Therapeutics Today

January 2011
Number 1

HAPPY NEW YEAR TO ALL OUR READERS!

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Cardiovascular effects of cocaine. A recent article in the journal of the American Heart Association (AHA) reviewed the cardiovascular (CV) effects of cocaine ***(Circulation 2010; 122: 2558-69)***. The use of cocaine has evolved from chewing the leaves of the *Erythroxylon* coca bush thousands of years ago, to purification of cocaine hydrochloride over 100 years ago (and its use in tonics and elixirs), to insufflating and injecting the fine white water-soluble form, to a smokable freebase form called "crack" in the 1980s. Cocaine acts on many systems within the body to bring about its CV effects including: stimulation of the sympathetic nervous system, effects on the sodium and potassium channels (primarily at high doses), promotion of thrombosis via several mechanisms and stimulation of the release of vasoconstrictor agents from endothelial cells. Clinically, it increases myocardial oxygen demand by increasing heart rate and blood pressure in a dose-dependent manner, while reducing oxygen supply via coronary vasoconstriction (so-called myocardial oxygen supply-demand mismatch). It worsens myocardial performance, causes arrhythmias and atherosclerosis and prolongs the PR, QRS and QT intervals.
Cocaine is associated with a number of CV diseases. Compared with non-users, cocaine users have a 3.8 to 6.9-fold **increased incidence of MI** and this risk increases by 24-fold in the first hour after cocaine use: MI occurs in ~6% of all patients presenting to the emergency dept with cocaine-associated chest pain (CACP). **Diagnosing MI in cocaine users** is challenging. Clinicians should have a high index of suspicion for cocaine use in young patients with chest pain. The article states that 12-hour observation with serial troponin measurement and ST-segment monitoring identifies acute MI in this group with high accuracy. **Therapy** of chest pain and acute coronary syndromes in cocaine-using patients is similar to that in patients with traditional risk factors with some exceptions: the AHA recommends that ACE inhibitors, ARBs, statins, diuretics, antiplatelet and antithrombin agents may be administered according to published guidelines to patients with CACP. **All β-blockers should be avoided in the acute setting** (due to potential for unopposed a-adrenergic stimulation resulting in pronounced systemic and coronary vasoconstriction). They should be prescribed at discharge only for selected patients. IV benzodiazepines may be given to relieve chest pain and to lower blood pressure and heart rate. Nitrates, as coronary vasodilators, may have benefits in CACP beyond those observed in traditional patients.
Heart Failure: With acute intoxication cocaine decreases myocardial contractility and ejection fraction and increases left ventricular end-diastolic pressure and end-systolic volume; long-term use is associated with left ventricular hypertrophy and prolonged deceleration time. The pathophysiology of cocaine-associated cardiomyopathy is unclear. **The primary goal of therapy in heart failure is to cease cocaine use** as this has been shown to be associated with a dramatic improvement in heart function. Cocaine-induced heart failure and cardiomyopathy should be treated as per published guidelines except for use of β-blockers, which should be avoided in the acute setting and only considered thereafter on a case-by-case basis.
Other CV diseases: current data show a 2-fold increased risk of both haemorrhagic and ischaemic **stroke** in cocaine users compared with non-users, with a higher proportion of haemorrhagic strokes in the current cocaine user group, compared with former users or non-users. Data on use of tissue plasminogen activator in ischemic stroke are limited but do not suggest a different outcome comparing cocaine users with non-users. However as before, the use of β-blockers should be avoided in the acute setting. **Cardiac arrhythmias** that occur within hours of cocaine use may result from the effects on sodium channels, while those occurring beyond several hours usually result from ischemia. The reported association between **endocarditis** and cocaine may be related to endothelial damage (also blamed for **erectile dysfunction**) or may be related to overall worse addiction and/or more frequent injections/ worse hygiene in IV cocaine use. The report also notes that:
1) **combining cocaine use with cigarette smoking** has additive effects on coronary vasoconstriction while markedly increasing the metabolic requirement of the heart for oxygen and
2) **use with ethanol** intensifies and prolongs the CV effects of both low- and high-dose cocaine.

Is all exercise equal in type 2 diabetes? Although it is accepted that regular exercise is beneficial for patients with type 2 diabetes (T2DM), it is unclear if the level of benefit varies according to the type of exercise. A recent randomised controlled trial evaluated the benefits of various exercise regimens on haemoglobin A_{1C} (HbA_{1C}) in individuals with T2DM ***(JAMA 2010; 304: 2253-2262)***. A total of 262 sedentary T2DM patients (defined as not exercising > 20 minutes for ≥ 3 days per week) with HbA_{1C} levels ≥ 6.5% were enrolled in a 9-month exercise programme as follows: a non-exercise control group (n=41), resistance training (n=73), aerobic training (n=72) and combined aerobic and resistance training group (n=76). The study design ensured that the total amount of time devoted to exercise each week was similar among the 3 active groups. The main outcome was change in HbA_{1C} level; secondary outcomes included measures of anthropometry and fitness. Results showed that **compared with the control group there was an absolute mean change in HbA_{1C} of -0.34% (p=0.03) in the combination training exercise group**; there was no significant difference between the control group and either of the other exercise groups. Of interest, the control group increased its use of diabetic medication during the study period while those in the combination training group decreased their diabetes medications. While all exercise groups reduced waist circumference (from -1.9 to -2.8 cm) compared with the control group, only the combination exercise group improved oxygen consumption compared with the control group. The aerobic training group lost a mean of 0.6kg fat mass, the resistance training group a mean of 1.4 kg and the combination training group lost a mean of 1.7kg fat mass compared with the control group (which had a minimal change of 0.1kg fat mass during the study period). The authors note that an absolute decrease of 1% in HbA1c levels has been associated with a 15-20% decrease in major cardiovascular disease (CVD) events and 37% decrease in microvascular complications, therefore the reductions noted in the combination training exercise group, albeit modest would be expected to reduce CVD and microvascular disease. An accompanying editorial ***(JAMA 2010; 304: 2298-2299)*** notes that these findings replicate a previous study in which combined aerobic and resistance exercise was more effective than either type of exercise alone for improvement of glycaemic control in T2DM. It notes that the American Diabetes Association has begun to recommend resistance exercise in recent years. Therefore, T2DM patients who wish to maximise the effects of exercise on their glycaemic control should be advised to perform both aerobic exercise (such as walking or jogging) and resistance exercise (such as weight lifting or working against a resistance load).

Why do patients stop taking statins? Statins are highly effective medicines for avoiding cardiovascular (CV) events. However, despite a favourable safety profile in the majority of patients, and evidence that low adherence is linked with worse outcomes, several studies have shown high rates of non-adherence. A recent systematic review, involving 22 studies (median sample size 20,000, median duration of follow-up 5 years), evaluated potential predictors of statin non-adherence (defined in terms of proportion of days covered and/or discontinuation) ***(Ann Pharmacother 2010; 44: 1410-21)***. The study identified age as a statistically significant predictor of adherence in all studies. **Age displayed a U-shaped relationship to non-adherence** in that younger patients (<50 years) and those aged ≥70 years displayed lower adherence and increased discontinuation compared to middle-aged adults. **Female gender was also associated with poorer adherence** in the majority of studies. Overall, patients with higher income were more likely to be adherent, irrespective of statin costs, as were patients with a history of CV disease (including MI, stroke, and hypertension) and diabetes mellitus. Although there was no clear pattern of association between the total number of medicines taken and adherence to statins, **there was a relatively strong relationship between the increasing number of non-cardiovascular medicines and lower statin adherence**. Data on the number of healthcare provider visits and adherence gave conflicting results. Several other variables were recorded in too few studies for pooling but suggested reduced adherence in ethnic minorities, in depressed patients and where direct statin costs were high to patients of lesser income. The authors conclude that those at high risk of non-adherence (e.g. younger patients on primary prevention and females) should be targeted for adherence interventions.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. This newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept of Therapeutics Trinity College, Trinity Centre, SJH. Tel: Direct Line (01) 473 0589 or 1850 727 727 Fax: (01) 473 0596 Email: nmic@stjames.ie