Pharmacological Treatment of Ischemic Stroke
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Introduction

A ischemic stroke (IS) is caused by the transient or permanent disruption of the Cerebral Blood Flow (CBF) to a single or several brain areas, during ≥24h, due to the blockade of a vessel.

The importance of stroke relies on its high impact worldwide since it has been estimated that around 11,569,538 of IS events took place worldwide during 2010, resulting in the loss of 39,389,408 Disability-Adjusted Life Years (DALYs)1. (Figures 1 & 2)

Objectives

• To show the current state of the ischemic stroke pharmacological treatment combining the Spanish and the USA’s guidelines.
• To highlight the importance of the combination of rt-PA with mechanical devices.
• To approach the new studies which are being carried out just now in research laboratories.

Clinical Situation

First Steps:

The Stroke Code (Código Ictus) has been created in order to coordinate the journey of the patient to and within the hospital section known as Stroke Unit (Unidad de Ictus).

The objective is to uncover the main cause of IS taking ≤60min, thus providing a suitable acute treatment.

Initial emergency evaluation:

• Analysis of a stroke rating scales e.g. NIHSS
• Blood Glucose measurement
• Baseline electrocardiogram
• Haematological study
• Chest radiography (only in Spain)
• Non-Contrast CT scan evaluation (≤45min)

Information adapted from:
• Guía para el diagnóstico y tratamiento del ictus from the Sociedad Española de Neurología (SEN 2006) used in the Spanish hospitals and its review published in 2011 (published online on 2014)
• Guidelines for the Early Management of Patients with Acute Ischemic Stroke from the American Heart Association/American Stroke Association (AH/A/ASA) used by the American doctors (2013)

Two approaches proposed by SEN:

1- Measures intended to improve or re-establish the Cerebral Blood Flow (CBF)
TREATMENT OF CHOICE:

Intravenous Recombinant Tissue Plasminogen (IV rTPA)

FDA approval 1996

Dose: 9mg/kg with a maximum dose of 90mg

Viability assessed by CT scan evaluation

Triggers the fibrinolysis of the thrombus.

Weaknesses:

• It is a highly time-dependent treatment:
  • Only displays effect on 50% of patients, with a rapid action in 21% of the cases3
  • Exhibits a later arterial re-occlusion in at least, 1/3 of patients
  • 50% of non-responder patients might suffer side-effects of the administration.

However, no other treatments have shown a higher potency or effectiveness than rt-PA.

NEXT STEP: Intra-arterial (IA) administration of rt-PA using Mechanical Thrombectomy devices.

Benefits:

• Reduction of the systemic concentration of the compound Direct infusion into the thrombus

• The technique: catheter manipulation

• Delayed administration (additional imaging techniques)

Research: New Approaches

Reperfusion: New Approaches

Restorative therapies:

Enhancement of growth factors (e.g. GAP-43, MARKS, CAP3, and BDNF).
Blockade of negative factors (e.g. Nogo-A, chondroitin sulphate, and siphrin A5).

In order to generate new neurons (lateral ventricle and dentate gyrus) which would migrate to the ischemic area.7

Anti-expressors have shown a positive indirect effect e.g. Fluoxetine (Prozac) at the FLAME study.

Upligation of Fibrinogenolysis

Fibrinogenolysis (Figure 6) can increase its catalytic efficiency with the activation of the AsienA2-plasminogen-plasmin complex. Administration of recombinant A2 allows to lower the rt-PA dose, preventing HT.8

Imaging-based Patient Selection

Characterizing the Ischemic Penumbra (Figure 7), the region where the reperfusion efforts focus, with new penumbral imaging devices.9

Positively tested in three trials: DEFUSE, EPHÉD and DEFUSE-2.

DEFUSE-3 is being conducted at the moment by Stanford University (USA).

Prevention of Haemorrhagic Transformation (HT)

This spectrum of hemorrhages within the area the stroke might be produced by the reperfusion process performed by rt-PA.

Approach: NEUROPROTECTIVE AGENTS10

• Inhibitors of MMP-2 and MMP-9: these matrix metalloproteinases are up-regulated.
• Deferoxamin (DFO): promising chelating agent produced by N. pinius.
• Estragon: reduces brain swelling and edema.
• Clobutinol (Pletal): guanidine-derivate with protective effect over endothelium.
• Glypride (Glibencamide): DMI medication which inhibits sulfurylase receptors e.g. SUR1 which is up-regulated after ischemia.

Conclusions:

• The pharmacological approach of IS has reached a point where rt-PA, cannot be object of further improvement.

• The future of this treatment is the combination of rt-PA with either, other compounds or mechanical devices.

• Mechanical thrombectomy is already included hospitalization and treatment protocols, displaying great results.

• Neuroprotective therapies, e.g. Uric Acid, are still under trial but showing promising outcome.

References:

3. International Neuro Products; Flow Restoration; Solitaire(TM) FR Revascularization Device; Condino.

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