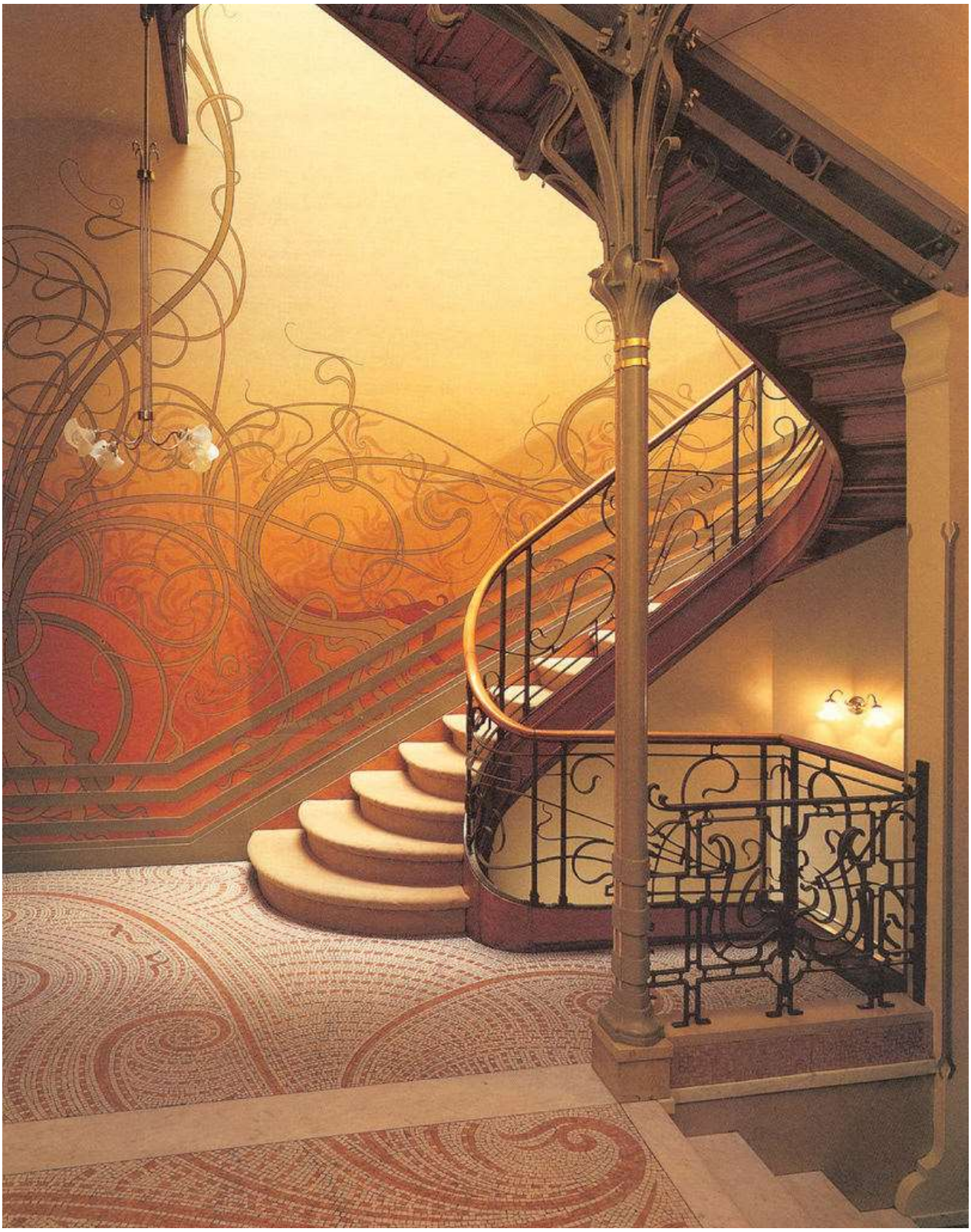
THE NORTHERN HOSPITAL

NICARDIPINE



Hotel Tassel, Art Nouveau 1893, Brussels, Victor Horta

“Life is the leaves which shape and nourish a plant, but art is the flower which embodies its meaning”

Charles Rennie Mackintosh

The radical ideas about modern building techniques introduced by French architect Eugene - le - Duc were highly influential. In particular they influenced the Belgian architect Victor Horta, who expanded on many of the concepts and the use of unusual materials.

After extending his first Art Nouveau exhibition in Paris, Horta returned to Brussels full of enthusiasm, and built Hotel Tassel - or Tassel House - between 1892 and 1893. With its ground breaking design, components and decoration, it was Horta’s expression of Art Nouveau on a grand scale. He designed every detail, from the door handles and stained glass windows to the mosaic flooring and furnishings. It was immediately recognized as the first Art Nouveau house, and is also one of the first examples of the concept of the Gesamtkunstwerk in contemporary architecture.

Hotel Tassel in this context describes a large private residence rather than a hostelry, and Horta created the four-storey townhouse for his friend, Professor Emile Tassel, a wealthy scientist and industrialist. Although the narrow building stands unobtrusively between a row of conventional houses, inside it displays the use of contemporary building materials, including steel, iron, and glass, that were only just starting to be introduced into domestic architecture at that time. Comprised of two buildings made of brick and stone, joined together by a steel structure covered with glass, the house allows natural light to flood down onto a spacious staircase, landings and an unconventional round entrance hall. Vertical elements of the Gothic Revival, extravagant curls of the Rococo, and reduced details of Le Japonisme have all been translated and assimilated into the building.

Avoiding the dark, narrow corridors that featured in many contemporary houses, Horta created a revolutionary open-plan arrangement, and established unity and coherence both inside and out with coordinating materials and a coiling, whiplash line that scrolls throughout the building. Soon adopted by others, this feature became known as Ligne Horta.

Susie Hodge, 50 Art Nouveau Works You Should Know, Prestel, 2015

As Romanticism in the early Nineteenth century had developed as a reaction to the cold and Godless science of the Seventeenth and Eighteenth century Age of Reason, so Art Nouveau developed at the end of the same century as a reaction to the soulless severity of the Industrial Revolution. The beautiful organic flowing lines of Art Nouveau merged the fine Arts with the Applied Arts and by the dawn of the Twentieth century it had become firmly established as the new modern style for the new modern century.

The 21st century management of stroke continues at an astonishing clip, and new modern agents are continually required for the new modern century, the latest of which comes to us in the form of nicardipine that replaces the older Twentieth century agents, hydralazine and labetalol

NICARDIPINE

Introduction

Nicardipine is a **dihydropyridine** calcium channel blocking agent.

It has been used extensively in the US as a first line IV antihypertensive agent, but has only recently become available for use in Australia.

It can be given orally for the treatment of hypertension but in Australia its use is primarily as a **titratable IV infusion** for the control of hypertension, in the setting of **stroke patients who are to receive thrombolytic therapy**.

It may also be used for the control of hypertension in other **acute hypertensive emergencies.**

Traditionally labetalol has been used for this purpose, however nicardipine has some useful advantages including:

- A more rapid onset of action
- A more predictable response
- A shorter half-life making it easier to titrate to clinical effect
- A lack of beta-blocking activity so may be safely used in in patients who have asthma or COPD

Nicardipine has an overall similar *safety* profile to labetalol

History

Nicardipine has been available in the US for many years.

It was approved by the FDA for clinical use in 1988.

Chemistry

Nicardipine is a dihydropyridine calcium channel blocking agent.

Classification

Calcium channel blockers themselves can be classified into two principle groups:

1. Dihydropyridines:

   The dihydro-pyridines act mainly on **arteriolar smooth muscle** to reduce peripheral vascular resistance and BP.

They have *minimal* effect on myocardial cells.

Examples include:

- Amlodipine
- Felodipine
- Lercanidipine
- **Nicardipine**
- Nifedipine
- Nimodipine
- Clevidipine

2. Non-dihydropyridines:

Non-dihydropyridines: act primarily on **cardiac** and **arteriolar** smooth muscle.

They reduce cardiac contractility, heart rate and conduction, with verapamil having the greater effect.

Diltiazem has a greater effect on arteriolar smooth muscle than verapamil.

Examples include:

- Verapamil
- Diltiazem

Preparations

Nicardipine hydrochloride as:

Ampoules:

- 1 mg/ ml in 10 ml ampoule (total 10 mg)

Mechanism of Action

Calcium channel blockers block the inward current of calcium into cells in vascular smooth muscle, myocardium and cardiac conducting system via the L-type calcium channels.

They act on coronary arteriolar smooth muscle to reduce vascular resistance.

Dihydropyridines such as amlodipine act mainly on arteriolar smooth muscle to reduce peripheral vascular resistance and blood pressure. They have minimal effect on myocardial cells.

Non-dihydropyridines (i.e. diltiazem and verapamil) act on cardiac and arteriolar smooth muscle. They reduce cardiac contractility, heart rate and conduction, with verapamil having the greater effect. Diltiazem has a greater effect on arteriolar smooth muscle than verapamil.

Pharmacodynamics

The antihypertensive effect of nicardipine will depend largely on the dose and the rate of administration.

The onset of action is rapid at around 5-10 minutes

The duration of action is around 15-30 minutes (but may be prolonged in some situations, beyond 4 hours)

A 50% reduction in effect is generally seen approximately 30 minutes after discontinuation of a continuous infusion.

Pharmacokinetics

Absorption:

- Nicardipine can be given orally or IV.

Distribution

- Nicardipine is strongly bound to plasma proteins over a wide range of concentrations.

- Nicardipine is excreted in very small amounts in human breast milk.

Metabolism and excretion:

- Nicardipine is almost completely metabolised by cytochrome P450-3A4.

  Less than 0.03% is excreted unchanged in the urine after oral or intravenous administration.

- The predominant metabolite in human urine is the glucuronide of the hydroxy form.

- The terminal half-life is around 60 minutes.

Indications

Indication for IV infusion is hypertensive emergencies.

Examples include:

1. **Acute hypertension associated with ischemic stroke patients who are to receive thrombolytic therapy.**

2. Acute hypertension associated with haemorrhagic stroke patients

3 Hypertensive encephalopathy/ PRES.

4. Acute hypertension in patients with subarachnoid haemorrhages

5. Aortic dissection, when treatment with short-acting beta-blockers is not appropriate, or in combination with a beta-blocker when blocking beta-alone receptors is not effective.

6. Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contraindicated.

Contra-indications/precautions

These will largely be those of the calcium channel blockers as a group, though the CVS adverse precautions will more significant when used IV

1. Hypotension, (contraindicated)

    - In general terms, a systolic BP < 90 mm Hg.

2. Cardiogenic shock, (contraindicated)

3. Bradycardia, (contraindicated)

4. Sick sinus syndrome (contraindicated)

5. Conduction delays, (contraindicated)

    - Second or third degree atrioventricular block without pacemaker.

6. Known hypersensitivity to nicardipine

7. Severe aortic stenosis:

    - Reduced afterload results in reduction of diastolic pressures in these patients which may in turn worsen rather than improve myocardial oxygen balance.

8. ACS:

- Nicardipine is contraindicated in **unstable angina** and in the immediate aftermath (i.e. 8 days) of a **myocardial infarction.**

  Increases in the frequency, duration, or severity of angina have been seen in chronic therapy with oral nicardipine.

  Induction or exacerbation of angina has been seen in a small percentage of patients (< 1%) of coronary artery disease who are treated with I.V nicardipine. The exact mechanism of this effect has not been established.

9. Hepatic impairment:

- Nicardipine should be used with caution in these patients with liver impairment/ failure.

  Since nicardipine is metabolized by the liver, it is recommended that the dosage regimen for elderly patients be used in patients with hepatic impairment or decreased hepatic blood flow.

10. Renal impairment:

- In patients with moderate renal impairment, significantly reduced systemic clearance occurs.

  The dosage regimen recommended for elderly patients should be used in in patients with renal insufficiency.

11. Elderly:

- The elderly are more sensitive to adverse effects.

  Use more conservative dosing regimens (see below)

12. Calcium channel blocker and Beta Blocker interaction:

- The combination of beta blocker and calcium channel blocker frequently causes conduction delay problems in the elderly, especially in the presence of renal impairment.

13. Give through large peripheral veins to help avoid local irritation / phlebitis.

Pregnancy

First and Second trimesters: There is limited human data available, but so far, no evidence of teratogenic or fetotoxic effects have been shown. However dose-related embryo toxicity has been observed in animal studies.

Third trimester: There is potential for a tocolytic effect which may interfere with spontaneous induction of labour.

May produce pulmonary oedema when used during pre-term labour.

Consider fetal monitoring as maternal hypotension may decrease placental blood flow.

Depending on the clinical situation, a more gradual regime should be used (see elderly regime below)

Breast feeding

Nicardipine and its metabolites are excreted in very small amounts in human breast milk.

Limited data is available with regard to breast feeding.

No adverse effects have been reported to date, but if nicardipine is the agent of choice, monitor infants for hypotension, drowsiness, lethargy, poor feeding and pallor.

Adverse Effects

These will largely be those of the calcium channel blockers as a group, though the CVS adverse effects will be more pronounced when used IV

1. Hypotension

   This is the principal adverse effect of IV nicardipine

   systemic hypotension and reflex tachycardia may occur with excessive dosage or excessive rates of administration. Infusion rate will need to be reduced or temporarily ceased.

   The risk of hypotension is greater in:

   - Children
   - Patients with renal impairment
   - Patients with hepatic impairment
   - Pregnant patients.

2. Negative inotropy

2. Bradycardia

3. Conduction delays

4. Myasthenia-like neuromuscular disease:

- Calcium channel blockers in general may increase risk of muscle weakness and respiratory depression (most case reports are with verapamil).

Dosing

Usual IV infusion dosage is:

- Initiate at **5mg/hr**
- As necessary, increase by **2.5 mg/hr** to a maximum dose rate of **15 mg/hr**

  Titrate the dose upwards every **5 (rapid) - 15 (gradual)** minutes as required.

Note that the elderly are more sensitive to adverse effects, use:

- Lower starting doses (1- 4 mg/hr)
- Smaller incremental rates (e.g. 0.5 mg/hr)
- Longer titration intervals (e.g. 30 minutes)

Therapeutic end points:

Adjust the infusion rate as needed to maintain the desired response as follows:

1. ≤ 185/110 mmHg for ischaemic strokes, prior to initiation of thrombolysis.

   Maintain ≤ 180/105 mmHg for duration of thrombolysis.

2. < 220/120 mmHg for ischaemic strokes (non-thrombolysed)

3. Systolic 140-160 mmHg for haemorrhagic strokes.

   Once blood the pressure goal has been achieved, gradually adjust dose rate to maintain the target blood pressure range.

   Usually this will be between **2 - 4 mg/hr.**

Monitoring:

Continuous haemodynamic monitoring should occur during the infusion, including ECG monitoring, according to local recommended protocols.

References

1. Cardene I.V Product Information, September 2010. Reference ID: 2901740

2. Nicardipine Use in the Mobile Stroke Unit - Preliminary RMH Mobile Stroke Unit Protocol, July 18th 2017.

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Acknowledgments:
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