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Treatment of Recent-Onset AF with the Pill-in-the-Pocket

Source: Alboni P, et al. *N Engl J Med*. 2004;351:2384-2391.

Although chronic oral antiarrhythmic prophylaxis and catheter ablation both enjoy great success for preventing recurrences of atrial fibrillation (AF), some patients are not appropriate candidates for either method, especially patients with infrequent recurrences of AF. Oral flecainide (FLEC) and propafenone (PRO) are highly efficacious in restoring sinus rhythm as demonstrated for hospitalized patients with recent onset AF.

Alboni and colleagues studied the feasibility of patient-administered FLEC or PRO for patients (n = 210) who had successfully responded to emergency room treatment of recent onset AF (< 48 hours). Study participants who experienced symptomatic recurrences presumed to be AF (n = 165) were advised to self-administer PRO or FLEC within 5 minutes of onset of new palpitations. Mean followup was 15 months.

Drug self-administration was effective in resolving symptoms in 94% of episodes, with a mean time to resolution of approximately 2 hours. There was a concomitant dramatic decline in the need for emergency room visits compared with the year prior to the study.

These results show promise for self-administration of PRO or FLEC for persons with recent onset of AF who have previously responded in the emergency room to antiarrhythmic treatment. Because the list of exclusions in this trial was long, clinicians will want to familiarize themselves with the full details of appropriate inclusion and exclusion before considering such methodology for their own patients in non-research settings. ■

Antibody Responses after Intradermal Flu Vaccination

Source: Belshe RB, et al. *N Engl J Med*. 2004;351:2286-2294.

The year 2004 was unusual in reference to problematic shortages of influenza vaccine (FLUVAX), resulting in vaccine rationing. One of the methods that might reduce the actual volume of vaccine needed in any season would be intradermal vaccination, as opposed to the traditional IM route currently advocated for FLUVAX administration. Support for this method is predicated upon the observation that intradermal vaccine provides greater exposure to macrophages and dendritic cells than IM, and hence induces a similar serum antibody response, using less vaccine.

Belshe and associates studied the immunogenicity of intradermal FLUVAX in 2 groups of adults: age 18-60, and age older than 60. The intradermal formulation they studied was 40% of the strength of standard IM vaccine, and was administered by a tuberculin syringe.

Amongst younger subjects, the immune responses of IM and intradermal administrations were essentially equivalent. In subjects older than 60 years, antibody titers were significantly lower than achieved by IM methodology, but were still sufficient to meet the criteria of the European Committee for Proprietary Medicinal Products that ensure vaccine adequacy. Conceivably, during times of vaccine shortage, administration of smaller volumes of FLUVAX intradermally, especially to younger recipients, would be a rational choice. ■

Isosorbide Dinitrate and Hydralazine in HF

Source: Taylor AL, et al. *N Engl J Med*. 2004;351:2049-2057.

Neurohumoral modulators such as ACE inhibitors, angiotensin receptor blockers, beta blockers, and aldosterone have all shown meaningful benefit for patients with chronic heart failure (CHF). Retrospective analyses of trials including significant populations of black patients have suggested that this group, which appears to have less intense activation of the renin-angiotensin-aldosterone system in CHF than non-black comparators, enjoys a significant responsivity to administration of nitrates and hydralazine.

This trial was performed to investigate the impact of nitrates (specifically, isosorbide dinitrate titrated to 40 mg t.i.d.) and hydralazine (titrated to 75 mg t.i.d.) in patients with NYHA Class II-IV CHF already receiving standard therapy, which includes ACE inhibitors, angiotensin receptor blockers, beta blockers, spironolactone, and digoxin. The primary efficacy end point was a composite of death from any cause, first hospitalization for heart failure, and quality of life.

The study was terminated early because of a statistically significant favorable impact of active intervention, including a 43% relative reduction in death from any cause, 33% reduction in first hospitalization, and improvement in quality of life. Black patients already receiving standard therapy for CHF may benefit from the addition of both hydralazine and nitrates. ■

Acetyl-L-Carnitine Improves Pain, Nerve Regeneration, and Vibratory Perception

Source: Sima AF, et al. *Diabetes Care*. 2005;28:96-101.

Diabetic peripheral neuropathy (DPN), with or without diabetic peripheral neuropathic pain (DPNP), is a commonplace and consequential complication of diabetes (DM). Treatment of DPNP has been enhanced by the recent FDA approval of duloxetine and pregabalin, but clinicians desire a broad range of therapies. Good control of DM has been shown to reduce progression of neuropathy, but other convincing preventative tools are lacking.

DM patients have been shown to be deficient in acetyl-L-carnitine (ALC), which may be etiologic in development of DPN. Animal data confirm preventative and therapeutic effects of ALC, including favorable impact upon generation of nitric oxide, lipid peroxidation, and prostaglandins.

To evaluate the potential clinical role of ALC, 2 identical one-year, double-blind, placebo-controlled studies were undertaken (total n = 1348). Study subjects underwent sural nerve biopsy, nerve conduction study, scoring of vibration sense, and symptom scores. Ranked symptoms included pain, numbness, paresthesias, weakness, postural dizziness, dyshidrosis, GI problems, and sexual dysfunction. ALC was dosed at 500 mg or 1,000 mg t.i.d. for one year.

Sural nerve biopsy showed positive effects, although nerve conduction velocity and amplitude did not improve. Vibration sense was improved, and pain was reduced in subjects receiving 1000 mg t.i.d. No patient discontinued ALC due to adverse effects. ALC shows promise as a therapeutic tool for diabetic peripheral neuropathy. ■

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Levodopa and the Progression of Parkinson's Disease

Source: The Parkinson Study Group. *N Engl J Med*. 2004;351:2498-2508.

Levodopa (LDPA) has proven a very valuable treatment for Parkinson's disease (PAR). Since PAR is characterized by a progressive decline in production of dopamine due to degeneration of the substantia nigra, it is pathophysiologically attractive to consider replacing insufficient dopamine by means of LDPA. Some concern has existed about whether LDPA treatment might actually accelerate decline in neurons of the substantia nigra. To address this question, the Parkinson Study Group enlisted patients with early PAR (n = 361) for randomization in a placebo controlled trial.

Subjects underwent daily treatment with carbidopa-levodopa at doses from 37.5/150 mg to 150/600 mg for 40 weeks, after which there was a 2-week withdrawal. No other anti-Parkinsonian medications were permitted during the trial. Symptoms and signs of PAR were assessed, as well as SPECT imaging to monitor the status of substantia nigra functionality.

As would be expected, PAR symptom severity was greater in patients treated with placebo than LDPA. SPECT data indicated a decrease in activity of the nigrostriatal dopamine nerve terminals, suggesting acceleration of the decline in CNS dopamine productivity (although a medication-induced alteration of the dopamine transporter could not be ruled out). These contrasting end points leave the issue of whether LDPA treatment alters disease progress unsettled. Despite convincing evidence for favorable effects upon signs and symptoms, the underlying pathology may be unaffected, or possibly even worsened. ■

Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 years after Bariatric Surgery

Source: Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693.

The long-term consequences of obesity include increased cardiovascular disease (CVD), diabetes (DM), and dyslipidemia. Although surgical interventions have provided meaningful short-term reductions in BMI and surrogate markers of cardiovascular risk, little is known about long-term impact.

This prospective study compared outcomes in subjects (n = 851) surgically treated for obesity (gastric banding, banded gastroplasty, or gastric bypass) with matched obese controls (n = 852) treated with conservative management such as lifestyle changes. Study groups did not differ meaningfully at baseline for cardiovascular risk profile. In addition to BMI, end points included mortality, incidence of diabetes, hypertriglyceridemia, and hyperuricemia.

Gastric bypass produced the greatest degree of weight loss amongst the surgical procedures; overall at 2 years, the conservative management group had experienced no statistically significant weight loss, compared to a 23.4% decrease in the surgery group.

Perisurgical mortality was 0.25%. Incident hypetriglyceridemia, DM, and hyperuricemia were lower in the surgery group. Similarly, improvement in pre-existing hypertension and DM were greater amongst patients treated surgically. Differences in mortality at 10 years were not specified, but were not sufficient to merit early study closure (either due to perceived benefit or harm). The balance of long-term effects of bariatric surgery appears favorable. ■