated group of women can be at avoiding pregnancy while taking a teratogenic drug electively; however, daunting challenges remain. We must develop better strategies for averting accidental exposure to teratogens due to unexpected conception, better methods to assess the teratogenicity of drugs, and more therapeutic options so that women need not take teratogenic drugs. Then, and only then, will we be able to breathe that sigh of relief.

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REFERENCES

1. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med 1995;333:101-6.
2. Physicians' desk reference. 49th ed. Montvale, N.J.: Medical Economics Data, 1995:2020.
3. Division of Epidemiology and Biostatistics, Center for Drugs and Biologics, Food and Drug Administration. Memorandum: maternal exposure to Accutane. Washington, D.C.: Public Health Service, February 11, 1988.
4. Surveillance for pregnancy and birth rates among teenagers, by state — United States, 1980 and 1990. MMWR Morb Mortal Wkly Rep 1993;42(SS-6):1-27.
5. Rosa FW. Retinoic acid embryopathy. N Engl J Med 1986;315:262.
6. Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in pregnancy and lactation. 4th ed. Baltimore: Williams & Wilkins, 1994.
7. Shepard TH. Catalog of teratogenic agents. 6th ed. Baltimore: Johns Hopkins University Press, 1989.
8. Mills JL, McPartlin JM, Kirke PN, et al. Homocysteine metabolism in pregnancies complicated by neural-tube defects. Lancet 1995;345:149-51.