

Future Therapeutic Management of Stroke: Neuroprotection, Intra-arterial Lysis

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CASE PRESENTATION

- 60 year old male – Sx onset 0900
- Collapsed at work with L side weakness
- Taken to local hospital by EMS - 1000

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PHYSICAL EXAM

- 125/65 P-58
- L hemiparesis, dysarthria, L sensory loss, L neglect, L facial droop
- NIHSS 11

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PMH

- Paroxysmal Afib
- NIDDM
- Hodgkin's Lymphoma (remission)

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LOCAL HOSPITAL

- Head CT – normal
- EKG – Atrial fib
- Call for transfer to UM – 1130

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KEY LEARNING POINTS

1. Identify promising neuroprotective drugs currently in clinical trials.
2. Indications for intra-arterial thrombolysis.
3. What is the evidence for neuroprotection with hypothermia?

NEUROPROTECTIVE DRUGS

- Glutamate antagonists
- Anti-inflammatory agents
- Calcium channel blockers
- Sodium channel blockers
- Potassium channel activators
- Free radical scavengers
- GABA receptor antagonists
- Serotonin antagonists
- Caspase inhibitors
- Others

CLINICAL TRIALS - GLUTAMATE RECEPTOR

<u>Drug</u>	<u>Mechanism</u>	<u>Results</u>
Selfotel	NMDA	D/C
Aptiganel	NMDA	AE's
MK 801	NMDA	AE's
Dextrorphan	NMDA	AE's
6V 150526	glycine/NMDA	negative
Eliprodil	NMDA	negative
NBQX	AMPA	AE's
Magnesium	NMDA channel	ongoing

CLINICAL TRIALS - OTHER

<u>Drug</u>	<u>Mechanism</u>	<u>Result</u>
Nimodipine	Ca blocker	negative
Flunarizine	Ca blocker	negative
Fos-phenytoin	Na blocker	negative
Maxipost	K blocker	negative
Enlimonab	anti-inflam	AE's
Leukarrest	anti-inflam	negative
Tirilazad	free radical	negative
Citicoline	free radical	negative
Ebselen	free radical	negative
NXY-059	free radical	positive benefit

MAGNESIUM

- Safety proven in stroke
- Late administration decreases efficacy
- FAST - Mag

FAST-Mag

- Early administration by EMS
- 50% treated < 1 hour
- All treated < 2 hours
- Trial ongoing

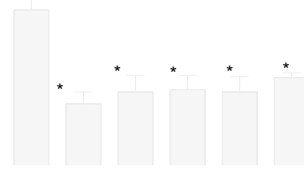
NXY – 059


- Traps carbon and oxygen radicals
- Preclinical trials positive in rats
- Preclinical trials positive in primates
- Significant dose response
- Still effective after 4 hours of ischemia in animals

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NXY-059 : window in permanent ischemia¹



Non-significant 20 % decrease in infarct size at 6 hours
¹Sydesff SG, et al. Br J Pharmacol 2002
 $p < 0.05$ vs control
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SAINT I Trial

- Placebo controlled trial
- Acute stroke < 6 hours
- 72 hours infusion of NXY-059
- Primary outcome
 - Disability as measured by Modified Rankin

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SAINT - I

- 200 centers – Europe, Asia, Australia
- Trial results not published yet
- Oral presentation – positive clinical benefit
- 1st positive clinical neuroprotective trial!!
- Decreased hemorrhage with tPA use
- No significant AE's
- SAINT 2 – ongoing in US, international

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INTRA-ARTERIAL THROMBOLYSIS

- Two randomized trials – PROACT 1 & 2
- Tested prourokinase vs. heparin <6 hours
- MCA occlusions only
- Recanalization improved with IA
- Mortality identical
- Relative risk reduction for outcome – 60%


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IA Clinical Practice

- Numerous clinical series published
- Basilar artery thrombosis series suggest benefit
- Benefit with basilar may be late (12-24 hours)
- MRI diffusion/perfusion may aid selection

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AHA RECOMMENDATIONS

- Recommended for MCA occlusions <6 hours – grade 2C
- Recommended for basilar artery thrombosis – grade 2C
- Caveats
 - combined IV/IA approach in clinical trials
 - Low dose IV __, angiography __, IA

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MECHANICAL CLOT RETRIEVAL

- Alternative to thrombolytics
- Useful when contraindications exist
- One large study - MERCI

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MERCI TRIAL

- Anterior circ strokes only
- Treatment <8 hours
- 151 patients entered

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MERCI RESULTS

- Recanalization in 46%
- Complication rate 7% (SAH, device fx, embolization)
- With recanalization, good outcome (46% vs. 10%) and mortality improved (32% vs. 54%)
- ICH rate 7.8%

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HYPOTHERMIA

- Known to be neuroprotective for years
- Positive results in 2 studies with global ischemia
- Multiple mechanisms for neuroprotection
- COOL AID

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COOL AID TRIAL

- Randomized trial 40 patients
- Entry <12 hours
- Endovascular cooling (33°C) for 24 hours
- Endpoint – clinical assessment & MRI

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COOL AID

- 18 patients received hypothermia
- Clinical outcomes similar
- MRI outcomes similar
- Appeared to be well tolerated
- Further studies

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CASE (cont'd)

- Patient arrived at tertiary hospital (1210)
- NIHSS 12
- Angiography
 - occlusion superior division of R MCA
 - infused with IA t-PA
 - TIMI 3 flow after clot dissolution

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Outcome

- Resolution of deficits
- Discharge NIHSS—2
- Only deficits are facial droop and mild sensory change

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Questions??

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