Background and Rationale

- Aneurysmal subarachnoid haemorrhage (aSAH) is a disease that predominantly affects the young. Those that survive the initial event can go on to experience complications to include cerebral artery spasm (vasospasm), leading to ischaemic neurological deficits (delayed cerebral ischaemia, DCI) that yet further increase morbidity and mortality.
- Vasospasm risk in particular correlates with Fisher grade (blood load on CT) and can be diagnosed clinically (focal neurological deficit of no other cause) or radiographically (CT angiogram).
- Smooth muscle relaxants that cross the blood brain barrier (BBB) may be useful in preventing vasospasm. Ideally an agent that does not cause systemic hypotension would be ideal.
- Extracellular calcium is the main source of calcium for contraction in large cerebral arteries (unlike systemic arteries which rely on intracellular calcium). Animal studies showed nimodipine was more potent than other centrally acting calcium channel blockers (CCBs) e.g. nidefipine which was initially studied in more detail. Amlodipine does not cross the BBB.
- Nimodipine is a highly protein bound (95%) lipid soluble CCB with rapid enteral absorption (1h peak concentration), low bioavailability (predominantly first-pass hepatic metabolism) of 13%, which is rapidly eliminated with a half life of 1-2h (terminal elimination half life 8-9h). Bioavailability is further reduced by co-ingestion of food. Increased bioavailability with co-ingestion of drugs that inhibit CYP-450. Importantly there is a significant reduction in bioavailability of nimodipine with many antiepileptics (seizures also complicate aSAH) to include phenytoin and carbamazepine.

Advantages and Disadvantages

- Advantages
  - Simple, cheap, effective
  - Reasonable physiological rationale, no other proven effective treatment for prevention
- Disadvantages
  - May cause systemic hypotension (independent risk factor for poor neurological outcome if untreated, otherwise co-administering vasopressors with unclear benefit-harm)
  - Degree of enteral absorption often unknown, drug interactions, GI perfusion in particular if stress-induced cardiomyopathy
  - Route; why would enteral administration be more efficacious over intravenous?
  - Not dose titrated; one size fits all? Very rarely dose adjustments made (interactions, hypotension)

Key studies

- Nimodipine enterally
  - Allen (US) 1983 NEJM
    - MC RCT DB and stratified to center/surgeon; near normal neurology on entry to trial; enteral nimodipine (0.7mg/kg loading then 0.35mg/kg 4hrly thereafter) vs placebo for 21d, start <96h (preoperatively) aSAH; n=116
    - Persistent (d21) severe neurological deficit or death attributable to vasospasm 8/60 in placebo vs 1/56 in Rx group P=0.03(similar baseline neurology and fisher grade)
  - Philippon (Fr) 1986
- MC RCT DB aSAH <72h, Hunt and Hess 1-3 and without early complications (eg hydrocephalus) 60mg 4hrly vs placebo for 21d (NB use of TXA); n=70
- Neurological deficit caused by vasospasm at d21 in 12.9% (nimodipine) vs 28.2% (placebo), P<0.05; non-statistically significant reduction in vasospasm on angio
  - Pertruk (Ca) 1988 J Neurosurg
    - MC RCT DB of enteral nimodipine 90mg 4hrly vs placebo <96h (preoperatively) aSAH with significant presenting neurology (grade 3-5 on Hunt and Hess) n=154
    - Good outcome at 3m (on Glasgow outcome score, GOS) 29.2% nimodipine vs 9.8% placebo P<0.001; (note whilst large increase in mortality with nimodipine, mostly from grade 3 group; 28% vs 4.8% these were predominantly explained by other causes such as rebleed, higher fisher score etc… hypotension was not implicated)
  - Pickard (UK) 1989 BMJ
    - MC RCT DB; nimodipine 60mg 4hrly versus placebo (note did not specify aneurysmal cause of SAH) <96h of onset of bleed for 21d (NB. 130 discontinued early; mainly due to no vasospasm on angiogram; 70 nimodipine, 60 placebo); n=554
    - Nimodipine reduced cerebral infarction; 22% vs 33% (RRR 34%) and reduced poor outcomes (dead, vegetative state & severe disability) 20% vs 33% (RRR 40%) at 90d

- **Nimodipine intravenously**
  - Ohman 1988 (Fin) Neurosurg
    - MC RCT DB; IV placebo vs nimodipine (up-titrated to 0.5mcg/kg/min continuously for up to 7-10d immediately post aSAH diagnosis; if operated late could be continued for further 2-3d post-op) then oral (60mg 4hrly vs placebo) for 21d. Hunt & Hess 1-3; (NB in both groups 4mg dexamethasone 6hrly given); n=213
    - Significant reduction in mortality with early surgery (looked at <72h, 4-7d vs =/>8d). At 3m 83.7% of nimodipine group were independent vs 78.9% in placebo. Mortality by ischaemic deterioration was significantly lower p=0.01 (1% vs 8.3%)
  - Numerous small RCTs IV vs oral nimodipine
    - e.g. Kronvall (2009, J neurosurg) n=106, Soppi (2012, World Neurosurg) n=174
    - No difference in clinical efficacy in the studies I found

- **Nimodipine intra-arterially**
  - Haley 1993 (US) J Neurosurg
    - MC RCT DB; <7d from onset of aSAH, high dose IV nicardipine (0.15mg/kg/h) vs placebo for up to 14d following haemorrhage; n=906
    - Symptomatic vasospasm during treatment period less (32% vs 46%, P<0.001) in treatment group, but no difference in outcomes at 3m (death or good outcome)
    - More HHH therapy in placebo group; questioned whether HHH as effective for DCI

### Summary (my practice)
- Nimodipine is the only treatment with high-level evidence to prevent vasospasm and DCI in aSAH
- I routinely give nimodipine early (<72h) to all patients with aSAH presenting for active management as soon as initial haemodynamic stability has been achieved, irrespective of timing of aneurysm fixation. I preferentially use the enteral route (60mg 4hrly), but where vomiting or concerns re absorption exist I use continuous IV infusion. I continue treatment for 21d, changing to enteral when able. I do not use Nimodipine in pregnancy (cat C; teratogenic) rather treat early if DCI occurs
- Where hypotension exists (post fixation of aneurysm in euvoalaemic patient) I consider potential causes of high plasma concentrations (cirrhosis, CYP450 inhibitors) that may require personalised approach to dosing. However overall in this group I will administer low dose vasopressors (noradrenaline) in order to tolerate ongoing nimodipine administration, but review benefit-harm at moderate-high levels
- Intraarterial vasodilators seem to be effective in treatment of symptomatic radiological vasospasm