Therapy of stroke – from experimental studies to clinical trials

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Abstract:
Ischemic stroke (IS) kills 5.5 million people each year worldwide and is the leading medical cause of neurological disability in adult population. Despite many years of active research for effective therapy of IS, acetylsalicylic acid (ASA) and recombinant tissue activator (rt-PA) remain the only approved medications. ASA has weak effect but can be used in almost all patients with IS. According to very strict inclusion criteria, rt-PA can be used only for small number of patients and its use is limited by hemorrhagic complication. Effective, well-tolerated treatments with extended therapeutic window are needed to decrease disability and improve patients’ prognosis. The idea of neuroprotective agent is that it interferes with mechanisms involved in ischemic cascade, among many others, glutamate release, cell calcium overload and formation of free radicals.

The problem with neuroprotectants is that fine results obtained in models of ischemia are not reproducible in clinical trials and general perception of neuroprotectants is that they work in animals but they fail in humans. It is very likely that problems begin in preclinical part of evaluation.

To improve quality of experimental studies, STAIR introduced recommendations for quality of preclinical drug testing that should be fulfilled before a new agent reaches clinical trial. Appropriate animal studies should include characterization of full dose-response curve, evaluation in models of both permanent and transient focal ischemia, independent laboratory verification and ascertainment of time-window.

It should be remembered that because of previous negative trials with neuroprotectants, no such drug has been introduced to the market.

Key words:
ischemic stroke, experimental models, clinical trials, neuroprotection, thrombolysis