Drugs of the Future 2008, 33(12): 1071-1076

CCC: 0377-8282/2008

Meeting Report

An overview of stroke management from the 6th World Stroke Congress

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CONTENTS

Abstract

The 6th World Stroke Congress was organized by the World Stroke Organization (WSO) and took place in Vienna on September 24-27, 2008. The biennial meeting was attended by approximately 3,000 medical doctors, scientists and other professionals from all over the world with a common interest in reducing stroke burden, one of the major challenges in medicine. A number of interesting scientific sessions, posters and teaching courses covered many aspects of stroke management, including recent approaches, novel therapies in basic and clinical research, large clinical trials, potential targets and biomarkers of the disease. We have selected and summarized some of the most compelling aspects of the congress here.

Introduction

As many as 20 million stroke events occur in the world every year and stroke has become the second most important cause of death, with 5.7 million deaths per year. It is also the primary cause of disability. The incidence of stroke is expected to increase by up to 30% by 2020, and stroke is not only seen in developed countries, but also in low- and middle-income countries. During this year's World Stroke Congress, Prof. Geoffrey A. Donnan, president of the World Stroke Organization (WSO), appealed to professionals to implement novel and effective strategies in the management and prevention of stroke worldwide (1). Top-level scientific sessions and posters presented the last advances in basic research, clinical applications, recovery and rehabilitation, and opened discussions on future directions for reducing the disease.

Blood pressure management in stroke

Hypertension has been established as a risk factor for stroke, but it remains unclear whether it should be treated during the acute ischemic stroke process or not. Both the European Stroke Initiative and the Stroke Council of the American Stroke Association recommend in their statements and guidelines against lowering blood pressure (BP) in ischemic stroke patients who are not otherwise candidates for thrombolysis (2, 3). Nevertheless, this has long been debated and there are multiple studies describing the benefits of hypertension treatment on edema formation, rebleeding and hematoma expansion in patients with cerebral bleeding. There is also evidence for leaving high BP levels untreated to avoid a reduction in cerebral perfusion pressure and blood flow to viable ischemic tissue in the absence of normal autoregulation (4). The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study, a prospective, double-blind, placebo-controlled, randomized phase II trial, evaluated the use of candesartan in acute ischemic stroke patients with severely elevated BP levels. Data from 342 patients showed that no significant cardiovascular or cerebrovascular events occurred as a result of hypotension (5, 6).

E.C. Sandset et al. presented data from the Scandinavian Candesartan Acute Stroke Trial (SCAST), which is currently the largest study in this area, with 2,500 stroke patients expected to be enrolled (6, 7). This randomized, placebo-controlled, double-blind study in patients presenting with stroke within 30 h and systolic BP of 140 mmHg or above is evaluating the efficacy of therapy with candesartan at 4 or 16 mg/day based on the number of deaths or major disabilities and vascular deaths, myocardial infarctions or stroke events occurring at 6 months. At the moment of data cut-off (April 2008), 1,280 patients were included and only 16% reported vascular events after treatment with the angiotensin I antagonist. Sandset and the SCAST team invited interested centers to participate in the trial. The final data are expected to be available in mid-2009 (7).

Highlights from clinical trials

Recent studies have demonstrated that hyperthermia is associated with a worse prognosis of ischemic and

hemorrhagic stroke events (8, 9). Therapy with high doses of paracetamol has been shown to produce a small decrease (0.3-0.4 °C) in body temperature after 2-4 h in normothermic and subfebrile patients diagnosed with acute ischemic anterior circulation stroke (10, 11). In order to assess the possible association between decrease in body temperature and clinical outcome in stroke, a large trial known as Paracetamol (Acetaminophen) In Stroke (PAIS) is being conducted in The Netherlands. PAIS is a multicenter, randomized, double-blind, placebo-controlled phase III study of paracetamol given at 6 g/day for 3 days in patients with acute stroke. H.M. Den Hertog, as part of the steering committee of the PAIS trial, reported that an interim analysis of data from 1,360 patients showed evidence of an effect on functional outcome in acute stroke following the paracetamol-induced decrease in body temperature (12).

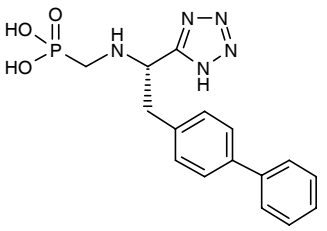
Clazosentan, an endothelin receptor antagonist, has been found to significantly and dose-dependently decrease moderate and severe vasospasm in patients with aneurysmal subarachnoid hemorrhage (SAH). Evidence of a reduction in vasospasm-related morbidity/mortality by clazosentan therapy has also been obtained (13). Based on these results, Actelion is developing another trial, Clazosentan to Overcome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage (CONSCIOUS-2), to evaluate whether decreasing vasospasm with clazosentan therapy can improve clinical outcome (vasospasm-related morbidity and all-cause mortality) in patients with aneurysmal SAH treated by surgical clipping. A. Raabe and the study team took the opportunity at the World Stroke Congress to present the trial to other investigators in a scientific poster. CONSCIOUS-2 is a randomized, double-blind, placebo-controlled phase III clinical trial in which clazosentan is given at 5 mg/h up to day 14 after aneurysm rupture. This study plans to enroll 765 SAH patients and is currently recruiting participants (14, 15). Results may become available as early as the second half of 2009 (16).

The current American (AHA/ASA) and European (ESO) guidelines for the prevention of stroke recommend the use of extended-release dipyridamole plus aspirin (200/25 mg b.i.d.) in noncardioembolic stroke patients as a primary choice over aspirin monotherapy (50-325 mg once daily) or clopidogrel (75 mg once daily) (17, 18). R. Sacco from the University of Miami, USA, and D. Leys from Lille University Hospital in France presented results from the Prevention Regimen for Effectively Avoiding Second Strokes **(**PRoFESS**)** study and opened a debate on how it could affect current international guidelines (19). PRoFESS was a randomized, double-blind, placebo- and active-controlled phase IV clinical trial undertaken to determine whether extended-release dipyridamole (200 mg b.i.d.) plus aspirin (25 mg once daily) is superior to clopidogrel (75 mg daily) and to compare telmisartan to placebo for preventing a second stroke in patients who had suffered a recent one (N = 20,332) (20). Overall, no significant differences in the risk of recurrent stroke (approximately 9%) or major hemorrhagic events (around 4%) were observed between the study arms. Moreover, disability after recurrent stroke (modified Rankin Scale and Barthel Index) and cognitive function (Mini-Mental State Examination score) were similar across study groups. In summary, there was no evidence to suggest that any of the treatments was superior to the other in terms of efficacy, questioning the AHA/ASA and ESO guidelines' recommendation of aspirin plus dipyridamole as a first choice, instead of clopidogrel, for the prevention of stroke. It was nevertheless felt that no changes in the current guidelines will be made at present (19, 21, 22).

Novel therapies

The endothelin-converting enzyme inhibitor **CGS-26303** (Novartis) has been found to prevent and reverse cerebral vasospasm after experimental SAH. A recent study investigated the expression of endothelial nitric oxide synthase (eNOS), neuronal NOS (nNOS), inducible NOS (iNOS), heme oxygenase HO-1 and HO-2 in a rat model of SAH in order to explain the attenuation of vasospastic response obtained with CGS-26303. Using an RT-PCR methodology, dose-dependent overexpression of eNOS mRNA in brain tissues was observed after treatment at 0.24, 0.8 or 2.4 mg/100 g/day compared to control. In contrast, the other enzymes appeared to be similar in both treated and control groups. These results suggest that the decrease in cerebral vasospasm by CGS-26303 may result from the overexpression of eNOS in brain tissue and endothelin biosynthesis in basilar arteries (23).

K. Deguchi et al. from Okayama University presented recent results reporting the antioxidant effects of **biliverdin** (NSC-62793) in a model of ischemic brain



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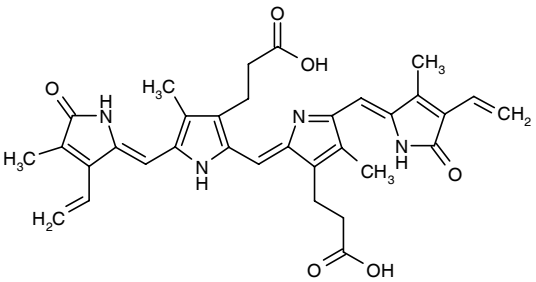


Biliverdin

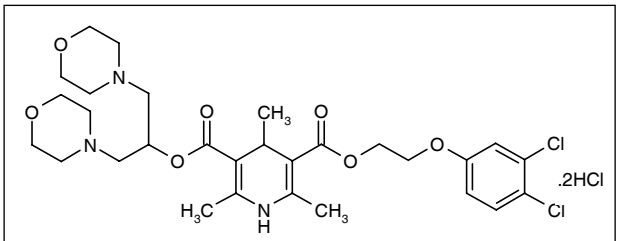
injury in rats. Biliverdin was administered at 100 mg/kg i.p. following middle cerebral artery occlusion and the compound was rapidly and dose-dependently converted to bilirubin at 30 min, which returned to control levels after 4 h. The compound significantly decreased infarct volume in the cerebral cortex of the animals after 2 days. Moreover, immunohistochemical assays showed a reduction in injured cells in the ischemic core in the biliverdin-treated group. These results suggest a potential strategy for ischemic brain damage treatment (24).

N.G. Bazan and researchers at Louisiana State University have recently evaluated the platelet-activating factor (PAF) receptor antagonist **LAU-0901** in a model of focal cerebral ischemia in rats. Animals undergoing 2-h middle cerebral artery occlusion subsequently received LAU-0901 at 60 mg/kg i.p. for 4 weeks. A significant improvement was measured in the neurobehavioral assessment score, including postural reflex and forelimb-placing tests, on days 1 through 30 compared to controls. Histopathological evaluation showed that the treatment with LAU-0901 was associated with a 19% increase in noninfarcted brain tissue. These results suggest that the agent may have potential use in the clinical setting for the treatment of focal ischemic stroke (25).

A presentation by A. Chamorro from the Hospital Clinic in Barcelona suggested that uric acid may be a beneficial agent for treating acute stroke. Studies conducted by this center have demonstrated that uric acid levels are inversely correlated with central nervous system disorders and stroke. Additional experiments in combination with recombinant tissue plasminogen activator (tPA) showed synergistic neuroprotection in both experimental stroke and clinical studies. Uric acid administration was safe in healthy volunteers and patients and clinical efficacy studies are planned (26).

Researchers at the University of Florence have recently identified a novel series of poly [ADP-ribose] polymerase (PARP) inhibitors that have been found to protect against experimental ischemia-induced brain damage in several animal models. The lead compound from this series, **UPF-796**, decreased infarct volume at 10 mg/kg i.p. and improved neurological scores after 7 days in multiple middle cerebral artery occlusion models of stroke. Nevertheless, it was previously found that PARP inhibitors did not attenuate oxygen/glucose deprivation (OGD) damage in the hippocampus in the two-vessel occlusion model of global ischemia in gerbils. **UPF-1035** and **UPF-1069** were then identified as selective PARP2 inhibitors (IC_{50} = 0.09 and 0.3 μM, respectively). Experiments with selective PARP2 inhibitors revealed increased postischemic CA1 cell loss in organotypic hippocampal slices and reduced OGD damage in mixed cortical cells. These data provide proof for the potential activity of PARP1 and PARP2 inhibitors in the treatment of ischemia-induced brain damage (27).

V-10153 (Vernalis) is a recombinant version of human plasminogen that has shown safety in previously published studies in healthy volunteers at doses up to 4.8 mg/kg i.v., as well as thrombolytic efficacy in patients with acute myocardial infarction at doses up to 10 mg/kg i.v. Further results in terms of safety from the V-10153 Acute Stroke Thrombolysis Trial (VASTT) were presented by M. Hill et al. Patients were recruited in cohorts given escalating doses of 1, 2.5, 5, 7.5 and 10 mg/kg i.v. (n = 10 each). Results in the 1, 2.5 and 5 mg/kg cohorts showed a good safety profile, with bleeding events being the most common adverse event reported. There was an additional 5 mg/kg cohort of 10 patients due to two significant bleeding events in the first cohort. In the 7.5 mg/kg group, 3 of 9 patients recruited had significant bleeding events and the trial was halted. V-10153 demonstrated efficacy in the first three dose groups (n = 40), with 40% having modified Rankin Scores of 0-2 between day 30 and day 90. There were apparently higher response rates in patients with peripheral lesions and/or early treatment (3-6 h). The full data will be given on completion of the



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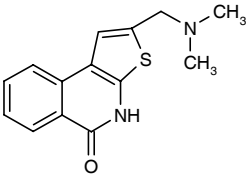

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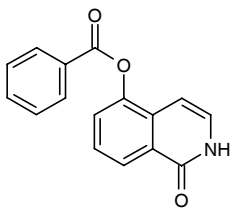

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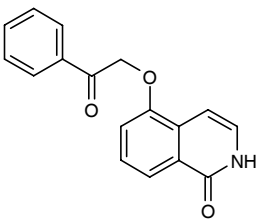

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blinded review of CT angiograms. Further studies are currently planned at the 5 mg/kg dose (28).

New targets

Scientists at the University of Wisconsin have studied the role of galectin-3 protein in postischemic tissue remodeling. A member of a class of carbohydrate-binding proteins, galectin-3 has been found to play a critical role in multiple cell functions, including cell proliferation, angiogenesis and differentiation. Microarray and immunohistochemical assays led to the discovery that the protein is expressed in activated microglia/infiltrating macrophages and activated astrocytes in the ischemic brain. In vitro, galectin-3 was found to induce the proliferation of brain endothelial cells and neural progenitors. Moreover, intracerebral infusion of a mouse anti-galectin-3 antibody for 7 days attenuated postischemic angiogenesis and decreased ischemia-induced proliferation of neural progenitors. Inhibition of this protein is a potentially useful therapeutic approach to increase plasticity and recovery after stroke (29).

Another novel potential target for ischemic stroke therapy is the transcription factor NF-κB, which is involved in neuronal inflammation and cell survival. Researchers from the University of Heidelberg have observed activation of NF-κB mainly in neurons in mice with experimental ischemic brain damage. Further experiments demonstrated that inhibiting IKK kinase had protective effects in neurons via downregulation of NF-κB expression (30).

Biomarkers

In stroke management, one of the current limitations is the early diagnosis of patients at high risk of events. During the congress, several presentations focused on the investigation into tools for early diagnosis of stroke. D-dimer has been found to be an accessible marker for differentiating small- or large-artery infarctions in ischemic stroke patients. R. Brouns et al. measured D-dimer concentrations in plasma using the VIDAS D-dimer test or Triage Stroke Panel (TSP) techniques in 109 ischemic stroke patients who were classified into small- or large-artery infarction cohorts according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Both tests showed higher D-dimer levels in the patients with large-artery infarction compared to the small-artery infarction subjects. Concentrations of the biomarker greater than 445 ng/ml by VIDAS or 300 ng/ml by TSP were associated with an accuracy of 0.88 and 0.85, respectively. In contrast, D-dimer plasma levels were not correlated with clinical severity or infarct volume. Both VIDAS and TSP may be cheap tests for the differentiation of both etiologies of stroke infarctions; although TSP is a slightly less accurate alternative than the VIDAS test, it is more rapid (31).

S.R.R. Bekarovska and a team at Skopje in the Republic of Macedonia reported data on the use of C-reactive protein (CRP) as a biomarker of stroke severity. Sixty-four acute ischemic stroke patients were classified into groups according to severity scores on the National Institutes of Health Stroke Scale (NIHSS; mild, NIHSS < 8; moderate, NIHSS 8-16; and severe NIHSS > 16), to examine the correlation between CRP and stroke outcome. Increased levels of CRP correlated with stroke severity, as patients in the mild, moderate and severe groups were associated with median CRP values of 13.22, 26.66 and 47.55, respectively. In addition, 6 patients died and all had CRP above 55. Measures of CRP concentrations may therefore be a means of predicting stroke severity and outcome (32).

S.A. Dambinova et al. evaluated the association between the immediate risk of transient ischemic attack (TIA) and acute ischemic stroke with high levels of NR2 peptide in two studies (N = 80 and N = 119). In the first study, NR2 peptide showed a sensitivity in diagnosing TIA/stroke of 83% and a specificity of 84% at a cutoff of 1.0 ng/ml. In the second study, these values were 98% and 94%, respectively, for stroke lesions greater than 2 cc at a cutoff of 1.0 ng/ml. NR2 peptide correlated with new lesions of stroke on neuroimaging and may be able to differentiate cerebral ischemic events from stroke-like events (33).

Researchers at Tel Aviv Sourasky Medical Center and the Hebrew University of Jerusalem reported that acetylcholinesterase (AChE) and cholinergic status (CS; measured by the total circulating capacity for acetylcholine hydrolysis) may be potential diagnostic values in stroke. Analysis of AChE and CS in serum samples of 264 acute ischemic stroke patients differentiated patients from controls with 97% specificity and 80% sensitivity. The cholinergic parameters also correlated with results obtained for fibrinogen, IL-6, CRP and white blood cell count tests (34).

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