Pharmacology & Therapeutics 153 (2015) 79–89

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate Editor: Michael Curtis

Pharmacological therapy of acute ischaemic stroke: Achievements and problems

Antonio Moretti, Federica Ferrari, Roberto F. Villa *

Laboratory of Pharmacology and Molecular Medicine of Central Nervous System, Department of Biology and Biotechnology, University of Pavia, Italy

ARTICLE INFO

Available online 12 June 2015

Keywords:
Acute ischaemic stroke
Therapy
Thrombolysis
Clinical and experimental studies

ABSTRACT

Acute ischaemic stroke (AIS) is a leading cause of death and disability worldwide. Its incidence and prevalence increase considerably with age and numbers will grow with an ageing population. Consequently, the impact of AIS on costs is soaring.

AIS is caused by the abrupt occlusion of an intracranial vessel resulting in reduced blood flow to the brain region supplied. The ischaemic core (which is irreversibly lesioned) is surrounded by the *penumbra* region with less severe flow reduction, lower functional impairment and potential recovery.

Therefore, the fundamental treatment of AIS relies on prompt recanalisation and reperfusion of the threatened, but potentially salvageable, ischaemic *penumbra*. With this aim, intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) remains the current strategy. However, thrombolysis is underused, owing to various exclusion criteria that limit the number of treated patients.

Other thrombolytics are under investigation. Endovascular therapy with mechanical recanalisation devices is also increasingly applied, though definite evidence of its benefit is lacking. Moreover, hypertension and hyperglycaemia are acute complications to be treated in AIS.

This review analyses the current *status*, the problems, the perspectives and the cost–effectiveness of the pharmacological therapy for AIS.

Contents

1. Introduction . . . 80
2. Treatment of acute ischaemic stroke . . . 80
3. Intravenous thrombolysis (IVT) . . . 80
4. Endovascular treatments (EVT) . . . 82
5. Other thrombolytic agents . . . 83
6. Antiplatelet therapy . . . 84
7. Hypertension . . . 84
8. Hyperglycaemia . . . 85
9. Cost–effectiveness of thrombolysis . . . 85
10. Conclusions . . . 85
Funding . . . 86
Conflicts of interest statement . . . 86
Acknowledgments . . . 86
References . . . 86

Acronyms and abbreviations: ACE, angiotensin converting enzyme; AH, anti-hypertensive; AIS, acute ischaemic stroke; BBB, blood brain barrier; BP, blood pressure; CBF, cerebral blood flow; CCB, calcium channel blocker; CNS, central nervous system; CT, computed tomography; DALY, disability-adjusted life year; EMA, European Medicines Agency; EVT, Endovascular Treatment; FDA, Food and Drug Administration; GABA, gamma-amminobutyric acid; HG, hyperglycaemia; ICA, internal carotid artery; ICER, incremental cost–effectiveness ratio; IVT, Intravenous Thrombolysis; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, Magnetic Resonance Imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; OTT, onset-to-treatment time; QALY, quality-adjusted life year; RCT, Randomised Clinical Trial; rtPA, recombinant tissue plasminogen activator; SICH, symptomatic intracranial haemorrhage; TICI, Thrombolysis in Cerebral Infarction scale.

* Corresponding author at: University of Pavia, Department of Biology and Biotechnology, Laboratory of Pharmacology and Molecular Medicine of Central Nervous System, Via Ferrata, 9-27100 Pavia, Italy. Tel./fax: +39 0382 986391.
E-mail address: robertofederico.villa@unipv.it (R.F. Villa).

http://dx.doi.org/10.1016/j.pharmthera.2015.06.004
0163-7258/

1. Introduction

Stroke is the third cause of death worldwide, with 16.9 million first-ever cases, 5.9 million deaths per year and a projected increase to 23 million cases (7.8 million deaths) in 2030 (Strong et al., 2007). Even more worrying, stroke is the main cause of chronic, severe adult disability. Stroke morbidity and mortality differ widely among countries, being higher in low- and middle-income than high-income countries (Feigin et al., 2014). Stroke incidence and prevalence increase sharply with age and the number is projected to rise with the growing of aged population. Not only stroke is a serious health problem, but also represents a dramatic public financial burden.

We focus on acute ischaemic stroke (AIS), which accounts for approximately 80% of all strokes (the remaining 20% are caused by intracerebral or subarachnoid haemorrhage). AIS is caused by an abrupt occlusion of an intracranial vessel resulting in reduced cerebral blood flow (CBF) to the brain region supplied. This triggers a complex cascade of pathophysiological events beginning with the failure of energy metabolism, and followed by membrane depolarisation, protein synthesis inhibition, glutamate release and overstimulation of N-methyl-D-aspartate (NMDA) receptors, Ca^{2+} influx, protease activation with damage to the cytoskeleton and membranes, microglia-activated inflammation, lysosomal membrane rupture with leakage of enzymes leading to cell death (Hossmann, 2006; Moskowitz et al., 2010; Villa et al., 2013).

Transient ischaemic attack (TIA) has been defined as a transient episode of neurological dysfunction caused by focal brain ischaemia without acute infarction. However, TIA presents a high risk of subsequent stroke (meta-analysis in Giles and Rothwell, 2007).

AIS is a disease of heterogeneous origin. The major AIS subtypes according to the etiological TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification are attributed to: (i) large-artery atherothrombotic disease, including artery-to-artery embolism; (ii) cardio-embolism (e.g. in cases of nonvalvular atrial fibrillation); (iii) small-vessel occlusion of small penetrating arteries resulting in lacunar strokes; (iv) unusual or undetermined causes. This differentiation is crucial owing to its prognostic and therapeutic implications.

A previous review has highlighted the failure of translating experimental results in the field of neuroprotection into clinical application (Moretti et al., 2015).

This review aims to examine the current *status* and problems and the future perspectives of the pharmacological therapy for AIS. We searched on PubMed until January 2015 for experimental and clinical studies, reviews and meta-analyses in English.

2. Treatment of acute ischaemic stroke

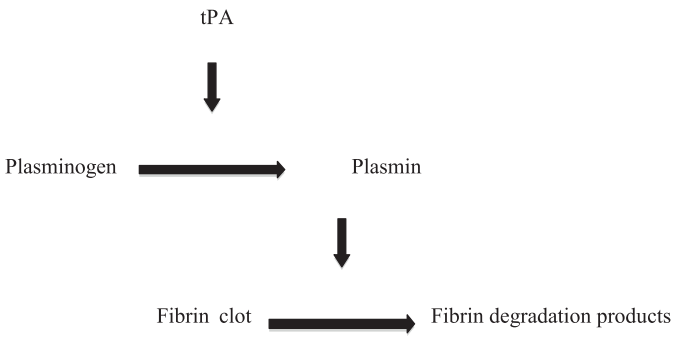
Assessment of neural circuitry loss in typically large vessel occlusions in AIS patients led Saver to estimate that 120 million neurons, 830 billion synapses and 714 km of myelinated fibres are lost every hour in which there is no treatment. Moreover, each hour the brain loses as many neurons as it does in almost 3.6 years of normal ageing: indeed "time is brain" (Saver, 2006).

Therefore, the primary aim of treatments is to restore CBF as soon as possible, preventing the spreading of irreversible injury due to the expansion of the infarct core into the ischaemic *penumbra*. The evaluation of a potential stroke patient must be rapid and based on clinical and neurological examination. The most common imaging modalities of parenchymal brain are noncontrast head Computed Tomography (CT), which can identify or exclude intracranial haemorrhage (an absolute contraindication to fibrinolytic therapy) and Magnetic Resonance Imaging (MRI). The associated critical cardiopulmonary complications are addressed and treated. The efficacy of these interventions has been greatly enhanced by the establishment of acute stroke units (Stroke Unit Trialist' Collaboration, 2013).

Thrombolysis is the only therapy approved for AIS (reviews in Brott and Bogousslavsky, 2000; Bentley and Sharma, 2005; Micieli et al., 2009; Donnan et al., 2011; Balami et al., 2013a, 2013b; Fugate and Rabinstein, 2014; Harsány et al., 2014. Cochrane review by Wardlaw et al., 2014. International Guidelines in: National Institute for Health and Excellence, 2008; The European Stroke Organization, 2008; Jauch et al., 2013; Minematsu et al., 2013).

Thrombolysis is currently used for Coronary Heart Disease (CHD) and acute pulmonary embolism. For AIS, early and as complete as possible recanalisation (restoration of blood flow at the occluded artery) and reperfusion (restoration of flow to the distal arterial bed) are crucial for salvaging the brain tissue in the *penumbra*, reducing neurological impairment, long-term disability and mortality. The high brain metabolic demand makes the time window for AIS thrombolysis much shorter than for CHD.

A thrombus is the final product of the complex blood coagulation process. The clot contains a mesh of fibrin and platelets. Thrombolytic drugs activate the endogenous antithrombotic system (fibrinolysis) by enhancing the conversion of proenzyme plasminogen into the active protease plasmin, which in turn breaks the cross-links between fibrin molecules. This causes fibrin dissolution and breakdown of intravascular thrombi (Murray et al., 2010):



First generation thrombolytics were streptokinase (no longer used) and urokinase. Second generation thrombolytics include pro-urokinase and alteplase (rtPA), but pro-urokinase was not approved by the Food and Drug Administration (FDA). Third and fourth generation thrombolytics are also being developed. The specificity for bound plasmin increases from first to fourth generation. Moreover, the more fibrin-selective the protease is, the higher is the probability that it activates the clot-bound rather than the circulating plasminogen.

3. Intravenous thrombolysis (IVT)

Tissue plasminogen activator (tPA) is a natural serine protease which is present in the intravascular compartment (originating from endothelial cells), the neurovascular unit and the brain parenchyma and is overexpressed in stroke-lesioned tissue. The function of tPA in the intravascular compartment is to promote thrombolysis by activating plasminogen. However, tPA can cross the blood–brain barrier (BBB), and has pleiotropic effects in the extravascular compartment. tPA can cause neurotoxicity by a complex mechanism including NMDA-evoked calcium influx, K^+-channel impairment, nitric oxide (NO) production through inducible (iNOS) and neuronal NO synthase (nNOS), and activation of microglia and neuroinflammation. tPA is actually a multifaceted modulator of neurotransmission and synaptic plasticity (Samson and Medcalf, 2006) endowed with beneficial effects in the intravascular space, but also with potentially harmful effects in extravascular compartments which may lead to cerebral oedema, haemorrhage and ischaemic cell death (review Yepes et al., 2009), though a recent study in the rat did not confirm its neurotoxicity (Sutherland and Buchan, 2013).