



Lessons from planning a beta test

Becky Trueman

School of Life Sciences, University of Nottingham, UK



Considerations when designing the beta test

- Choice of therapeutic agent
- Resources / Funding
- Capabilities of sites
 - Staffing
 - Models
 - Equipment



Glyceryl Trinitrate (GTN)

5mg/24hrs

- Positive ambulance-based trial (Ankolekar & Bath, Stroke 2013;44:3120-8)
- Positive in sub-group of patients treated within 6 hours in the MRC ENOS trial (Bath, Lancet 2014; 385(9968):617-28).

Potential mechanisms:

- Vasodilatation
- Neuroprotectant





Preclinical work on Glyceryl Trinitrate (GTN)

- A positive meta analysis of nitric oxide donors, with a time dependent effect
- However, only two studies in stroke models using GTN.
 - Lacking dose, time course of efficacy and administration route
 - Doses of GTN used in other rodent studies range from $<1\mu\text{g}/\text{kg}$ - $>100\text{mg}/\text{kg}$

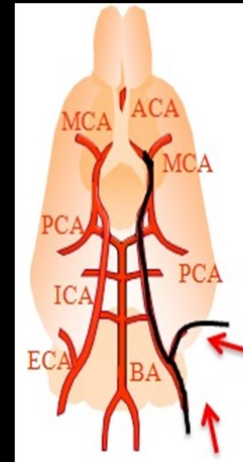


Model

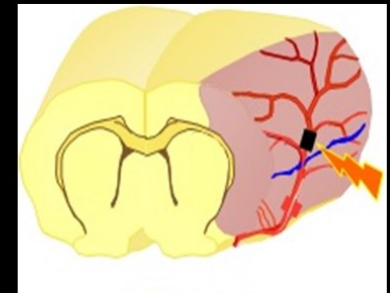
- **Species:** Mouse, **Strain:** C57Bl/6(J), **Sex:** Male
- **2 Models:**
 - Permanent distal (diathermy) MCAO
 - Intraluminal filament MCAO
(Occlusion duration to achieve an infarct of 20-30% hemisphere)

Treatment

- At reperfusion
- 4 hrs after occlusion



Intraluminal filament



Direct electrocoagulation of distal MCA

Images: I Mhairi Macrae



Outcome measures

48h after occlusion

Functional:

- Neuroscore
- Grip strength

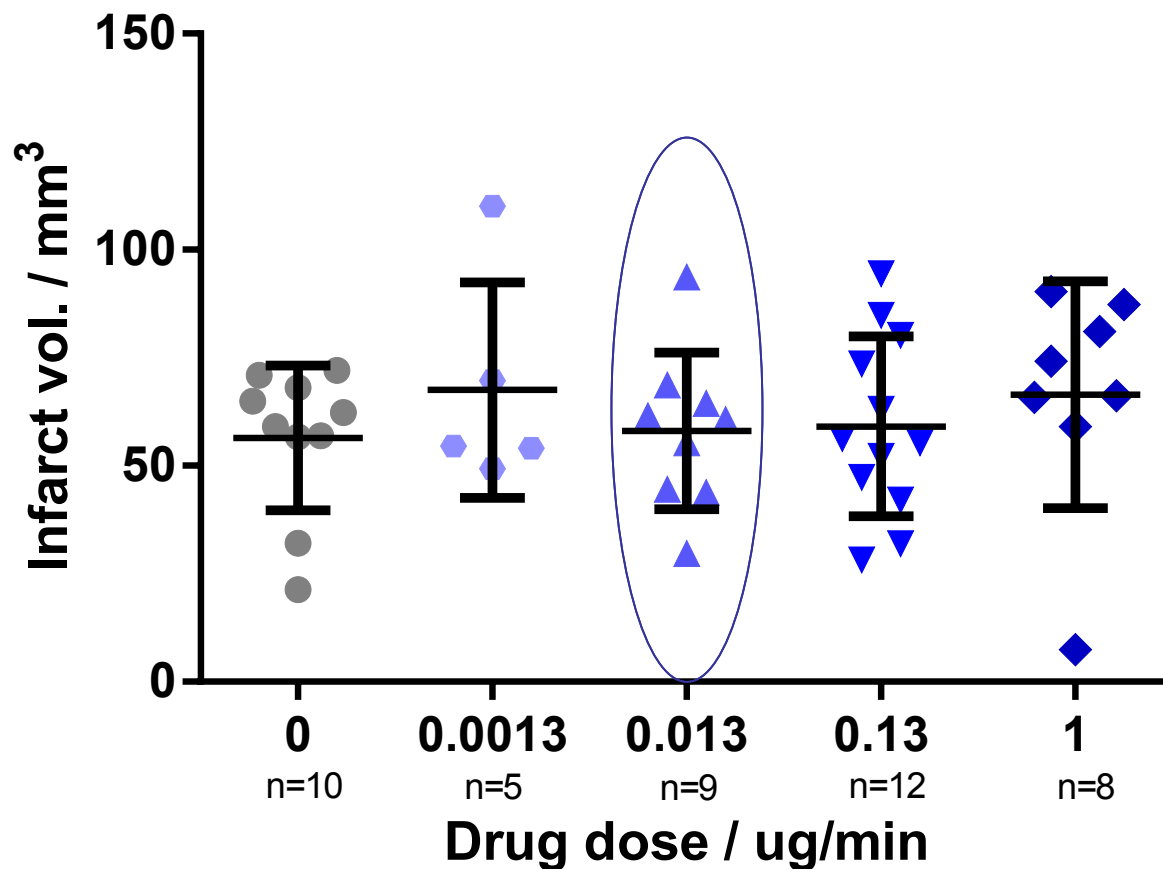


Infarct Volume:

- 2,3,5-triphenyltetrazolium chloride (TTC)

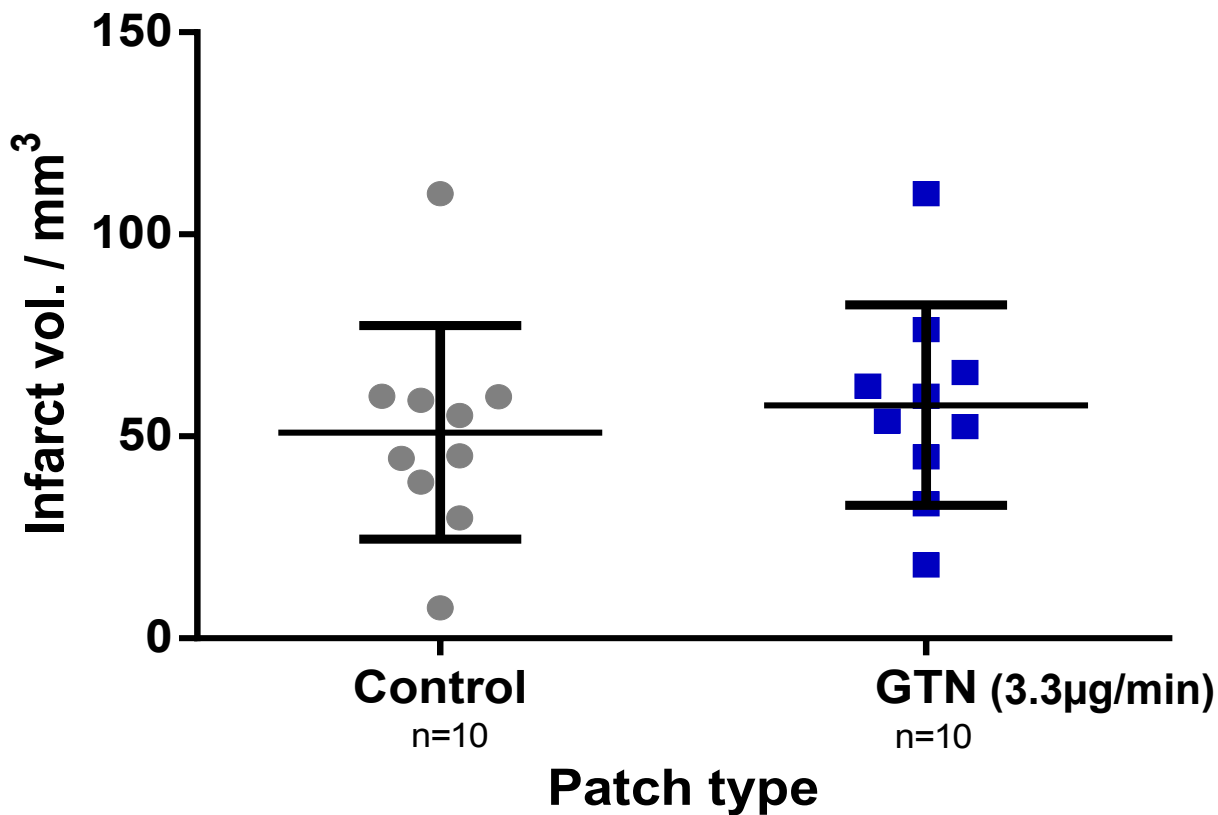


GTN dose response results: Infarct volume





Patch test: Infarct Volume





Choice of therapeutic agent

- Dose
- Delivery method
- Efficacy
 - Time point of treatment
 - Model
 - Sex
 - Strain

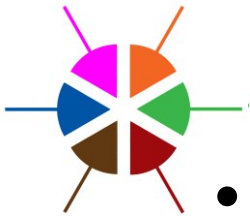


<http://www.alzet.com>



Issues / lessons learnt

- Amount of data indicating efficacy of (specific) drug:
 - model used
 - species / sex
 - set up (For example: anaesthetic, carrier gas)
- Delivery method adding to the complexity of the experimental design
- Time point of delivery
- Sourcing and shipping the drug
- Always going to be some compromise, but care that this is not to the detriment of the trial design



Positives

- Carrying out the process of designing the beta test enabled more effective development of the platform
- Tested of a number of the multipart protocols, and ensured relevant SOPs developed.
- Enabled the feasibility of central assessment of behavioural outcomes to be tested
- Further insights into complexity of designing multicentre trials
- Allowed smaller “alpha” tests of the system to take place, prior to future beta test



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