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The Sri Lanka Prescriber

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Cover picture

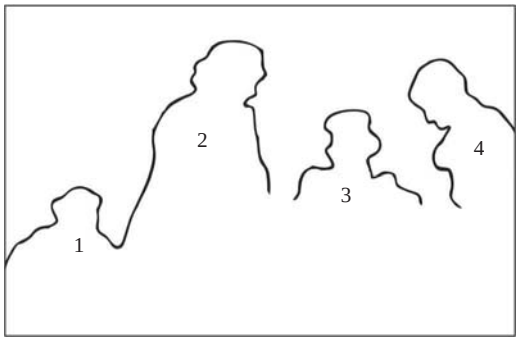
Catherine the Great of Russia (1729-96)

In eighteenth-century Russia smallpox exacted a terrible toll, and in 1768 the Empress Catherine expressed her willingness to be inoculated against the disease – as an example to her subjects. British physicians had been in favour at the Russian Court for more than two centuries, and the ambassador in London was ordered to obtain the services of one skilled in the art of inoculation. He consulted the great Dr. John Fothergill who recommended Thomas Dimsdale, a member of a Quaker family long connected with medicine, and author of *The Present Method of Inoculating for the Small-Pox* (1767). After some demur Dimsdale and his son Nathaniel went to St. Petersburg, where they were received with great courtesy. The Empress refused Thomas Dimsdale's request for assistance from the Court physicians on the grounds that they had no experience of the operation. The English physician had thus to shoulder a heavy responsibility, for though his patient had every confidence in him, the reactions of her subjects, if anything went amiss, were unpredictable. Catherine took the precaution of keeping relays of post-horses along the route from St. Petersburg to the frontier so that Dimsdale might flee the country in the event of disaster.

Three healthy children were inoculated to provide matter for the operation. At nine o'clock on the evening of 12 October, 1768, Thomas Dimsdale and his son were commanded to attend the royal patient. The child from whom the inoculum was to be collected was driven to the Palace in a coach – asleep and wrapped in a pelisse, and on arrival the party was taken by a back staircase to the Empress room. The proceedings were brief: Catherine received a puncture in each arm, and the child was put back to bed. The patient's recovery was uneventful, and after her son, the Grand Duke Paul, had also been inoculated, a great thanksgiving service was held. Dimsdale was created a Baron of the Empire, made a Councillor of State, and appointed Body-Physician to Her Majesty. In addition to a present of £10,000 he received £2,000 for expenses, an annuity of £500 and miniatures of his two patients.

Nathaniel Dimsdale also became a Baron of the Empire and received a gold snuff-box, set with diamonds. For his part in the historic event the child Markoff was ennobled, his new surname *Ospiennyi* being derived from *ospa*, signifying smallpox.

*Key to Illustration



1. Markoff
2. Thomas Dimsdale
3. Catherine the Great
4. Nathaniel Dimsdale

An update on local anaesthetics

Introduction

Local anaesthetics are commonly used in clinical practice. With the emerging health hazard associated with opioid misuse, local anaesthetics have emerged as a treatment option to relieve pain during invasive procedures and surgeries. They play a major role in the perioperative setting, where the current trend is moving from opioid sparing towards opioid free anaesthesia.

Local anaesthetic properties of the coca plant were identified centuries ago by the Incas in Peru. Since then, there have been a number of local anaesthetic agents which have been manufactured with varied potency and improved safety profile. However, it is essential to understand their pharmacological properties and the recommended doses to prevent both local and systemic toxicity which can result in devastating complications.

Mechanism of action

Local anaesthetics reversibly block the conduction of impulses in excitable tissues such as nerve cells and cardiac myocytes [1]. These drugs block the influx of sodium ions through ion channels located within the neuronal cell membrane [2]. The unionized fraction of the drug crosses the lipid bilayer of the neuronal cell membrane and blocks the voltage gated sodium channels from the interior, preventing further influx of sodium in to the cell [1]. This prevents propagation of an action potential.

These ion channels can exist in three states; a) a "Resting state" in which sodium ions are denied entry into the cell, b) an "Activated state" when the channel opens and facilitates entry of sodium into the cell, followed by c) an "Inactivated state" [2]. The maximum affinity of local anaesthetics to the receptor is during the activated and inactivated states.

Various local anaesthetic agents bind to different classes of neuronal fibres, based on the state of the sodium channel [2]. Rapid firing and smaller nerve fibres are more susceptible to the action of local anaesthetics [2]. Autonomic nerve fibres are therefore the most sensitive of all nerve fibres followed by sensory and finally the motor nerves. These differences in sensitivity are clinically evident in patients' recovering from spinal anaesthesia [2].

Pharmacology of local anaesthetics

As shown in Figure 1 the structure consists of three components [2,3]. An aromatic lipophilic group, a hydrophilic tertiary amine group and an intermediary chain which is the link between the two groups. This link classifies local anaesthetics into esters and amides.

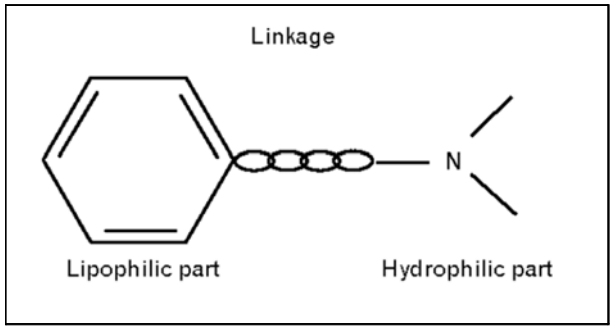


Figure 1. Basic structure of local anaesthetics [4].

By increasing the length of the carbon chains of all three components the lipid solubility, the potency and the duration of action can be increased [2,3], which can be advantageous during clinical use. Bupivacaine has a longer intermediate chain than lignocaine; therefore the potency of bupivacaine is more than that of lignocaine [1].

Factors influencing activity of local anaesthetics

- pKa: This is the pH at which both the ionized and unionized fractions of the drug exists in equal amounts [1,3]. Local anaesthetics are basic drugs prepared in an acidic medium. Hence a larger proportion of the drug exists in an ionized form. Since the rate of diffusion of a drug through the cell membrane is determined by the unionized fraction, local anaesthetics with a lower pKa have a faster onset of action (lignocaine pKa 7.8) when compared to those with a higher pKa (bupivacaine 8.1).

  In the presence of infection, the surrounding medium becomes more acidic thereby reducing the unionized fraction of the drug [3]. This together with increased vascularity of the area will "wash away" the local anaesthetic agents from the site of inflammation and renders these agents ineffective, thus limiting their use in the presence of infection. A similar mechanism termed as "ion trapping" can occur in a foetus in distress.

- Lipid solubility: This factor is closely related to the potency of the drug [1,3]. Higher the lipid solubility faster the onset of action of the drug giving a larger volume of distribution [3].

- Protein binding: Drugs with higher protein binding, has a longer duration of action [3]. Factors which decrease protein binding either due to disease states,

nutritional deficiencies, hypoxia, acidosis and hypercarbia can result in local anaesthetic toxicity due to an increased free unbound fraction of the drug.

- Molecular weight of the drug: Local anaesthetics with lower molecular weight will diffuse readily through the neuronal membrane resulting in a faster onset of action.
- Addition of a vasoconstrictor as an adjuvant: This will influence the potency and duration of action of the drug. Local anaesthetics are vasodilators at clinical doses and vasoconstrictors at sub-clinical doses [3]. Low dose adrenaline in a concentration of 1:80,000 (12.5 micrograms/mL) aid vasoconstriction in tissues, thereby prolonging the action of the drug and delaying absorption [2].

Pharmacokinetics

Absorption: Depends on a number of factors such as rate of injection, dose, vascularity and site of injection [3]. Route of administration can vary from topical spray, subcutaneous infiltration, intravenous, perineural, epidural and intrathecal.

Distribution: Amide local anaesthetics are more protein bound compared to ester group drugs. Therefore, patients with low serum proteins can manifest an exaggerated response to amides and develop toxicity with inappropriate doses.

Metabolism and elimination: Esters undergo rapid hydrolysis by plasma cholinesterase, therefore have shorter half-lives and their metabolites can predispose to allergic reactions. Amides undergo a slower metabolism in the liver and accumulate in liver failure and during reduced hepatic blood flow [3].

Doses

Local anaesthetics are available in various concentrations. Depending upon the drug, its concentration and site of infiltration the correct dose needs to be calculated to avoid toxicity.

The box 1 illustrates, the calculation of volume of bupivacaine (0.5%) required for a patient weighing 50 kg.

Box 1: Calculation of bupivacaine volume

0.5% bupivacaine = 5 mg/ml

Weight of the patient = 50 kg

Maximum safe dose = 2 mg/kg = (50 × 2 = 100 mg)

Maximum volume = 100 mg/5 = 20 ml

Table 1. Safe doses of commonly used local anaesthetics

Drug	*Dose*
Lignocaine	3mg/kg (without adrenaline) 7mg/kg (with adrenaline)
Bupivacaine	2mg/kg (with or without adrenaline)
Levo-bupivacaine (levo enantiomer of bupivacaine)	2mg/kg (up to 2.5mg/kg) with or without adrenaline
Prilocaine	6mg/kg (without adrenaline) 9mg/kg (with adrenaline)
Ropivacaine	3-4mg/kg (with or without adrenaline)

Table 2. Physicochemical characteristics of commonly used local anaesthetics

Drug	*Class of drug weight*	*Molecular*	*pKa*	*Protein binding (%)*	*Onset of action*
Lignocaine	Amide	234	7.8	70	Fast
Bupivacaine	Amide	288	8.1	95	Moderate
Levobupivacaine	Amide	288	8.1	95	Moderate
Prilocaine	Ester	220	7.7	55	Fast
Ropivacaine	Amide	274	8.1	94	Moderate

Local anaesthetic toxicity

They range from allergic reactions (to parent drug, metabolites or preservatives), local tissue toxicity or systemic toxicity depending upon the chosen concentration, volume and site of injection.

Iatrogenic injuries can occur during peripheral nerve blocks if the drug is injected intra-fascicular resulting in degeneration of the axons leading to neurological damage [1]. Surgical factors such as prolonged use of tourniquet and patient factors such as pre-existing neuropathies can make patients more vulnerable to such damage [1].

Systemic toxicity can occur due to an overdose or an inadvertent intravascular injection of a drug into the circulation. Systemic signs and symptoms are related to the involvement of the central nervous system and the cardiovascular system.

Central nervous system toxicity manifests as a biphasic response, excitation followed by a state of depression. The reason being, the inhibitory neurons are initially inhibited leaving the action of excitatory neurons unopposed, resulting in an excitation phenomenon.

Initially the patient may complain of metallic taste in the mouth, circum-oral numbness, tinnitus, blurred vision and dizziness which will be followed by seizures and coma [5].

Cardiovascular manifestations include conduction block leading to bradycardia, asystole, ventricular tachyarrhythmias and collapse and can be irreversible. Bupivacaine is more cardiotoxic than lignocaine [1] but its pure S-enantiomers ropivacaine and levo-bupivacaine are less cardiactoxic.

Medical staff should be familiar with the management of local anaesthetic toxicity and it is useful to have the current guidelines displayed where appropriate to enable early initiation of treatment (Box 2) [5]. Such critical events should be documented, audited and the patient should be informed and a diagnosis card provided.

What is new in local anaesthetics?

Local anaesthetics are found to have antibacterial properties in higher doses as well as antimetastatic properties. Further studies are required to confirm these effects [3].

Intravenous lignocaine is used to treat neuropathic pain and acute post-surgical pain after colorectal surgery [3].

Box 2: Management of severe local anaesthetic toxicity [5]

Immediate management

Stop injecting the local anaesthetic

Call for help early and use the "ABCDE" approach

Give high flow oxygen and maintain a patent airway. May require early tracheal intubation. Hyperventilation will aid in counteracting metabolic acidosis which occurs with toxicity

Establish intravenous access and draw blood for investigations as appropriate without undue delay in initiating treatment

Treat convulsions as per current guidelines (benzodiazepines/ small doses of thiopental)

Continuous assessment of cardiovascular parameters

Treatment

If in cardiovascular collapse start CPR early as per current advanced life support protocols. May require a longer period of resuscitation (1 hour)

If not in cardiovascular collapse, treat complications such as hypotension and arrhythmias as per current guidelines (avoid using lignocaine as an anti-arrhythmic)

Definitive treatment: Lipid emulsion, **20% Intralipid** (know where it is stored in your institution) Propofol is NOT a suitable alternative

Dose: Initial **bolus 1.5ml/kg over 1 minute and start on an infusion of 15ml/kg/hour**

After 5 minutes repeat the same bolus dose (1.5ml/kg) if patient deteriorates or in the presence of persistent cardiovascular instability. **Can repeat 2 such doses 5 minutes apart** and continue the infusion at a rate of 15ml/kg/hour or increase to **30ml/kg/hour** after 5 minutes if patient remains unstable or deteriorates further

Maximum cumulative dose for 20% Intralipid = 12ml/kg

Patient should be transferred to a higher level of care

Assess for pancreatitis and do serum assays of lipase/amylase for 2 days

Novel agents such as liposomal preparations, venoms which block sodium channels and various polymers have been extensively studied with a view to provide local anaesthetics with a longer duration of action and better safety profile [3]. A drug to reverse the adverse effects of local anaesthetics experienced during dental procedures, such as drooling and persistent discomfort due to numbness is been investigated. Non-selective alpha antagonist phentolamine is currently been tested to mitigate such effects [3].

Conclusions

Local anaesthetics block conduction of nerve impulses by blocking the voltage gated sodium channels.

There are two main classes of drugs namely, esters and amides. Efficacy of these drugs is based mainly, on their pKa, lipid solubility and protein binding.

There are a number of indications for their use. Selection of local anaesthetic type, the specific agent, dosage form, concentration and volume must be tailored to the needs of the individual.

Since an ounce of prevention is better than a pound of cure, medical staff should be vigilant when administering local anaesthetics to patients. Early detection of features of toxicity and treatment is essential to prevent catastrophes.

Further reading

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Conflict of interest: none.

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Self-assessment questions

1. The following local anaesthetics are structurally amides
- a. Bupivacaine
- b. Levobupivacaine
- c. Lignocaine
- d. Prilocaine
- e. Ropivacaine

2. Which of the following responses are correct regarding the maximum allowable local anaesthetic dosage without the addition of a vasoconstrictor, when administered to a 60kg patient for suturing of a forearm laceration?
- a. 0.5% bupivacaine 20 ml
- b. 0.5% bupivacaine 24 ml
- c. 0.5% bupivacaine 10 ml
- d. 2% lignocaine 9 ml
- e. 2% lignocaine 20 ml

3. Absorption of local anaesthetics depend on
- a. Dose of drug
- b. Protein binding
- c. Rate of injection
- d. Site of injection
- e. Vaso-activity of the drug

4. A 28-year-old mechanic is admitted to the Accident and Emergency unit with a laceration to his left middle finger. You are the on-call medical officer. What would be the best combination of drugs which can be used to suture his laceration as an out-patient procedure?
- a. 2% lignocaine with 0.5% bupivacaine
- b. 2% lignocaine with 1:200,000 adrenaline
- c. 2% lignocaine with 100,000 adrenaline
- d. 0.5% bupivacaine with 200,000 adrenaline
- e. 0.5% bupivacaine with 100,000 adrenaline

(Answers on page 11)

Atrial fibrillation: an update on management

Summary

Atrial fibrillation carries a markedly increased risk of stroke and left ventricular dysfunction, and is associated with reduced quality of life.

In light of the potential for poor outcomes and the likely understated presence of silent atrial fibrillation, opportunistic screening should be carried out in general practice.

Modifying the risk factors for atrial fibrillation is the cornerstone of management with adjuvant drug therapy to help maintain sinus rhythm, control the ventricular rate and reduce the risk of cerebral thromboembolism.

The need for anticoagulant therapy can be assessed by using the revised CHA_2DS_2-VASc score. Direct oral anticoagulants are now preferred to warfarin in those who qualify for their use.

Catheter ablation is an effective option to improve survival in patients with left ventricular dysfunction. It also improves quality of life and reduces arrhythmia-related hospital admissions.

Keywords: antiarrhythmic drugs, anticoagulants, apixaban, catheter ablation, dabigatran, rivaroxaban, thromboembolism

*(Aust Prescr 2019; **42**: 186-91)*

Introduction

Atrial fibrillation is the most common arrhythmia detected in clinical practice and accounts for over 30% of hospital admissions for cardiac rhythm problems.[1] The burden of disease appears to be increasing with higher prevalence and rates of atrial fibrillation-related hospital admissions. This illustrates the need for a renewed approach to its management.[2]

Epidemiology

The prevalence of atrial fibrillation in Australia is 2-4%, with a predominance in older people[3]. This is likely to be an underestimation because silent atrial fibrillation (asymptomatic, subclinical) has not been taken into account. Most atrial fibrillation in Australia is non-valvular.[4] Atrial fibrillation is associated with a significant increase in the long-term risk of stroke (2-5-fold higher than matched patients without atrial fibrillation), heart failure, impaired quality of life and all-cause mortality.[1] It is important for GPs to recognise the strong association of certain risk factors with atrial fibrillation. These predominantly include obesity, obstructive sleep apnoea, hypertension,[5,6] valvular heart disease and genetic predisposition.[7,8]

Classification

Classification of atrial fibrillation according to duration of the arrhythmia is shown in Box 1.

Valvular atrial fibrillation is only considered an entity if the patient has moderate to severe mitral stenosis or a mechanical heart valve. All other forms of atrial fibrillation are referred to as 'non-valvular atrial fibrillation'. This distinction influences the choice of anticoagulant therapy.[3]

Box 1 Classification of atrial fibrillation according to duration

Paroxysmal

Episodes that last less than 7 days, whether they revert spontaneously or undergo direct current cardioversion.

Persistent

Episodes that continue for more than 7 days and do not self-terminate.

Long-standing

Continuous for more than 1 year, despite a rhythm-control strategy.

Permanent

When the patient and the treating physician decide to accept that the patient will remain in atrial fibrillation and will not attempt to achieve sinus rhythm. Often after a rhythm-control strategy has been unsuccessful.

Screening of patients for atrial fibrillation

Silent atrial fibrillation is present in around 10% of patients who have an ischaemic stroke.[9] Hence all patients with ischaemic stroke should be screened either by a 12-lead ECG or preferably by a 24-hour Holter recording. Monitoring by implanted loop recorders may be a better monitoring strategy especially for candidates with recurrent transient ischaemic attacks and cryptogenic stroke.[10]

Opportunistic screening (pulse check and ECG) of all patients over the age of 65 years in general practice is now strongly recommended by international guidelines. This follows clear demonstrable benefits to increased quality-adjusted life-years and a reduced incidence of stroke.[11-13] We may soon have eHealth tools like smartphone ECG devices which might contribute to higher detection rates of silent atrial fibrillation.[14,15] However, more research is needed before the routine use of these tools. Also, we need more data to establish the burden of atrial fibrillation detected by these devices before starting therapy.

Diagnostic work up

An ECG is essential to confirm a diagnosis of atrial fibrillation. Additional investigations are needed to determine the cause. All patients should undergo a full blood count, urea and electrolytes and thyroid function tests. An echocardiogram should be performed to detect underlying cardiac abnormalities, such as valvular pathology, left atrial size and volume, as well as the presence of left ventricular dysfunction. In select patients who require acute rhythm control, transoesophageal echo-cardiography is performed to look for thrombus in the atria before attempting an electrical or pharmacological cardioversion.

Risk stratification tools

The CHA_2DS_2-VASc score is the most widely accepted tool for assessing risk of a stroke in clinical practice and is easy to use. It is endorsed by European[13] and North American guidelines.[16] The 2018 Australian atrial fibrillation guidelines recommend a 'sexless' version of the CHA_2DS_2-VASc score, known as CHA_2DS_2-VA (Table 1).[3] They recommend considering anticoagulation for a CHA_2DS_2-VA score of 1. In contrast, the North American guidelines recommend anticoagulation for a CHA_2DS_2-VASc score of at least 2 in men and at least 3 in women.[3,16] Other risk scores, including ATRIA and ORBIT, do not show major differences in predicting a high risk of stroke.

Bleeding risk can be estimated using the HAS-BLED score (Table 2).[17] Although higher bleeding risk scores can be used to alert the patient and the doctor, they should not discourage anticoagulation. The net benefit to the patient usually favours stroke prevention with anticoagulation over the risk of major bleeding.[3] This requires shared decision making with the patient after discussing the risks and benefits of the treatment strategy.

Table 1 **The CHA_2DS_2-VA score**

Risk factor	Definition	Points
C	Congestive heart failure which includes: • symptomatic HFrEF and HFpEF • moderately-severely reduced left ventricular function in the absence of previous symptoms	1
H	Hypertension – whether or not blood pressure is currently elevated	1
A	Age ≥ 75 years	2
D	Diabetes	1
S	Previous stroke or transient ischaemic attack or history of systemic thromboembolism	2
V	Presence of vascular disease: • previous myocardial infarction, or • peripheral arterial disease, or • complex aortic atheroma or plaque on imaging	1
A	Age 65-74 years	1

Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular atrial fibrillation whose CHA_2DS_2-VA score is ≥2 (high quality of evidence), unless there are contraindications to anticoagulation, and should be considered strongly if CHA_2DS_2-VA score is 1 (moderate quality of evidence).[3]

HFrEF heart failure with reduced ejection fraction
HFpEF heart failure with preserved ejection fraction
Source: reference 3

Table 2 **The HAS-BLED score**

Risk factor	Clinical characteristic	Points
H	Hypertension • systolic blood pressure >160 mmHg	1
A	Abnormal liver OR kidney function • dialysis/renal transplantation/serum creatinine ≥ 200 mmol/L • cirrhosis or bilirubin 2x upper limit of normal with AST/ALT/ALP 3x upper limit normal	1 each
S	Stroke	1
B	Bleeding • history of bleeding or a bleeding diathesis	1
L	Labile INRs	1
E	Elderly • >65 years	1
D	Drugs OR alcohol • concomitant use of antiplatelets/NSAIDs • ≥8 drinks/week	1 each

HAS-BLED score ≥3 is considered as a high-risk of bleeding

ALP alkaline phosphatase
ALT alanine aminotransferase
AST aspartate aminotransferase
NSAIDs non-steroidal anti-inflammatory drugs
Source: reference 17

Treatment strategies

The management of atrial fibrillation revolves around stroke prevention, aggressive risk-factor management, and acute and long-term rate or rhythm control. Catheter ablation may also be considered.

Stroke prevention

Anticoagulation reduces the relative risk of stroke by around 70% in patients with atrial fibrillation. The options include warfarin or direct oral anticoagulant drugs such as factor Xa inhibitors – apixaban and rivaroxaban – and the direct thrombin inhibitor dabigatran. Aspirin is no longer recommended as an alternative.

Direct oral anticoagulants are recommended as first-line therapy over warfarin in patients with non-valvular atrial fibrillation, provided there are no absolute contraindications to their use (see Box 2).[18] Dose reduction of direct oral anticoagulants may also be required depending on patient characteristics (see Table 3).[3] Direct oral anticoagulants are noninferior to warfarin in reducing the risk of stroke and systemic embolism in these patients and have significantly lower rates of major haemorrhage.[19] Evidence is lacking for their use in patients with mitral stenosis or a metallic valve replacement, hence warfarin is the drug of choice to prevent systemic thromboembolism in this population.

For those receiving warfarin, INR should be measured by routine laboratory tests at least weekly initially and then monthly. Dose modifications of warfarin should be aimed at maintaining the INR between 2 and 3. When switching from warfarin to a direct oral anticoagulant, after warfarin is stopped, the direct oral anticoagulant can be started when the INR is less than 2.[18]

The expert consensus is that patients with concurrent atrial fibrillation and ischaemic heart disease undergoing percutaneous coronary intervention should receive triple therapy with aspirin, clopidogrel and anticoagulation for as short a time as possible (no longer than six months immediately post percutaneous coronary intervention in stable coronary artery disease). They should then continue dual therapy with clopidogrel and anticoagulation for at

least 12 months after percutaneous coronary intervention before considering stopping antiplatelet therapy and continuing anticoagulation as monotherapy.[20-23] Current evidence does not support substituting clopidogrel with the newer $P2Y_{12}$ antiplatelet drugs prasugrel and ticagrelor.

Box 2 Absolute contraindications to direct oral anticoagulants

Severe renal impairment:
- CrCl <30 mL/min with dabigatran
- CrCl <15 mL/min with apixaban*
- CrCl <15 mL/min with rivaroxaban*

Liver impairment e.g. cirrhosis (Child Pugh C)

Current active bleeding or coagulopathy

Previous life-threatening haemorrhage while on a direct oral anticoagulant

Documented previous anaphylaxis to a direct oral anticoagulant

* International European guidelines approve the use of apixaban and rivaroxaban in patients with CrCl as low as 15 mL/min, however this is not reflected in Australian guidance (see Table 3).

CrCl creatinine clearance
Source: reference 18

Percutaneous left atrial appendage occlusion may be considered as an option in patients with atrial fibrillation at increased risk of stroke who have contraindications to long-term anticoagulation. This is because of the propensity for bleeding or poor drug tolerance.[24]

Rate control versus rhythm control

To date, randomised controlled trials do not suggest superiority of one strategy over the other.[25]

Rhythm control

Rhythm control may be given priority for:
- those with underlying left ventricular dysfunction
- highly symptomatic patients in spite of rate-control therapy
- patient preference (some patients may not want to remain on rate-control drugs because of their symptoms or intolerance to the drugs)
- paroxysmal or early persistent atrial fibrillation.

In the acute setting, any patient who is haemodynamically unstable should undergo immediate synchronised electrical cardioversion. When the patient is haemodynamically stable, acute rhythm control may be desired if they are symptomatic or if it is their first episode with an onset of less than 48 hours. Flecainide and amiodarone are the two drugs available for acute pharmacological cardioversion.[26]

Table 3 Dose adjustment of direct oral anticoagulants in non-valvular atrial fibrillation

Direct oral anticoagulant	Clinical factors	Dose adjustment
Apixaban	At least two of: • serum creatinine ≥133 micromol/L • age ≥80 years • weight ≤ 60 kg	5 mg twice a day to 2.5 mg twice a day
Rivaroxaban	At least one of: • CrCl 30-49 mL/min • combination with dual antiplatelet therapy	20 mg daily to 15 mg daily
Dabigatran	At least one of: • CrCl 30-50 mL/min • age ≥75 years • combination with dual antiplatelet therapy	150 mg twice a day to 110 mg twice a day

CrCl creatinine clearance
Source: reference 3

In patients with haemodynamically stable atrial fibrillation lasting more than 48 hours, or of unknown duration, acute rhythm control should be ideally attempted only after anticoagulation for three weeks. Anticoagulation should be continued for at least four weeks after cardioversion. It is still reasonable to attempt an acute cardioversion, only after the transoesophageal echocardiogram has excluded a left atrial thrombus.[16]

Drugs with the strongest evidence for long-term rhythm control are amiodarone, flecainide and sotalol. Given its high adverse-effect profile, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.[3] Flecainide can be started in patients with structurally normal hearts (confirmed with an echocardiogram) who do not have underlying coronary artery disease. Treatment should be started at 50 mg twice a day and titrated up to a maximum dose of 150 mg twice a day, depending on tolerance. Patients should be concomitantly prescribed an atrioventricular nodal blocking drug (e.g. metoprolol) in conjunction with flecainide. Sotalol is also an option for patients intolerant to amiodarone and flecainide. However, the QT interval should be closely monitored, and sotalol is relatively contraindicated in patients with chronic renal impairment.

Rate control

Treatment options for acute rate control are beta blockers, non-dihydropyridine calcium channel antagonists and amiodarone. Again, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.

First-line therapies for long-term rate control, in patients without left ventricular dysfunction, are beta blockers (e.g. metoprolol), non-dihydropyridine calcium channel blockers (e.g. verapamil), or digoxin (with monitoring of serum concentrations). The RACE II trial remains the most recent comprehensive evaluation of strict control.[27] It found that a lenient approach – heart rate target <110 beats per minute – was not associated with worse outcomes than a stricter approach of <80 beats per minute at rest or <110 beats per minute with exercise.[27]

In patients with left ventricular dysfunction who are not being considered for rhythm control, or who have failed rhythm control, first-line rate control therapy would be with beta blockers which have survival benefit in heart failure (e.g. bisoprolol, carvedilol, controlled-release metoprolol or nebivolol), or digoxin. Non-dihydropyridine calcium channel blockers are contraindicated in patients with left ventricular dysfunction.

Risk-factor management

Aggressive management of intercurrent risk factors like obesity, obstructive sleep apnoea, hypertension, diabetes, heart failure, valvular heart disease and excess alcohol is important.[6] Long-term sustained weight loss reduces the burden of atrial fibrillation and maintains sinus rhythm.[28] The Australian guidelines therefore endorse intensive weight loss (at least 10% of body weight) with a target body mass index below 27 kg/m^2.

Exercise is also recommended as it improves aerobic capacity and reduces disease burden. The CARDIO-FIT study showed that arrhythmia-free survival with and without rhythm-control strategies was greatest in patients with high cardiorespiratory fitness compared to adequate or low cardiorespiratory fitness.[29]

Australian guidelines[3] recommend:

- blood pressure no more than 130/80 mmHg at rest, and 200/100 mmHg with exercise
- continuous positive airway pressure therapy if the apnoea-hypopnea index is at least 15/hour
- an HbA1c of no more than 6.5% (48 mmol/mol)
- lipid targets as per the cardiovascular risk profile
- smoking cessation
- no more than three standard drinks of alcohol per week.

Catheter ablation

Catheter ablation delivers radiofrequency energy resulting in isolation of the pulmonary veins and other contiguous venous structures. It has been shown to be a successful therapy in patients with atrial fibrillation.[30] The subgroups that benefit most appear to be patients with paroxysmal and persistent atrial fibrillation who are symptomatic and those with left ventricular dysfunction.[31,32] Catheter ablation also significantly improves quality of life and is associated with significantly fewer hospital admissions.[33] It is important to discuss with the patient that procedural success rates vary and 20-30% of people may require a second procedure within 12 months. Major complication rates from the procedure are 1-7% and are related to the experience of the operator and the centre.[30,31,34] The decision to do catheter ablation should be made after a detailed discussion between the patient and the cardiac specialist.

Conclusion

Treatment strategies for atrial fibrillation include stroke prevention, risk-factor management, rate and rhythm control, and catheter ablation. These have reduced the morbidity and mortality associated with this condition. However, there is growing literature on various aspects of atrial fibrillation management necessitating constant updates for physicians.

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Answers for self-assessment questions on local anaesthetics

1. TTTFT

The intermediary chain between the lipophilic and hydrophilic group classifies local anaesthetics to esters and amides. Bupivacaine, lignocaine, levobupivacaine and ropivacaine are amides whereas prilocaine is an ester.

2. FTFTF

The maximum dose for bupivacaine without the addition of a vasoconstrictor is 2mg/kg. Since the patient is 60kg this would amount to (2*60=120mg). 0.5% bupivacaine contains 5mg/ml. Therefore 120mg/5mg= 24ml.

Lignocaine maximum recommended dose without the addition of a vasoconstrictor is 3mg/kg. 2% lignocaine contains 20mg/ml. Therefore (60*3= 180mg/20mg= 9ml)

3. TFTTT

Absorption of local anaesthetics depends upon the site of injection (peak plasma levels have been documented after intrapleural injection), rate and dose of injection including vaso-activity of the drug. Protein binding determines the duration of action of the drug.

4. TFFFF

Lignocaine is fast acting and bupivacaine has a longer duration of action compared to lignocaine due to increased protein binding property. Therefore, this combination would be the best option for this procedure. Adrenaline is a potent vasoconstrictor. Therefore, it's use is contraindicated near end-arteries such as the fingers which could result in irreversible vasospasm.

Current information about drug registration

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Cabozantinib	Cabozanix	Capsule, 20 mg	Sun, India	Emerchemie	Protein kinase inhibitor
Canagliflozin	Invokana	Tablet, 100 mg & 300 mg	Janssen, Italy	Emerchemie	Type 2 diabetes mellitus
Caspofungin	Casdin	Injection, 50 mg & 70 mg	Gufic, India	Slim	Invasive candidiasis
Daclatasvir	Dasvir	Tablet, 60 mg	Genix, Pakistan	Ceyoka	Hepatitis C virus NS5A inhibitor
Dapagliflozin	Forxiga	Tablet, 5 mg & 10 mg	Astra Zenexa, USA	Hemas	Type 2 diabetes mellitus
Eltrombopag	Revolade	Tablet, 50 mg, 25 mg	Glaxo, UK	Baurs	Thrombopoietin receptor agonist
Empagliflozin	Emzin	Tablet, 10 mg & 25 mg	Acme, Bangladesh	Mega Pharma	Type 2 diabetes mellitus
Empagliflozin	Empazin	Tablet, 10 mg & 25 mg	Delta, Bangladesh	Hyena	Type 2 diabetes mellitus
Empagliflozin	EG	Tablet, 10 mg & 25 mg	Aristopharma, Bangladesh	Hemas	Type 2 diabetes mellitus
Empagliflozin	Empavic	Tablet, 10 mg & 25 mg	Biopharma, Bangladesh	Truvic	Type 2 diabetes mellitus
Empagliflozin	Xenglu	Tablet, 25 mg, 10 mg	Hilton, Pakistan	Sunshine	Type 2 diabetes mellitus
Empagliflozin	Empa	Tablet, 25 mg	Nipro, Bangladesh	Imedra	Type 2 diabetes mellitus
Empagliflozin	Jardiance	Tablet, 25 mg	Boehringer Ingelheim, Germany	Hemas	Type 2 diabetes mellitus
Enzalutamide	Bdenza	Capsule, 40 mg	BDR, India	Pharma Asociates	Prostate cancer
Enzalutamide	Xtandi	Capsule, 40 mg	Catalent, USA	Baurs	Prostate cancer
Eribulin	Halaven	Injection, 0.5mg/mL	Biogen, USA	Baurs	Antineoplastic agent
Ertapenem	Invanz	Injection, 1g	MSD, France	Baurs	Carbapenem
Gadoteric acid	Dotarem	Injection, 0.5 mmol/mL	Guerbet, France	Dimo	Contrast medium

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Golimumab	Simponi	Injection, Pre-filled pen, 50 mg/0.5 mL	Baxter, USA	Pettah Pharmacy	Tumour necrosis factor alpha (TNF-α) inhibitor
Neratinib	Hernix	Tablet, 40 mg	Beacon, Bangladesh	Emerchemie	Protein kinase inhibitor
Nimotuzumab	Biomab Egfr	Injection, 50 mg/10 ml	Biocon, India	Medmart	Anti-EGFR monoclonal antibody
Nintedanib	Cyendiv	Capsule, 100 mg & 150 mg	Catalent, Germany	Hemas	Idiopathic pulmonary fibrosis
Osimertinib	Tagrix	Tablet, 80 mg	Beacon, Bangladesh	Emerchemie	Tyrosine kinase inhibitor
Osimertinib	Tasso	Tablet, 40 mg & 80 mg	Julphar, Bangladesh	Tabrane Healthcare	Tyrosine kinase inhibitor
Osimertinib	Tagribo	Tablet, 40 mg	Techno, Bangladesh	Amgen	Tyrosine kinase inhibitor
Palbociclib	********	Capsule, 125 mg	Aizant, India	AVH	Protein kinase inhibitor
Pertuzumab	Perjeta	Injection, 420 mg in 14 mL	Roche, Germany	Baurs	Breast cancer
Regorafenib	Regonix	Tablet, 40 mg	Beacon, Bangladesh	Emerchemie	Protein kinase inhibitor
Ribociclib	Kisqali	Tablet, 200 mg	Novartis, Singapore	Baurs	Protein kinase inhibitor
Secukinumab	Cosentyx	Injection 1mg/10mL	Novartis, Switzerland	Baurs	Interleukin inhibitors
Secukinumab	Fraizeron	Injection, 150 mg/mL	Stein AG, Switzerland	Baurs	Interleukin inhibitors
Sufentanil	********	Injection 50 mcg/mL	Yichang, China	Slim	Opioid anesthetic
Tafluprost	Taflotan	Eye drops, 15 mcg/mL	Santen, Japan	Baurs	Ocular hypertension
Terlipressin	Novapressin	Injection, 1 mg	BF Biosciences, Pakistan	Emerchemie	Oesophageal varices

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