The Weekly Probe

11th March 2016 **Volume 13 Issue 5**

Antidote for dabigatran (Pradaxa) –Up till late last year when a patient on Pradaxa presented with bleeding, management was limited to dialysis or supportive treatment with blood products which are only partially effective. However pharmacy will stock the new unpronounceable antidote idarucizumab.
This is a monoclonal antibody fragment which binds dabigatran with an affinity 350 times greater than thrombin. Consequently, idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity.

The main indication is **life threatening bleeding requiring reversal or urgent surgery**.
Your first call (like other life threatening NOAC bleeds) is to the **Haematologist at St George for approval**
The dose is 2 ampoules drawn up into a 50ml syringe and given as a slow IV push of 2 vials of 2.5g over 5-15mins with a N/S flush). The SAS and TGA paperwork are filled out retrospectively after each use but like other SAS drugs the patient needs to be consented and the paperwork needs to be filled out ASAP to get further supply of the drug after each use.

It is now stocked in the pharmacy at Sutherland.

How effective is this? A study from NEJM June 2015 looked at 90 patients with life-threatening bleeding or those requiring urgent surgery requiring dabigatran reversal. Idarucizumab was found to normalise diluted thrombin time and ecarin clotting time in 88-98% of patients, an effect which was evident within minutes of administration. Concentration of unbound dabigatran remained below 20ng/mL (no clinical effect) at 24 hours in 79% of patients. 1 patient had a thrombotic event within 72 hours after idarucizumab administration.

HEMLICH/FLUTTER VALVE- issues seen at “St Elsewhere” are sometimes encountered in our own Department / Hospital so here’s a reminder not to use the Heimlich valve included in the pleurocath kits. Give it to your child as a cheap musical instrument / choking hazard but this valve should NEVER be used in the circuit in the ED given risk of misalignment and tension pneumothorax developing. It should be discarded at the start of the procedure. Once again -

THROW THIS AWAY!!

Legionnaire’s Disease alerts – there have a number of cases over the last couple of weeks of Legionnaire’s disease. The patients have visited certain parts of the city since late February, so consider this diagnosis when looking at patients with atypical pneumonia. Testing includes urine for Legionella urinary antigen test yet sputum may be sent for culture (specific request). In addition to usual care, contact the public health unit via switch if you have concerns.

Zika Virus – a additional component to the alert from the Ministry of health re Zika virus :

- Link between virus and congenital malformation is uncertain
- If there has been travel to virus affected region (Central and Sth America, West Indies + American Samoa) **and** pregnant:
    - Exposure in last 2 weeks and symptomatic – PCR (blood and urine) + serology
    - "" "" "" and asymptomatic – PCR and serology for storage
    - Exposure 2-4 weeks ago - asympt or symptomatic in past - serology + PCR urine
    - Exposure > 4 weeks ago - - asympt or symptomatic in past - serology
- On your pathology request include when and where the patient travelled, symptom onset, vaccines recently given, previous flavivirus (dengue ior West nile virus)
- Note tests will take ~ 4 weeks to return, does not give info if a foetus is infected or harmed, and there is no treatment once the result is received.
- If not pregnant generally only people with symptoms of Zika virus infection and a travel history need to be tested.
- Men who have travelled to areas with ongoing Zika virus transmission whose partner is pregnant should abstain from sexual activity (vaginal, anal, or oral) or consistently use condoms for the duration of the pregnancy, whether symptomatic or asymptomatic.
- Men who have had a confirmed Zika virus infection, whose partner is not pregnant should abstain from sexual activity (vaginal, anal, or oral) or consistently use condoms for 3 months following the resolution of symptoms. Those with possible viral symptoms should abstain while awaiting test results.
- Speak to the ID or micro consultant if you have any questions.

THIS WEEK

DYSTONIA

A 30 yo man presents with 1 day history of painful spasms in his left trapezius associated with difficulty talking secondary to masseter spasm. No trauma, fevers, neuro, ENT, opthalmological or cardioresp symptoms.
He denies any medications except alprazolam for anxiety.
On exam – normal obs – discomfort secondary to rotation of head to right and dysarthria secondary to inability to fully open his mouth. No abnormality noted with his extraocular movments. No other abnormalities on exam.

The patient is treated as dystonia, a diagnosis that can present quiet dramatically , is occasionally missed, yet is a "satisfying" illness to treat, as the patients are very grateful with rapid and complete relief of symptoms.

Dystonias present as sustained muscle contraction frequently associated with twisting or repetitive movements or abnormal postures.

Dystonia is usually classified on the location that the dystonia involves, or if primary or secondary:

- ***primary*** *(no identifiable cause).* By definition, primary dystonias are unaccompanied by other neurologic abnormalities, except tremor and occasionally myoclonus. May be focal or generalised .
- ***Secondary-*** *to*

  drugs*:*

  - phenothiazines- Chlorpromazine (largactil) ; Promethazine (Phenergan); Prochloperazine (stemetil) Thioridazine; Fluphenazine, Trifluperazine,
  - butyrophenones eg haloperidol,
  - anticonvulsant agents (eg phenytoin, carbemazepine),

- levodopa,
- serotonin reuptake inhibitors (SSRIs),
- chloroquine, ecstacy, cocaine
- diazepam – couple of cases

-**hereditary neurodegenerative and metabolic diseases**: Huntingtons disease, Wilsons, lysosomal storage diseases eg Neimann-Pick; aminoacidurias eg homocysteinuria; mitochondrial disease; Parkinsonian syndromes eg Parkinsons disease, multi system atrophy, progressive supranuclear palsy, corticobasal degeneration;

-**acquired intracerebral structural lesions** (lesions of the basal ganglia, tumour, AVM, trauma, haemorrhage, SAH, MS, perinatal injury, kernicterus, anoxia, encephalitis, HIV encephalopathy); may produce hemidystonia or focal limb dystonia

-toxins (carbon monoxide*)*

-psychogenic.

Pathology: The underlying abnormality is thought to be due to neurotransmitter imbalance in the nigrostriatum (ie, basal ganglia) with relative cholinergic excess + dopaminergic deficiency).

Drug related Dystonia- most common cause for acute dystonias

Incidence: about 2% of patients on phenothiazines will develop dystonia. 25% of those are on haloperidol and depot phenothiazines. 50% occurs within 48hrs and 85% within 4 days.

Risk factors: Male; <15yrs; Family history of dystonia; alcohol use; drug abuse especially cocaine. Individual susceptibility is important. It is unrelated to the chemical structure, milligrams or duration of treatment.

Dystonia's can present with tongue protrusion, a clenched jaw, torticollis, oculogyric crisis or opisthotonus. The patient will have slurred speech due to the clenched jaw, intermittent tongue protrusion & opisthotonus.

The description of the sensation may be vague, but **muscle tension worsened by movement** is a common feature. Patients are sometimes falsely labelled hysterical.

Dystonic reactions are reversible. Tardive dyskinesia is similar in the clinical presentation but irreversible.

Acute dystonia can present as an emergency with a compromised airway due to laryngeal or respiratory muscle involvement. Control of the airway with intubation & ventilation may be necessary.

In the vast majority of cases however there will be time for a thorough history & examination.

- Oculogyric crisis: begins with blephorism followed by upward deviation of the eyes.
- Oromandibular crisis: involves the tongue and pharynx together with pulling of the mandible upwards and downwards.
- Lingual dystonia: sustained protrusion or upward deviation of the tongue.
- Torticollis: shoulder elevation ipsilateral to the side to which the chin is turned.
- Jerking of the head.
- Trunk twisting: involves various movements such as increased lordosis, scoliosis, kyphosis, tortipelvis and opisthotonus (hence can be misdiagnosed as tetanus).
- Generalized dystonia is where there is involvement of the trunk and one other body part.

Tests? Most present 24-48 hours after phenothiazine (chlorpromazine, thioridazine, prochlorphenazine) or butyrophenone (droperidol, haloperidol) use or an increase in the dose. **No investigations** are required & **the diagnosis is a clinical one** in this setting.

The use of an anticholinergic drug such as Cogentin (benztropine) 1-2mg iv or imi to a maximum of 6mg will reverse the symptoms.
The onset is more rapid when given iv, usually 1-2mg aliquot's in adults. Refer to the drug handbook for kids.

Cogentin (benztropine) relieves the muscle spasm within 30 mins and the maximum effect occurs within 90mins. It acts more rapidly and has fewer side effects than diphenhydramine (Benadryl) which can also be used alone or in combination with benztropine. Benztropine is preferred as it

provides a more complete blockade. Due to the long half life of some of the precipitating medication, it may help to prevent a recurrence of the symptoms by prescribing 0.5-1mg bd of oral benztropine for 1-2 days.

Progress – The patient improved marginally after 2mg IV cogentin yet symptoms completely resolved after 4mg. He later admitted to using cocaine 1-2 days prior.

CADASIL SYNDROME

18yo man presents with dysarthria and headaches. His mother rings to advise that she has a diagnosis of CADASIL syndrome (her mother died also in mid 40s with “MS” yet she thinks it probably was also CADASIL). What is this?

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common form of hereditary cerebral angiopathy

What is it ? It is a chromosomal abnormality which results in protein accumulation and occlusion of small-medium sized cerebral arteries.

Who? Both sexes. All races. Age of onset mean 46 yo yet as young as 8yo. The mean age at death has been reported to be 61 years after a mean disease duration of ~ 23 years

How do they present? Classic tetrad of dementia, psychiatric disturbances, migraine, and recurrent strokes yet mix / presence of elements is variable.

- TIAs / infarcts – most common presentation especially in males
- Migraines – may be first sign especially in females– may be associated with aura and focal neuro deficits- may be followed later by TIA then CVAs
- With further subcortical injury, there may be a progressive subcortical dementia and functional decline. The cortex involved will affect symptoms with potential sensory or motor changes mood changes, psychosis, memory or gait / movement disorders and urinary incontinence.
- Seizures and ICH may be seen.

Labs – genetic testing – sensitivity approaching 100%

Imaging - Hyperintensities on T2-weighted imaging or FLAIR are seen in the periventricular and deep white matter especially involving the temporal lobes or external capsule. May also see microbleeds

Treatment – Aspirin is often used to reduce thrombotic complications yet no evidence of benefit yet. Problem with bleeds so antiplatelet or anticoagulants are often avoided. Treatment focuses on management of headaches, mood and psychiatric disturbances, and rehabilitation following a brain ischemic injury.

Progress: Sadly MRI showed evidence of bilateral subcortical and peri ventricular white matter hyperintensity suggestive of CADASIL.

NEXT WEEK’S CASES

A patient with headache and undergoes a LP, the findings c/w a viral meningitis. However 2 days later he develops a different headache on standing. What has occurred and how can we prevent this?

And a review of the most important article of the decade which will change your perspective on drinking!

JOKE / QUOTE OF THE WEEK

Please forward any funny and litigious quotes you may hear on the floor (happy to publish names if you want)

THE WEEK AHEAD

Tuesdays - 12:00 – 13:45 Intern teaching -Thomas & Rachel Moore
Wednesday 0800-0900 Critical Care Journal Club. ICU Conf Room / 12.00-1.15 Resident MO in Thomas & Rachel Moore
Thursday 0730-0800 Trauma Audit. Education Centre / 0800-0830 MET Review Education centre / 1300-1400 Medical Grand Rounds. Auditorium.

Editor: Peter Wyllie