Letters to the Editor

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BW619C89, a Glutamate Release Inhibitor, Protects Against Focal Cerebral Ischemic Damage

In reporting the effects of the glutamate release inhibitor BW619C89 on ischemic injury, Leach and colleagues1 describe a simple method of correcting for the effects of edema on apparent stroke volume. The issue is of central importance to studies of this type, because without such a correction a treatment or agent that reduces infarct edema will erroneously appear to cause a reduction in actual infarct size. Edema can increase apparent infarct size by about 25%,2,3 but the importance of accounting for edema has not been widely appreciated, and such corrections are in fact rarely performed in published reports. The method described by Leach and colleagues is attractively simple but will unfortunately underestimate the expansion of infarcted tissue by edema. This method corrects for edematous expansion of left hemisphere infarcts with the equation (Left-Hand Infarct Area)×(Right-Hand Area/Left-Hand Area). Suppose that in a hemisphere section of 2000 mm², a 400-mm² area is infarcted. If the infarcted area expands by 20% because of edema, the apparent infarct area will be 480 mm² and the total left hemisphere area will expand to 2080 mm². Using the equation of Leach et al, the apparent infarct area is corrected to 480×(2000/2080)=462 mm², a value only partly corrected for edema. The underestimation stems from an assumption implicit in the equation that the edematous expansion of the left hemisphere results from edema distributed uniformly through both the infarcted and noninfarcted areas. In fact, the edema is restricted almost entirely to the infarcted tissue and to white matter contiguous to the infarct.4 The equation will provide a better correction to the extent that edema causes significant expansion outside the infarcted area, but it will always underestimate edematous expansion except in the extreme and unrealistic case of the percent expansion of the infarct being equivalent to the percent expansion of the entire rest of the hemisphere.

An alternative and equally straightforward approach is to measure and compare the areas of uninfarcted tissue, particularly uninfarcted gray matter, in both the control and lesioned hemispheres.2 This approach nearly eliminates the effect of edema on stroke volume measurements. Use of this method ensures that treatment-induced reductions in apparent stroke volume represent actual preservation of brain tissue rather than simply reduction in infarct edema. This method has been compared with the traditional method of stroke volume assessment and found to be superior.1

These comments are not meant to impugn the results of the study by Leach et al, as it is highly unlikely that the magnitude of the effect demonstrated with BW619C89 could be ascribed solely to a reduction of infarct edema. We do wish to point out that the described method of correcting for edema, while better than no correction, will only partly negate the effect of edema on apparent stroke volume.

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References


Response

In our evaluation of the effects of BW619C89 on focal ischemic damage in a rat model of middle cerebral artery occlusion,1 we originally attempted to use the method of Swanson et al2 to correct for edema. This method advocates summing the areas of each section to obtain the volume (after multiplying each sum by the distance between sections) before applying correction for edema. We, however, elected initially to use the Swanson equation to correct each sectional area individually for edema and then sum to give the final corrected volume rather than to total all areas. For control data, the area-by-area correction using our equation produced data 13% higher than those obtained by using an area-by-area computation of the method of Swanson et al [eg, total infarct volume of 143±26 mm³ (n=8) (Swanson method) versus 165±12 mm³ (n=8) (Leach et al)] and a 16% higher value when comparing our control data with the Swanson method of total volume [eg, total infarct volume of 138±20 mm³ (Swanson method) versus 165±12 mm³ (Leach et al)]. Our problem was that when correcting for BW619C89-treated animals using the Swanson equation on an area-by-area basis, we were confronted with negative numbers in those sections on the border zone with noninfarcted tissue. Also, by observation of each section, it was clear that edematous expansion of the left hemisphere in many BW619C89-treated animals existed where there was no apparent imaged infarct, implying that edema still existed in peripheral salvaged or noninfarcted tissue, when BW619C89 had dramatically reduced the total infarct volume. Edema may well be restricted in control tissue entirely within the infarct.1 Our work with BW619C89, however, appears to imply that after treatment with this agent, some salvaged or noninfarcted tissue bordering the infarct may also become edematous (vasogenic edema?).4 Recovery of this tissue may take longer than the 48 hours at which our animals were evaluated for neuroprotection. The equation of Swanson et al may be inappropriate for “control” infarcted tissue but may overcompensate for edema in the BW619C89-treated animal, such that BW619C89 actually fares better in its neuroprotective efficacy when assessed using this equation [total infarct volume of 47±11 mm³ (n=8) (Swanson method, total volume) versus 69±12 mm³ (n=8) (Leach et al, area-by-area), equivalent to 66% reduction or 58% reduction in total infarct volume, respectively]. As the letter
from Drs Swan and Sharp points out, our equation (Leach et al) will provide a better correction if edema occurs outside the infarcted region. Data calculated using both equations and either area-by-area correction or total volume figures still demonstrate the efficacy of BW619C89 in this rat model of focal ischemia.

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References


Risk Factors for Cervical Atherosclerosis in Patients With Transient Ischemic Attack or Minor Ischemic Stroke

Palomaki et al^2 report a relationship between symptomatic carotid stenosis and traditional vascular risk factors. Age, smoking, hypertension, serum triglycerides, regular light alcohol consumption (inverse association), and body mass index (marginal inverse association) were independent determinants of the presence of atherosclerosis. On the other hand, age and the ratio of high-density lipoprotein to total cholesterol (inverse association) were associated with the severity of extracranial carotid stenosis. Current smoking and female sex were predictors only of the percent stenosis and the length of lesions, whereas hypertension showed a significant association only with the length of lesions. Such a risk-factor profile discrepancy between the presence and the severity of extracranial carotid stenosis has been observed previously in the literature.2-5 The inconsistent association of traditional risk factors to the severity of extracranial carotid stenosis may indicate the presence of additional factors (eg, hemodynamic factors) that could contribute to the severity of carotid stenosis. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 387 of 1360 patients (28.5%) had severe (70% to 99%) angiographically defined extracranial carotid stenosis on one side with none-to-mild (<30%) on the contralateral side. If traditional risk factors are associated with atherosclerosis at the carotid bifurcation, how can one explain the asymmetric nature of carotid disease?

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References


Response

To find out the potential determinants of atherosclerosis in our study, extracranial parts of all 11 major cervical arteries were evaluated. Among those who had atherosclerosis (180 of 294 patients), the severity of the disease was assessed by using three indexes. These were computed separately for the total length, total thickness, and percent stenosis of the plaques, accounting for all visible atherosclerotic lesions in all 11 arteries, and we did not analyze the plaques at or near carotid bifurcations separately. However, five traditional risk factors showed a significant association with the total length of the plaques, and percent stenosis and the thickness of the plaques were explained by four and two risk factors, respectively. According to this variability, traditional risk factors seemed to predict in particular the overall dissemination of atherosclerotic disease instead of being strong determinants of the grade of stenotic plaques. Among other factors, hemodynamic forces could have a role, and platelets may have an influence on the development of atherosclerotic lesions.1 In early atherosclerosis, the sites of predilection are vessel orifices and bifurcations; here the flow patterns may be complicated, possibly augmenting platelet adhesion to the vascular endothelium at these sites. Platelets, in turn, could contribute to the development of stenotic lesions in at least two ways: by stimulating the migration and proliferation of vascular smooth muscle cells and by formation of thrombi that become consolidated and incorporated into the vessel wall.1 In general, the presence of relatively few (and partly inconsistent) associations between traditional risk factors and the severity of atherosclerosis in our study suggests that other factors not included (and perhaps not identified at all) may also be involved.

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Denial of Illness and Depression in Stroke

The extensive review on denial of illness in stroke by Ellis and Small highlighted phenomenological and etiologic aspects of denial of illness pertaining to physical disability in stroke patients. However, authors have failed to discuss the relationship between poststroke depression and denial of illness. This letter is intended to focus on the prevalence of denial of depression in poststroke depression and its correlation to lesion location; in addition, the relationship between denial of illness concerning physical disability and poststroke depression will be discussed.

Gainotti suggested that the depression in patients with right hemispheric lesions may be recognized due to their tendency to deny depression and also by their failure to express the affect. Fedoroff et al,3 in their study of acute stroke patients, found that 5% of poststroke patients deny depressed mood although they fulfill the criteria for depression. Among patients with depression, approximately 10% presented with denial of depressed mood. Of patients with denial of depression, 60% had right hemispheric
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