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INSIDE

Statins, Rhabdomyolysis, and the FDA

ABSTRACT & COMMENTARY

Source: Graham DJ, et al. *JAMA*. 2004;292:2585-2590.

A SERIES OF REPORTS APPEARED IN A RECENT ISSUE OF *JAMA* dealing with the withdrawal of Baycol (cerivastatin or ceriva) from the market in 2001. The lead article is an analysis of a large database demonstrating an extremely high rate of rhabdomyolysis (rhabdo) with ceriva and, particularly, the combination of ceriva and gemfibrozil.[1] The next article is a detailed commentary on the FDA and the subsequent actions taken by pharmaceutical companies.[2] In addition, there are pro and con articles regarding the corporate response of Bayer, regarding the actions taken by the company from 1999 until Baycol was first withdrawn from the US market in 2001.[3-6] Fontanarosa et al contribute to this interesting regulatory political story.[3] The current crisis regarding Vioxx and other Cox-2 agents echoes the ceriva story, with suspicion by many that the drug companies (Bayer and Merck) had sufficient data regarding serious adverse reactions to warrant discontinuation of marketing well before the decision was made.

The lead article in *JAMA* is an analysis of 11 large health-plans, regarding the incidence rates of rhabdo per person-years of treatment, and the relative risk of rhabdo with specific statins. This is an extensive survey establishing the incidence of rhabdo in individuals treated with statins, fibrates, or the combination. Rhabdo is defined as severe muscle injury, with a creatine kinase level more than 10 times the upper limit of normal. Severe rhabdo is a subset of individuals with a CK > 10,000 IU/L, or 50 times the upper limit of normal. Relative risk estimates were obtained for gender, age, and the presence of diabetes. The database included 252,000 patients, most were exposed to statin or fibrate monotherapy and 7300 person-years of combinination therapy. Twenty-four patients had rhabdo; almost all had muscle pain or weakness for a week (range 1-30 days prior to admission), and 18 had severe rhabdo. The incidence of rhabdo for monotherapy with atorvastatin, pravastatin, and simvastatin was comparable. However, the incidence rate for ceriva or gemfibrozil as monotherapy was much greater than that of the other statins. No rhabdo was reported for fenofibrate monotherapy. The incidence rate

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for rhabdo of a statin-fibrate combination was almost 3-fold vs statins alone. The NNT for 1 year for a case of rhabdo was approximately 1700, with statin-fibrates vs 10-13 patients for combination ceriva-gemfibrozil. Risk with rhabdo was increased in subjects over 65 and diabetics. Gemfibrozil use alone was associated with a 5.5-fold rhabdo increase, ceriva alone with a 10-fold increase in risk, and the combination of non-cerivastatin and gemfibrozil with a 12-fold increased risk vs statin monotherapy. Ceriva had a 1400-fold risk when used with gemfibrozil! Graham et al conclude that use of atorva, prava, or simva has a "relatively low risk of rhabdo." They suggest that higher risk subjects, ie, diabetics, or combination drug therapy, should be counseled to stop the statin immediately if any symptoms suggestive of rhabdo occur. This is particularly important in that there likely will be a substantial increase in the number of patients treated with statins over the next several years.

Another article carefully reviews much of the medical and legal record with respect to the safety of ceriva.[2] Many aspects of the regulatory process are examined. Documents from litigation, as well as the published literature are reviewed. Ceriva was launched in the United States in the spring of 1998. Almost immediately, 6 cases of ceriva-associated rhabdo were reported as potential serious adverse drug reactions. In July 1998, rhabdo was added to the warnings in the ceriva packet insert. In 1999, reports of rhabdo with ceriva-gemfibrozil became available. Unpublished clinical trials demonstrated a high incidence of CK elevations and side effects using the 1.6 mg dose, with an estimate that combined ceriva-gembrozil were used in approximately 50% of rhabdo cases. In internal reports from early 2000, Bayer scientists confirmed that ceriva monotherapy was associated with a "substantial elevated risk of rhabdo compared with other statins." Elderly or thin women were thought to be at increased risk with the 0.8 mg dose. Label updates occurred in late 2000 and spring 2001. In August 2001, the drug was withdrawn from the US market. Graham and colleagues describe the history of prescription drug evaluation by the FDA in considerable detail. Federal funding constraints have impacted adversely on the FDA, with respect to pre- and post-marketing safety, and the pressure has increased for "more and faster new approvals", without additional funds for safety surveillance.

The overall experience of rhabdo in long term non-ceriva statin trials are reported, with an estimated 5.3 per 100,000 person years with active treatment vs 3.3 per 100,000 person years with placebo. The ceriva data is much more worrisome, with an increased risk of rhabdo, 65 times more than the other statins combined. Mortality rates with rhabdo were very high compared to other statins. It was subsequently discovered that combined gemfibrozil-ceriva use increased ceriva blood concentrations by 500%. Graham and colleagues focus on the interactions between the pharmaceutical industry and the FDA, and suggest that FDA actions might have been delayed because of inadequate spending for safety monitoring after the release of ceriva. They discuss the conflict of interest that is present in reporting details of drug safety by a pharmaceutical company regarding risks vs benefits of a drug to be FDA approved. Graham and colleagues conclude that serious flaws exist in the current system for severe adverse drug reaction (ADR) reporting and monitoring. They recommend establishment of an independent board for monitoring of drug safety or toxicity (or to provide sufficient support to the FDA for this purpose). Once a drug is approved for marketing, there are no automatic re-reviews. Graham and colleagues state that provision of "post marketing fees and regular re-review of approved drugs might enhance patient safety in the United States."

In an article by Strom,[4] an epidemiologist at the University of Pennsylvania, the FDA post-marketing surveillance system is described.[4] Identification of

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possible ADRs after marketing "relies on spontaneous voluntary reporting to industry regulators of reactions observed in clinical practice, fundamentally a 1950's era approach." The large majority of such reports are received by the manufacturers and not the FDA; (almost 300,000 annually). Strom agrees with Psaty et al[2] in calling for complete public disclosure of the results of all clinical trials, and suggests that pharmaco-epidemiology studies be included as well. He charges that the ceriva matter indicates that "critical gaps" remain in the FDA safety system. "The resources expended to ensure drug safety are extremely limited." He questions oversight by pharmaceutical companies because of the "inherent conflict of interest" related to possible adverse effects of newly marketed drugs. "No organization is charged with developing and testing new methods for improving physician's use of drugs in clinical practice." A 1990 GAO study found that half of approved drugs have serious adverse effects undetected before approval. The ability of the FDA and others to insure safety "are extraordinarily limited." Furthermore, "there is indeed a conflict of interest in asking an industry to monitor its own drugs." Strom also calls for bolstering the FDAs efforts to monitor drug safety and establish a national center for drug surveillance to "complement the regulatory mission of the FDA." Another article weighs in on this theme, placing much of the blame on industry, "yet the major problem with the current system for ensuring the safety of medications is that drug manufacturers are largely responsible for collecting, evaluating, and reporting data from post-marketing studies of their own products. This approach has many inherent problems."[3] Fontarosa and colleagues mention the SSRI and Cox-2 problems, focusing on the recent withdrawal of Vioxx from the market. They echo Psaty et al, and state that unpublished data obtained from company documents indicate that "the company was well aware of the risks of rhabdo and the interaction of ceriva with gemfibrozil even as early as 4 months after the launch of ceriva." They state that "companies also have financial incentives and economic pressures that may influence the interpretation of adverse event data and may delay full reporting to the FDA." Fonterosa and colleagues are pessimistic as to whether the FDA can overcome the loss of trust and confidence of healthcare workers and the public regarding "its first absolute priority to protect public health." The approval process must uncouple post-marketing surveillance from the drug approval process. They concur with demands for an independent drug safety board or agency that would specifically oversee post-marketing surveillance of drugs and devices. In yet another article, a Bayer lawyer states, "Bayer's conduct in the marketing of ceriva from 1997 until its voluntary withdrawal. . . was responsible, appropriate, and consistently motivated by the concern for the safety and welfare of patients."[5] Psaty et al robustly respond to this article.[6]

COMMENTS BY JONATHAN ABRAMS, MD

The 6 articles in the December 1, 2004, issue of *JAMA* represent a detailed overview of drug safety in the United States. Not only does the withdrawal of cerivastatin reflect the current situation, but problems with antidepressants in youngsters and, more recently, the identification of adverse reactions with the 3 Cox-2 inhibitors, raise important questions regarding the ability of the FDA to effectively police ADRs after release of a drug. The pressures on the FDA from Big Pharma companies and the US Congress to speed up the drug approval process, as well as in funding changes, leaving the FDA surveillance system without sufficient support, are critical matters. Whether or not a new drug safety Czar is the answer is not clear. It would appear that specific legislation enhancing the FDA's surveillance and safety abilities, independent from the drug approval process, might suffice, as opposed to setting up an entirely new federal commission or agency. Nevertheless, there is unfortunately too much evidence over the past several years that "Something is Wrong in Denmark." The problems in part are complicated by the enormous popularity of the SSRIs, statins, and Cox-2 inhibitors, resulting in billions of dollars in sales in the United States, and even more worldwide. Multiple recent newspaper and television reports dealing with the current Cox-2 inhibitor story accentuate the problem. Some of these drugs are like a fancy car; fine if you can afford it, but not a truly better means of transportation than a standard automobile. Regarding Baycol, the unexpected hazard was identified very early after release was either unrecognized or not acted upon, or both, until ultimate withdrawal from the market, arguably later than it should have been. This is, alas, very similar to the problem with the Cox-2 inhibitors, which have already achieved remarkable sales, when compared to Baycol. In the case of both ceriva and Cox-2 adverse events, it is regrettably true that these drugs are not essential, and that many alternatives are available. This may not be the case for SSRI therapy in teenagers and children, where depression can lead to suicide and severe psy-

chological disturbances, for which an effective dose would be highly valuable. No matter which side of the safety argument one is on, it is clear that there is enough blame to go around, including the FDA and big pharmaceutical companies. Vigilance and hyperalertness may not be sufficient after a new drug has been approved, which could result in hundreds of thousands, if not millions, of new users. It is now clear that such patients may serve as an unwanted sensor to detect rare but extremely harmful adverse effects. Let us hope that there will be more light than heat arising from these unhappy experiences in the years ahead. ■

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Niacin Plus Statins For Low HDL

ABSTRACT & COMMENTARY

Synopsis: *The addition of niacin to patients with known CAD on statins raised HDL cholesterol and reduced atherosclerosis progression.*

Source: Taylor AJ, et al. *Circulation.* 2004;110: 3512-3517.

ALTHOUGH GOOD AT LOWERING LDL CHOLESTEROL, statins do not raise HDL enough in many patients. Niacin is the most effective therapy for low HDL, but little information exists about combination niacin and statin therapy on cardiovascular outcomes. Thus, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study was conducted at Walter Reed Army Medical Center to evaluate the effect of adding niacin to statins on carotid intima-media thickness (CMT) in patients with known coronary artery disease (CAD). This was a double-blind, randomized, placebo-controlled study in 167 patients with CAD documented by myocardial infarction or coronary revascularization. Patients on statins with LDL < 130 and HDL < 45, and no known contraindication to niacin, were randomized to placebo or extended-release niacin starting at 500 mg for 30 days, then 1000 mg for 11 months. Only 4 patients had their statin dose changed during the study. The primary end point of CMT change at 1 year was increased in the placebo group by 0.044 mm (P < .001) and was unchanged in the niacin group, 0.014; P = 0.23. LDL was 89 at baseline and was unchanged by niacin therapy. HDL averaged 39 in the niacin group at baseline and increased to 47 (P < .001); there were no changes in the placebo group. Triglycerides also decreased in the niacin group (164 to 134; P < .01), but fasting glucose increased (107 to 123; P = 0.017). CRP measures were unchanged by niacin. Patients without insulin resistance (diabetes or metabolic syndrome) on niacin had the lowest progression rate of CMT. Cardiovascular events occurred in 3 niacin patients and in 7 placebo patients (P = NS). Study drug adherence was > 90%, and not different between placebo and niacin. No patient had liver tests > 3 times the upper normal limit, and none had myositis. The majority of patients on niacin noted skin flushing. Taylor et al concluded that the addition of niacin to patients with known CAD on statins raised HDL cholesterol and reduced atherosclerosis progression.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Although it is well-known that niacin raises HDL levels, the value of this effect, in addition to statins and its tolerability, has been poorly defined. The coronary drug project evaluated niacin monotherapy and showed a reduction in nonfatal myocardial infarction and 15-year mortality, but other studies employing niacin included it with other agents, making it difficult to tease out the effects of niacin alone. This is the first study of moderate-dose niacin added to statins in a systematic, controlled fashion. The study was not powered for clinical outcomes, but rather used CMT as a surrogate. Despite an average duration of statin therapy of about 5 years and average LDL levels of 85 to 90, the placebo group showed progression in CMT. There are several explanations for this: The low HDLs, high triglycerides (average > 150), or failure to drive the LDL below 80 in all the statin patients. Niacin addressed the first 2 issues and showed a lack of progression, thus, indirectly supporting the value of raising HDL and lowering triglycerides. These results are also concordant with the results of a small study of the effect on vessel walls of infusing man-made HDL.

Niacin seemed to be well-tolerated at this dose. Although most patients had skin flushing, few discontinued therapy. Also, liver tests were not alarmingly elevated (> 3 times the upper limit), but the report did not give the actual liver function test data. So elevations < 3 times the upper limit probably were observed. No muscle problems were reported. Thus, this long-acting niacin preparation given at bedtime in moderate doses seems like a reasonable approach to those with low HDL on adequate statin therapy.

Since most of the subjects were on simvastatin, we do not know if more potent statins with greater LDL-lowering would have worked just as well. Also, the role of fibrates, which also increase HDL and reduce triglycerides, either alone or in combination with statins, is unclear. However, the fibrate statin combination probably has more potential for adverse effects. Finally, the suggestion that patients with diabetes or the metabolic syndrome do not do as well on the statin and niacin combination requires more study. ■

Left Ventricular Remodeling With Chronic Right Ventricular Apical Pacing

ABSTRACT & COMMENTARY

Synopsis: *Chronic apical right ventricular pacing in patients with congenital heart block is associated with late findings consistent with deleterious left ventricular remodeling.*

Source: Thambo JB, et al. *Circulation.* 2004;110: 3766-3772.

In this paper, Thambo et al report results of a study conducted on a small group of patients with congenital complete AV block to see whether or not they suffered any detrimental effects from chronic pacing from the right ventricular apex. The study population was composed of 23 patients with a mean age of 24 years. Each had received a dual chamber pacemaker with ventricular pacing from the RV apex at least 5 years previously. Only patients without other cardiac abnormalities were included in the study. These patients with congenital AV block were then compared to a control group of 30 healthy volunteers who were matched for age, gender, weight, and height. All of the congenital AV block patients had undergone clinically indicated echocardiography prior to initiation of pacing. Patients in both groups underwent echocardiography and exercise testing as part of the study. During the study echocardiogram, Thambo and colleagues evaluated the following parameters of ventricular dyssynchrony: 1) interventricular dyssynchrony, defined as the difference between the aortic and pulmonary preejection delays; and 2) septal to posterior wall motion delay, defined as the shortest interval between maximum displacement of the left ventricular septum and that of the posterior wall at the papillary muscle level. The following hemodynamic variables were also evaluated: left ventricular filling time, cardiac output, left ventricular stroke volume and ejection fraction, and the severity of mitral regurgitation. Tissue Doppler imaging was used to assess intra-left ventricular dyssynchrony and delayed longitudinal contraction.

In the group with congenital AV block, the echocardiographic ejection fraction was 69 ± 6%, and no patient had significant mitral regurgitation prior to receiving their pacemaker. The escape rhythm was junctional (QRS width less than 120 msec) in 19 patients and ventricular (QRS width greater than 120 msec) in 4 patients. Pacing was first instituted at an average age of 8 ± 4 years. Ten patients had initially received an epicardial pacing device before being later converted to a transvenous system. At the time of the long-term measurements made in this study, all patients were programmed in either VDD or DDD/DDDR modes with 100% ventricular pacing.

After long-term endocardial pacing, 3 patients manifest New York Heart Association functional class II or III heart failure. Their left ventricular ejection fractions were 39%, 41%, and 45% respectively. The remaining patients were asymptomatic and had left ventricular ejection fractions greater than 55%. In the congenital AV block group, echocardiographic examination after chronic right ventricular pacing showed LV remodeling with LV dilatation and asymmetrical hypertrophy. The ratio of posterior wall to septal wall thickness was 1 ± 0.1 before implantation vs 1.3 ± 0.2 after long-term RV pacing. Measures of both interventricular dyssynchrony (55 ± 18 vs 25 ± 8 m/sec) and of the septal to posterior wall motion delay (84 ± 26 vs 41 ± 16) were greater after long-term right ventricular pacing than before implantation. Similar findings consistent with dyssynchrony were not seen in the healthy control subjects.

Mean resting cardiac output was decreased in the congenital AV block patients during chronic right ventricular pacing, compared with that measured in the control patients (3.8 ± 0.6 vs 4.9 ± 0.8 L/min). Stroke volume

was also lower in the paced group. The ratio of the area of mitral regurgitation to the area of the left atrium was higher in the paced group than in controls (16 ± 8 vs 5 ± 2). Estimates of interventricular dyssynchrony, intraventricular left ventricular dyssynchrony, the extent of left ventricular myocardium displaying delayed longitudinal contraction, and septal to posterior wall motion delay were all significantly higher after chronic RV pacing in the congenital AV block group than in controls. During exercise testing, the performance of patients with chronic RV pacing was significantly worse than that of matched controls (123 ± 24 vs 185 ± 39 watts). Heart rates during exercise were not significantly different between the groups.

Thambo and colleagues conclude that chronic apical right ventricular pacing in patients with congenital heart block is associated with late findings consistent with deleterious left ventricular remodeling. Although symptoms are only reported by a few individuals, patients with congenital complete heart block have lower peak exercise capacity than matched controls, presumably due to this electromechanical dyssynchrony.

COMMENT BY JOHN P. DiMARCO, MD, PhD

This paper provides some intriguing new insights into the management of patients with congenital complete AV block. Often these patients present with few or only minor symptoms as children, teenagers, or as young adults. At first it was uncertain whether or not these patients would benefit from permanent pacing. However, even in the absence of reported symptoms, implantation of a dual chamber pacemaker significantly improves exercise performance in such patients. There are also numerous reports of unexpected sudden death among unpaced patients with congenital AV block, and this is another reason to recommend pacing. Longevity in congenital AV block patients after dual chamber pacing has been thought to be restored to normal. This paper by Thambo and colleagues, however, suggests that chronic right ventricular atrial pacing fails to restore these patients to their full functional potential due to dyssynchrony induced by pacing from the right ventricular apex.

Although it may seem attractive to proceed with biventricular pacing systems in patients with congenital complete heart block based on these data, we must be cautious. Many young individuals with pacemakers will require multiple procedures over the years, since problems with lead malfunction are more common in young, physically active individuals. Adding a third pacing lead in might produce a short-term benefit in many, but any advantage might be negated by the increased complexity of the devices, which entails an increased risk of future lead malfunction. If reliable and more durable biventricular systems become available, however, they may become the preferred pacing mode in the future for virtually all patients who require ventricular pacing, not just those with congenital AV block. ■

A New Novel Anti-Arrhythmic Agent

ABSTRACT & COMMENTARY

Synopsis: *RSD1235 shows promise as an agent for the management of atrial fibrillation.*

Source: Roy D, et al. *J Am Coll Cardiol.* 2004;44: 2355-2361.

RSD1235 IS A NEW ANTIARRHYTHMIC COMPOUND that has unusual electrophysiologic properties. It is a mixed frequency-dependent sodium channel and an atrial-preferential potassium channel blocker. In animal models it has been effective in terminating and preventing recurrence of atrial fibrillation. In preclinical trials and in studies on normal volunteers, the drug has not been shown to have effects on ventricular refractoriness or the QT interval. This study examines the efficacy of intravenous infusions of RSD1235 for terminating recent onset atrial fibrillation.

Patients were eligible for the study if they had persistent atrial fibrillation with a duration between 3 and 72 hours at the time of randomization. Anticoagulation was managed in accordance with current guidelines. Patients were required to be hemodynamically stable. The major exclusion criteria included prolongation of the QT interval or QRS duration, recent unstable cardiac disease (ischemia, heart failure, or surgery), reversible causes of atrial fibrillation, concurrent treatment with known QT prolonging drugs or class I or class III antiarrhythmic drugs, electrolyte imbalance or significant renal or hepatic dysfunction. Preenrollment treatment with rate control agents was permitted.

Patients were randomized to one of 3 groups. Each group received 1 or 2 10-minute intravenous transfusions with a 30 minute interval between the 2 infusions. The infusions were either placebo followed by placebo, RSD1235 0.5 mg per kg followed by 1.0 mg/kg, if required and RSD1235 2.0 mg/kg followed by 3.0 mg/kg, if required. The primary efficacy end point was termination of atrial fibrillation. Secondary end points

included the number of patients who remained in sinus rhythm, at 0.5, 1, and 24 hours after the end of the last infusion and the time to conversion of sinus rhythm after first exposure to study drug. Patients in whom atrial fibrillation persisted 1 hour after the end of the last infusion could be electrically cardioverted.

During the infusion, the patient was monitored continuously. The infusion could be discontinued if the patient developed either hypotension or hypertension, significant bradycardia, or other conduction abnormalities.

A total of 56 patients were enrolled, randomized, and received study drug. There was no significant difference in clinical characteristics between the 3 groups. The mean duration of atrial fibrillation was less than 24 hours in all 3 groups.

The cumulative AF termination rate within 30 minutes after the last infusion was 61% in the high dose RSD1235 group, 11% in the low dose RSD1235 group, and 5% in the placebo group. Of the 11 terminations in the high-dose RSD1235 group, 10 of 18 patients converted to sinus rhythm, and one converted into atrial flutter. The median time to termination of atrial fibrillation was 11 minutes after the start of the first infusion. All patients who converted did so within 10 minutes of the end of the last infusion. One patient in the high dose RSD1235 group went back into atrial fibrillation by 1 hour after infusion. RSD1235 did not significantly prolong the QTc or the QRS intervals at either high or low dose. In the high-dose RSD1235 group, the predrug QTc at baseline was 434 ± 7 m/sec. At the end of the first infusion, it was 449 ± 9 m/sec, and at the end of the second infusion, it was 447 ± 17 m/sec. There were no clinically significant changes from baseline systolic blood pressure within groups or between groups. Two patients developed hypotension in the placebo group, and 1 case of transient hypotension was noted in the high-dose RSD1235 group. No episodes of significant AV block during atrial fibrillation or sinus bradycardia were noted. There were 4 mild adverse events reported by 2 RSD1235 patients that were thought to be either definitely or probably study drug related. One patient reported paresthesias and 1 patient reported paresthesia, nausea, and hypotension. Episodes of nonsustained ventricular tachycardia and frequent ventricular premature beats were seen with some frequency in all 3 groups. However, no patient developed torsade de pointes, sustained ventricular tachycardia, or ventricular fibrillation in response to the drug infusion. Several complications were, however, noted with electrical cardioversion. One placebo patient developed a transient cerebral ischemic attack 24 hours after electrical cardioversion, despite a therapeutic prothrombin time. Severe bradycardia with hypotension immediately after electrical conversion, pulmonary edema, and recurrent atrial fibrillation each occurred in 1 placebo patient. One patient in the low-dose RSD1235 group developed ventricular fibrillation when he received an asynchronous electrical shock during a cardioversion attempt.

Plasma levels of RSD1235 were measured. The median plasma level at the time of atrial fibrillation conversion was 1.3 μ/mL. The mean terminal elimination half life of the drug after infusion was 3.1 hours.

Roy et al conclude that RSD1235 shows promise as an agent for the management of atrial fibrillation. In this acute conversion study, it was not associated with any drug induced proarrhythmia or serious adverse events.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Pharmacologic therapy for atrial fibrillation has often been limited by the ventricular proarrhythmic effects of antiarrhythmic drugs. It has, therefore, been a goal of pharmacologists to develop agents that would specifically affect atrial electrophysiology. RSD1235 is a new agent developed by Cardiome Pharma which seems to have a favorable electrophysiologic profile in that it blocks frequency dependent sodium channels and potassium channels only in the atrium.

Studies on the termination of atrial fibrillation are highly dependent upon the patient population studied. When studies are carried out in patients with very recent onset atrial fibrillation (less than 48-78 hours), relatively high spontaneous conversion rates over a 12-24 hour period may be seen. In atrial fibrillation of longer than 3 days duration, both spontaneous and pharmacologic conversion rates are expected to be much lower. In this study, Roy and colleagues used a short period of observation to measure drug effect. Because of this, the conversion rates on both placebo and after a subtherapeutic dose of RSD1235 were quite low. A significant drug effect in the high dose group was clearly demonstrated. This relatively high acute conversion rate, combined with the absence of effects on the QT interval and the QRS duration, make RSD1235 a promising agent worthy of further investigation. The drug's short half life is favorable for intravenous conversions but would hamper oral therapy. However, if an oral preparation could be developed and be shown to be safe, RSD1235 could be used for both outpatient self-administration, as well as possibly for chronic prevention of recurrence. The absence of untoward effects on the ventricle, if confirmed in further studies, would make RSD1235 safe for unmonitored, outpatient loading and for chronic prophylactic use. ■

CME Questions

7. **The addition of niacin to statins:**
   a. reduces LDL cholesterol.
   b. raises HDL.
   c. raises triglycerides.
   d. raises CK.

8. **For the acute pharmacologic conversion of atrial fibrillation, RSD1235 shows?**
   a. Moderate efficacy
   b. Lack of Torsade de Pointes
   c. Few side effects
   d. All of the above

9. **Chronic right ventricular apical pacing for congenital complete heart block results in?**
   a. Left ventricular remodeling
   b. Higher stroke volume than controls
   c. Less mitral regurgitation
   d. All of the xabove

10. **Which therapy has the highest risk of severe rhabdomyolysis?**
    a. Cervistatin alone
    b. Gemfibrozil alone
    c. Other statins alone
    d. Gemfibrozil plus cervistatin

Answers: 7. (b); 8. (d); 9. (a); 10. (d)

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