A growing community of researchers has questioned the merits of the translational process in stroke and has championed the need for proof-of-concept studies to explain why >100 clinical stroke studies have failed. On the positive side, no published laboratory results or strong theoretical arguments have been advanced to indicate that human neurons, glia, and blood vessels are necessarily resistant to protection with drugs or devices. In fact, proof of principle has been established for many agents in cultured cells as well as in rodent and subhuman primate stroke models. Therefore, it is important to understand the reasons why an apparent disconnect exists between preclinical and clinical trial results. The answers may lie partly in shortcomings and breaches in the translational process that repeatedly compromise adequate drug testing in both preclinical and clinical arenas.

On the positive side, it may be argued that a formula for human brain protection has been established, that is, by delivering in a timely manner oxygen as well as glucose and by removing wastes from ischemic tissue. That formula has met with success for reperfusion strategies in vivo and for maintaining cultured cells and brain slices in vitro. Some success has also been achieved using hypothermia to treat victims of cardiac arrest and global ischemia. The pleiotropic actions of hypothermia have taught us that protection may be better achieved by targeting multiple rather than individual death pathways as well as by reducing energy demand and energy consumption. Some of the same lessons may also apply to the promising and emerging field of preconditioning whose tissue-sparing effects appear to rely on upregulation of multiple endogenous protective mechanisms. Lessons from the transplant field are also instructive as surgeons have become increasingly sophisticated about maintaining organ viability ex vivo for many hours in the absence of a blood supply. Going forward then, protecting the brain is more than a theoretical exercise, although, like in other neurological diseases, there are no certainties or guarantees of therapeutic success.

So why the loss of confidence? My concerns revolve around specifics of the preclinical, translational, and clinical trial process that raise the possibility that efficacious strategies might have been abandoned prematurely or new drug candidates will be tested inadequately. O’Collins in 2007 examined 1026 experimental treatments for acute stroke (between 1957 and 2003), in which 114 drugs were advanced to clinical trials. An average score for the 114 drugs was disappointingly low (4.2 out of a maximum score of 10), reflecting poor adherence to the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations (a relatively recent and prudent set of drug development criteria). Also, the reduction in infarct size did not differ between drugs that were or were not taken into trials. Together, these observations reflect the existence of additional and as yet unspecified criteria for drug selection (proprietary issues?) that could be made more transparent going forward. Proprietary issues notwithstanding, it is possible that the decision-makers were seduced more by the compelling nature of the disease and its unmet needs and markets rather than by the compelling nature of the pharmacological data. Perhaps as an example of short-circuiting the discovery process, half of the 114 studies first reported the negative clinical trial results rather than publishing the preclinical data justifying the drug choice for clinical testing. Certainly, acute stroke research has truly missed an opportunity to reap the benefits of cross-fertilization from bidirectional research because most drugs that fail in clinical trials are abandoned by sponsors rather than back-tested in laboratory models. As a consequence, little is learned about the explanations for failure or strategies to improve the process going forward.

The single most significant confound that limits our ability to explain why drugs fail in clinical trials (and probably why the stroke field has been unsuccessful in anticipating these failures) is the lack of studies providing evidence for drug activity in the human brain. With the development of high-resolution molecular imaging and biomarker technologies, proof-of-principle studies are getting easier to access and are often missing in preclinical research as well. Without it, we lack the data to determine whether failure of a clinical trial is due to bad concept, poor target, bad drug, or ineffective administration (eg, timing, dosing). In that regard, it is worth contemplating whether any stroke investigators would join in a clinical trial of a novel thrombolytic agent that was not tested or shown convincingly to lyse clots in humans. Is it possible that trialists would accept the use of primary behavioral end points at 3 and 6 months without knowing in...
advance whether the thrombolytic agent adequately lysed clots, increased perfusion, or promoted recanalization? Probably not, and the same minimum standards should be adopted going forward in the brain protection field.

Regarding translation, much has been written about timing and dosing as well as failure to incorporate preclinical information into the trial. For example, NXY-059 was developed to scavenge oxygen radicals, but all cells in the brain generate reactive species. So the failure of NXY-059 in clinical stroke trials may be due to poor drug penetration and therefore the failure to reduce oxidative stress at its major source in the human brain. Enlimomab was intended as an anti-inflammatory drug but probably caused more inflammation than the ischemic process itself because of immunologic incompatibilities between mice and humans. Gavestinel was tested in a trial with advanced knowledge that the dosing was probably too low. The examples are many.

Regarding clinical trials and their end points, there is also a growing concern among stroke neurologists that infarct size does not correspond sufficiently well to behavior to justify it as an end point in clinical trials. Considering the unrefined nature of bedside behavioral tests used in trials (and the fact that behavioral scales often do not correspond to the lesion location and expected deficits in a particular patient), it is probably premature to draw this conclusion. In fact, recent data from Horstmann at the Max Planck in Leipzig supports the view that imaging can be useful to reflect the extent of neuropsychological impairment in a stable population of 12 patients after global ischemia. These investigators performed single-voxel morphometry to measure gray matter density in cuneus and retrosplenial territories and showed a significant correspondence between the loss of gray matter density and memory impairment. They also showed correspondence between drive reduction or loss of motivation and gray matter density loss within the medial thalamus plus anterior cingulate cortex. Whether such a relationship can be extrapolated to white matter damage has not been well investigated.

Regardless, a fundamental goal of brain protection is to preserve tissue. Stroke after all is a recurrent disease. Although small differences in infarct size (if they can be achieved) may not translate immediately to significant behavioral improvement for any given episode, differences do accumulate with recurrent attacks and it is becoming clearer that the risk of cumulative damage contributes to, for example, vascular cognitive impairment. One might wonder whether our colleagues in cardiology would endorse the use of a safe drug that decreases the size of myocardial infarcts by 5% to 10% per episode but does not reduce angina or exercise tolerance for any given attack. The potential for reducing the risk of ischemic cardiomyopathy and congestive heart failure could be important as could reducing the cumulative impact of repeated strokes.

Right now, the Food and Drug Administration does not accept surrogate end points and perhaps imaging could best be embraced as a biomarker instead. Imaging certainly has been used to great benefit in reperfusion trials and should be used in other brain protection paradigms as well. The penumbra occupies 30% to 40% of lesion volume within the first few hours after vessel occlusion. Hence, a reduction by 20% translates to a relatively small 5% to 10% of total lesion volume, so measuring the change in penumbra size would be a more suitable end point than total volume to assess brain protection strategies.

On the administrative side, there are reasons for concerns regarding drug selection and go–no-go decisions. For the most part, drugs are developed and given to the stroke community for testing by biotechnology and pharmaceutical companies and the final go–no-go decisions are made by upper management. Over the years, an imbalance in the decision-making process has evolved and the balance needs to be restored to achieve a full partnership between pharmaceutical companies and academia. Pharmaceutical companies have the potential to help patients with stroke immensely with resources and an organization of clinical and preclinical teams. Traditionally, however, team members do not communicate seamlessly leading to inefficient translation. The explanation may lie in differences: different backgrounds, different knowledge base, often different goals, different motivations, and different management, and this major shortcoming needs to be addressed going forward.

These limitations notwithstanding, there is reason for optimism. Science is a self-correcting process and important steps have already been launched to improve the implementation process in drug discovery. Stroke is a fascinating scientific and medical challenge and sophisticated tools are becoming available to interrogate the process with greater precision and to allow greater predictability. As a public health problem of course, we must continue to pay close attention to strategies that will preserve and restore brain tissue as well as neurological function.

Disclosures

None.

References


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Brain Protection: Maybe Yes, Maybe No
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