Letters to the Editor

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Safety Concerns With the Clinical Use of Erythropoietin in Acute Ischemic Stroke

To the Editor:

In their study published in *Stroke*, Ehrenreich et al report serious side effects after erythropoietin (EPO) therapy in acute ischemic stroke. These results call attention to the importance of meta-analysis of preclinical studies as a potential guidance of clinical stroke trials.[1] Actually, 2 recent meta-analysis studies evaluating the efficacy of EPO in animal stroke models have concluded that preclinical safety studies for the combination of EPO with thrombolytic therapy and the efficacy of EPO in animals with comorbidity such as hypertension and diabetes are needed.[2,3] Such studies are warranted before the design of further clinical stroke trials. For instance, activated protein C, which is another neuroprotectant molecule being tested in an ongoing stroke trial, minimizes side effects due to recombinant tissue-type plasminogen activator that was approved for acute stroke therapy.[4–7]

Since the first in vivo evidence of the protection by EPO in neonatal brain injury in 2003, numerous preclinical studies have confirmed the efficiency of EPO in neonatal hypoxic–ischemic encephalopathy and neonatal stroke in rodents.[8,9] Finally, a recent clinical trial has shown that EPO reduces the risk of disability in newborns with hypoxic–ischemic encephalopathy without apparent side effects.[10] Clinical trials in neonatal stroke are still ongoing.[7] It will be interesting to compare the results and to know the differences between the responses of adult and developing brain to exogenous EPO administration in stroke.

Because EPO has also a tissue repair capacity promoting neuroregeneration, repeated administration of the drug might also be beneficial both in adult and developing brain injury.[9,10] In this context, use of nonerythropoietic EPO derivatives such as carbamylated EPO may provide avoidance of side effects reported in acute stroke trial.[1,11] The results of ongoing clinical trial with carbamylated EPO in acute stroke are still awaited.[7] However, a safety concern with the repeated administration of EPO is immunogenicity of recombinant protein therapeutics.[12] Furthermore, modified derivatives of recombinant proteins, especially in the form of prolonged therapy, may elicit epitope spreading and induce the immune responses that could trigger thrombotic complications.[13]

Conclusively, all safety concerns should be evaluated in preclinical stroke studies with EPO and its derivatives and analogs.

Disclosures

None.

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