# The Sri Lanka
# Prescriber

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# How to manage warfarin therapy

## Summary

Long-term treatment with warfarin is recommended for patients with atrial fibrillation at risk of stroke and those with recurrent venous thrombosis or prosthetic heart valves. Patient counselling before commencing warfarin - regarding signs and symptoms of bleeding, the impact of diet, potential drug interactions and the actions to take if a dose is missed - is pivotal to successful use.

Scoring systems such as the CHADS2 score are used to determine if patients with atrial fibrillation are suitable for warfarin treatment. To rapidly achieve stable anticoagulation, use an age-adjusted protocol for starting warfarin. Regular monitoring of the anticoagulant effect is required. Evidence suggests that patients who self-monitor using point-of-care testing have better outcomes than other patients.

Key words: anticoagulants, INR, point-of-care services, warfarin

## Introduction

Warfarin is recommended for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism (Table 1).[1] Its use is limited by several factors including a narrow therapeutic range, and drug–drug and drug–food interactions. Bleeding, particularly in the setting of over-anticoagulation, is a major concern.

The decision to start warfarin therapy requires an assessment of its harms and benefits for each patient. This assessment should take into account the patient's medical, social, dietary and drug history, level of education and adherence to previous therapy.[2] While the risk of falls plays a part in the harm-benefit assessment, published data indicate the propensity to fall is not an important factor in this decision.[3] Educating the patient is essential before they start warfarin. This includes informing them about the signs and symptoms of bleeding, the impact of diet, potential drug interactions and actions to take if a dose is missed. The safety and efficacy of warfarin is critically dependent on maintaining the INR within the target range. Patients must agree to undergo regular blood tests during treatment.

## Stroke Prevention

In patients with non-valvular atrial fibrillation, the decision to start warfarin should be based on the CHADS2 score. This assigns 1 point each for congestive heart failure, hypertension, age 75 years and older, and diabetes mellitus, and 2 points for previous ischaemic stroke or transient ischaemic attack.[1]

The CHADS2 score reliably identifies patients at intermediate and high risk of stroke, but less reliably identifies those truly at low risk.[4] Anticoagulation with warfarin is recommended if the CHADS2 score is ≥2 and should be considered if the score is 1. The CHA2DS2-VASc score (Table 2),[5] introduced by the European Society of Cardiology, provides a more comprehensive assessment of the risk factors for stroke. It is better at identifying 'truly low-risk' patients with atrial fibrillation, and is now preferred over CHADS2.

The HAS-BLED score (Table 2)[5] has been developed to determine the risk of bleeding. Scores range from 0 to 9. Scores ≥3 indicate a high risk of bleeding, the need for cautious management and regular review of the patient. It is not the intention to use HAS-BLED scores to exclude warfarin, but to allow the clinician to identify risk factors for bleeding and to correct those that are modifiable.[6]

## Optimising warfarin management

A patient's response to warfarin is driven primarily through genetic variance in the hepatic clearance, and vitamin K handling. Diet, age and dose also influence the anticoagulant effect. Assessing the response is complicated by a delay of 2–3 days before the INR reflects any changes in warfarin dose.

### Starting warfarin

When commencing warfarin it is important to measure the baseline INR. If this is 1.4 or above, without warfarin, liver function and nutrition status should be assessed and specialist advice sought regarding the patient's suitability for anticoagulation with warfarin.

Warfarin is usually started with loading doses. The Fennerty warfarin loading protocol published in 1984 was efficient in the relatively young population tested, but it was subsequently shown to cause significant over-anticoagulation in the elderly.[7,8]

Another protocol, based on the Fennerty protocol, decreased the loading dose with increasing age. This age-adjusted protocol (Table 3*)[9] recommends a 10 mg starting dose for patients aged 50 years and under, decreasing to 6 mg for patients over 80 years old.

The age-adjusted protocol was superior to the Fennerty protocol and to empirical prescribing.[8] Patients more rapidly achieved a stable INR, had fewer results above 4.0 during the initiation phase and fewer doses withheld due to rapidly rising INRs.[8,9]

Warfarin can be safely started in the community setting, but a recognized initiation protocol should be used. Even purportedly 'safe' starting doses of 5 mg represent a large loading dose for a patient who requires a maintenance dose of only 1-2 mg, and can lead to marked over-anticoagulation in a few days if INRs are not monitored. There is generally a significant movement in INR on the third or fourth day after starting warfarin, regardless of whether an initiation protocol is adhered to, or a 'safe' dose of 5 mg is used.

When possible, a single strength warfarin tablet should preferably be prescribed so that doses are multiples of one tablet.[10] Patients should take their warfarin once a day at the same time in the evening, with INR testing in the morning. The INR should be measured daily for the first five days.

(*Table 3: Age-adjusted protocol for starting warfarin. See online with this article at www.australianprescriber.com/magazine/38/2/44/8)

*Table 1* **Indications, goals and duration of warfarin therapy** [1]

| Indication | Target INR (range) | Duration of therapy |
|---|---|---|
| Deep vein thrombosis of the leg or pulmonary embolism | 2.5 (2.0–3.0) | At least 3 months |
| **Atrial fibrillation or flutter** | | |
| Intermediate to high risk of stroke | 2.5 (2.0–3.0) | Indefinite |
| Elective cardioversion | 2.5 (2.0–3.0) | 3 weeks before scheduled cardioversion and for 4 weeks after successful cardioconversion |
| Mitral stenosis | 2.5 (2.0–3.0) | Indefinite |
| After stent placement and high risk of stroke | 2.5 (2.0–3.0) | Bare-metal stent (1 month) and drug-eluting stent (3–6 months) as triple therapy with clopidogrel and aspirin After initial triple therapy, continue warfarin and a single antiplatelet drug until 12 months after stent placement After 12 months, use warfarin alone |
| **Valvular heart disease** | | |
| Rheumatic mitral valve disease | 2.5 (2.0–3.0) | Long term |
| Mechanical prosthetic heart valves | Bileaflet or tilting-disk valves: 2.5 (2.0–3.0) in the aortic position and 3.0 (2.5–3.5) in the mitral position | Long term Recommended to use aspirin in addition, 50–100 mg daily, if low bleeding risk |
| Bioprosthetic valves in the mitral position | 2.5 (2.0–3.0) | 3 months after insertion |

*Table 2* **Scoring systems for assessing the risk of stroke (CHA$_2$DS$_2$-VASc) and bleeding (HAS-BLED) in patients with atrial fibrillation** [5]

| CHA$_2$DS$_2$-VASc | Score | HAS-BLED | Score |
|---|---|---|---|
| **C**ongestive heart failure | 1 | **H**ypertension (systolic blood pressure >160 mm Hg) | 1 |
| **H**ypertension | 1 | **A**bnormal renal and liver function (1 point each) | 1 or 2 |
| **A**ge ≥75 years old | 2 | **S**troke | 1 |
| **D**iabetes mellitus | 1 | **B**leeding tendency/predisposition | 1 |
| **S**troke/transient ischaemic attack/thromboembolism | 2 | **L**abile INRs (if on warfarin) | 1 |
| **V**ascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) | 1 | **E**lderly (e.g. age >65 years old) | 1 |
| **A**ge 65–74 years old | 1 | **D**rugs or alcohol (1 point each) | 1 or 2 |
| **S**ex **c**ategory (i.e. female sex) | 1 | | |
| Maximum score | 9 | Maximum score | 9 |

### Maintenance therapy

Once the patient has had two consecutive INRs in the target range, the INR can be measured at increasing intervals depending on its stability. Once the dose and INR are stable, patients can usually be well controlled with 4–6-weekly testing, but some patients will require more frequent testing. Dose adjustment is not required for minor INR fluctuations, if the result remains within the patient's target range.

When adjusting maintenance doses for high or low INR values, it is important to think in terms of adjusting the dose as a percentage-based change. There is a reasonable linear relationship between dose and INR response during maintenance dosing, so a 10% dose increase will result in an increase of approximately 10% in the INR.[11] A 1 mg increment is a major adjustment for a patient normally receiving 2 mg daily (50% adjustment), and would result in a major INR change, but not for a patient receiving 10 mg daily (10% adjustment). Table 4 gives an example of the dose changes that may be needed to maintain the INR within a target range of 2-3.

For INR ≥5 follow the Australian consensus guidelines.[12] In all cases of out-of-range INRs, possible causes for altered INR should be considered to determine if they are reversible. For example, if the INR has been elevated by antibiotics it can be expected to fall when the course is finished. This can be factored into the dosing and monitoring requirements.

Warfarin is subject to multiple interactions including:

- diet – for example beetroot, liver, green leafy vegetables (decreased INR)
- drugs that may increase INR – macrolide antibiotics, imidazole antifungals, sulfamethoxazole/ trimethoprim, amiodarone, statins, some non-steroidal anti-inflammatory drugs, and some complementary medicines such as St John's wort
- weight loss or weight gain
- excess alcohol

The risk of bleeding is minimized by regularly monitoring the INR, and ensuring the patient understands the action of warfarin and how to recognize the signs of bleeding. Patients should have their INR checked after any dose changes,

the addition of any potentially interacting drugs, or dietary changes.

To prevent INRs outside of target range:

- consider potential warfarin–drug interactions
- wait at least 48 hours before testing INR after any change of dose, as earlier testing will not reflect the full response to the dose adjustment
- if INR drifts below the target, avoid excessive increases in dose
- provide ongoing patient education.

Although bleeding can occur in the target range, the risk increases with a rising INR. Elevated INRs between 4.5 and 10, and not associated with bleeding or a high risk of bleeding, can be safely managed by withholding warfarin and carefully monitoring the INR. Vitamin K1 can be given orally or intravenously to reverse the effect of warfarin in patients with INRs above 10 or those with bleeding or a high risk of bleeding. In patients who are not actively bleeding, it is important to avoid overtreatment as this will make it difficult to re-establish control of the INR. The initial intravenous dose of vitamin K should probably not exceed 0.5–1 mg. If immediate reversal is required, prothrombin complex is preferred to fresh frozen plasma.[12]

**Warfarin management strategies**

Approaches for managing patients taking warfarin include:

- usual care by the GP
- patient self-monitoring
- laboratory care program.

Anticoagulation clinics coordinate and optimise the delivery of anticoagulant therapy by providing specialised monitoring and management. Patients treated in anticoagulation clinics spend more time in the therapeutic range (50.4% vs 35%). They also experience less significant bleeding (8.1% vs 35%), major or fatal bleeding (1.6% vs 3.9%) or thromboembolic events (3.3% vs 11.8%).[13] In general practice it should be possible to have patients within the therapeutic range 60% of the time.

Some centres use computer-assisted warfarin dosing.[14] This assists in achieving a stable state of anticoagulation faster, and increases the overall percentage of time in the target range, potentially reducing the frequency of testing. It also reduces the risk of bleeding and thromboembolic events and is more cost-effective than manual dosing using clinical assessment.[15]

**Point-of-care testing**

Point-of-care testing of the INR can be done in general practice, in other locations such as pharmacies, or by the patients themselves (known as self-monitoring). These approaches are more convenient for patients than visits to an anticoagulation clinic in a pathology practice or in a hospital.

The convenience of self-monitoring can be extended further to a model of self-management. Patients use algorithms to determine any necessary dose adjustments following INR measurement.[16] Evidence supports the practice of self-monitoring, with or without self-management, but an essential prerequisite is the ability of the patient to correctly, competently and safely use the testing devices.[17]

*Table 4* **Suggested dose changes for maintaining INR within a target range of 2–3**

| INR | DOSE RANGE |
| --- | --- |
| <1.5 | Increase by 20% |
| 1.6–1.9 | Increase by 10% |
| 3.1–3.4 | Decrease by 10%, adjustment may not be necessary |
| 3.5–3.9 | Decrease by 20%, consider holding one dose |
| 4.0–4.9 | Hold dose until INR returns to range then decrease by 20–30% |

A number of randomized controlled trials of both self-monitoring and self-management have been included in systematic reviews and meta-analyses.[16,18-20] In three systematic reviews, self-monitoring and self-management had similar results to routine care in a hospital clinic. Patients undertaking self-monitoring had significant reductions in thromboembolic events and death, with more time in the target range, compared to those who did not self-monitor.[18-20] A further systematic review of 22 randomized controlled trials showed similar results including a 26% reduction in death.[21] A recent meta-analysis also found that patients who self-monitored had a reduced risk of thromboembolic events.[16]

Few studies have compared INR point-of-care testing by GPs with laboratory testing. A systematic review included three studies, but none showed improvements in the proportion of patients within the target range.[22]

An Australian trial of point-of-care testing in general practice included INR testing as well as other tests. While it showed improvements in glycated haemoglobin (HbA1c) and some lipid profiles, there was no such improvement for anticoagulated patients.[23]

There is evidence of a poor understanding of INR testing, including therapeutic guidelines, among physicians and GPs in several countries, including Australia.[24] The possibility remains that the improved outcomes achieved by self-management may be because patients more consistently follow therapeutic guidelines, especially if they manage their doses using software algorithms.

**Conclusion**

Warfarin can be a challenging drug to manage, but if used appropriately it can be effective for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism. Regular monitoring and good patient education are important for successful treatment.

Conflict of interest: none declared

**References**

1. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(Suppl 2):7S-47S.

2. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. Cleve Clin J Med 2003;70:361-71.

3. Man-Song-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med 1999;159:677-85.

4. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost 2012;107:1172-9.

5. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation 2012;126:860-5.

6. Amerena JV, Walters TE, Mirzaee S, Kalman JM. Update on the management of atrial fibrillation. Med J Aust 2013;199:592-7.

7. Fennerty A, Dolben J, Thomas P, Backhouse G, Bentley DP, Campbell IA, et al. Flexible induction dose regimen for warfarin and prediction of maintenance dose. Br Med J (Clin Res Ed) 1984;288:1268-70.

8. Roberts GW, Druskeit T, Jorgensen LE, Wing LM, Gallus AS, Miller C, et al. Comparison of an age adjusted warfarin loading protocol with empirical dosing and Fennerty's protocol. Aust N Z J Med 1999;29:731-6.

9. Roberts GW, Helboe T, Nielsen CB, Gallus AS, Jensen I, Cosh DG, et al. Assessment of an age-adjusted warfarin initiation protocol. Ann Pharmacother 2003;37:799-803.

10. Guidelines and Protocols Advisory Committee. Warfarin therapy management. British Columbia, Canada: British Columbia Ministry of Health; 2010. www.bcguidelines.ca/guideline_warfarin_management.html [cited 2015 Mar 3]

11. Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose- effect relationship. Clin Pharmacokinet 1986;11:483-504.

12. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS, et al. An update of consensus guidelines for warfarin reversal. Med J Aust 2013;198:198-9.

13. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 1998;158:1641-7.

14. Wright DF, Duffull SB. A Bayesian dose-individualization method for warfarin. Clin Pharmacokinet 2013:52;59-68.

15. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol 2011;154:311-24.

16. Heneghan C, Ward A, Perera R; Self-Monitoring Trialist Collaboration, Bankhead C, Fuller A, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet 2012;379:322-34.

17. Self-monitoring for patients on warfarin? Evid Based Med 2010;15:161-4.

18. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet 2006;367:404-11.

19. Christensen TD, Johnsen SP, Hjortdal VE, Hasenkam JM. Self-management of oral anticoagulant therapy: a systematic review and meta-analysis. Int J Cardiol 2007;118:54-61.

20. Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, et al. Self-monitoring and self- management of oral anticoagulation. Cochrane Database Syst Rev 2010;4. CD003839.

21. Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Ann Intern Med 2011;154:472-82.

22. Gialamas A, St John A, Laurence CO, Bubner TK; PoCT Management Committee. Point-of-care testing for patients with diabetes, hyperlipidaemia or coagulation disorders in the general practice setting: a systematic review. Fam Pract 2010;27:17-24.

23. Bubner TK, Laurence CO, Gialamas A, Yelland LN, Ryan P, Willson KJ, et al. Effectiveness of point-of-care testing for therapeutic control of chronic conditions: results from the PoCT in General Practice Trial. Med J Aust 2009;190:624-6

24. Kristoffersen AH, Thue G, Ajzner E, Claes N, Horvath AR, Leonetti R, et al. Interpretation and management of INR results: a case history based survey in 13 countries. Thromb Res 2012;130:309-15.

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# Management of acute organophosphorus insecticide poisoning

## Introduction

Acute organophosphorus (OP) insecticide poisoning is a major global health problem causing about 200,000 deaths every year. Management of severe acute OP poisoning is a challenge. Presence of different types of OPs with varying clinical features, time of poisoning onset, and response to treatment makes management difficult especially in resource poor settings. This paper describes basic principles in management of acute OP poisoning.

Studies from Sri Lanka suggest that most patients are brought to a peripheral hospital within 1 hour of poisoning. Since patients can develop acute cholinergic crisis within 20 minutes of ingestion, some patients will be severely ill on admission requiring prompt resuscitation. Any patient admitted with acute OP poisoning should be resuscitated and stabilized before considering gastric decontamination. Treatment includes resuscitation of patients involving administration of oxygen, a muscarinic antagonist (usually atropine), fluids, and an acetylcholinesterase reactivator (an oxime that reactivates acetylcholinesterase by removal of the phosphate group).

## Initial resuscitation of the patient

Check airway, breathing, and circulation. Place patient in the left lateral position to reduce risk of aspiration of stomach contents. Provide high flow oxygen, if available. Intubate the patient if airway or breathing is compromised or having a low score in the Glasgow Coma Scale (less than 8). Two wide bore IV cannulae should be inserted for fluids and drugs in an ill patient. Set up an infusion of 0.9% saline. At the same time, administer intravenous atropine as below.

## Atropinisation of the patient

Intravenous administration of the antimuscarinic atropine is the most important antidote in the management of acute OP poisoning. Acting as a competitive antagonist at the muscarinic receptors, atropine reduces the primary pathology in acute OP poisoning: the muscarinic over-stimulation caused by excessive accumulation of acetylcholine at the cholinergic synapses.

The goal is adequate atropinisation of the patient without causing atropine toxicity. Initially atropine is given as intravenous bolus doses until patient achieves a clear chest devoid of rhonchi and crepitations, dry axillae, pulse at least 80 bpm, and systolic blood pressure >100mmHg. Fixed dilated pupils may occur if excessive atropine is administered.

The initial atropine dose is decided according to the severity of the cholinergic crisis, varying from 0.6 mg (1 vial) for relatively well patients to 3mg (5 vials) for sick patients. If there is no improvement across the board in the above variables 5 minutes after the first bolus dose, a second bolus dose should be rapidly given. To achieve quick atropinisation without causing atropine toxicity, you should use double the initial dose and keep the patient under observation for another 5 minutes. If again there is no consistent improvement at that time (~10 min after the first atropine dose), administer another dose (double the previous dose). This doubling dose regime should be continued until the patient is adequately atropinised (i.e. the above mentioned therapeutic targets have been achieved)

Atropine is then administered as an infusion at an initial rate 10-20% of the total dose required to atropinise the patient per hour. Patients should be carefully monitored for signs of atropine need or atropine toxicity and the infusion altered and further bolus doses given as necessary. This titrated approach to administration of atropine has been shown in Bangladesh to markedly increase the speed of resuscitation and reduce mortality over a more classical fixed approach.

Tachycardia is not a contraindication to atropine since it may be caused by many other factors such as hypoxia and nicotinic stimulation. Clinical judgment is needed about additional doses of atropine if the heart rate and blood pressure are slightly below their targets but the chest is clear. More atropine at this point may not be needed. Severe hypotension may benefit from vasopressors. The value of vasopressors versus higher doses of atropine is not yet clear.

## Gastric decontamination

Gastric decontamination may be considered once the patient is adequately atropinised and stable, with a preserved airway. Administration of activated charcoal within 2 hours of poisoning is probably the safest method of gastric decontamination, with the

likelihood of some benefit, 60 to 100g of activated charcoal can be administered through a nasogastric tube.

There is no clinical trial evidence to suggest that gastric lavage is effective in acute OP insecticide poisoning. However, if the patient is stable with adequate atropinisation within 1-2 hours of ingesting a large potentially fatal dose of OP insecticide, gastric lavage can be considered. The vital signs of the patient including oxygen saturation should be monitored throughout the lavage and a medical officer and nursing officer should be present during the procedure. Drugs, oxygen and other necessary equipment should be available to resuscitate the patient if a need arises. Gastric lavage should not be performed in struggling non-cooperative patients. If the patient's consciousness is impaired, lavage should be done with a cuffed endotracheal tube in situ.

**Pralidoxime**

The best way of giving oximes in acute OP poisoning is unclear. Pralidoxime has been used in relatively low doses: that is 1g 6 hourly for 2 days. However, the WHO recommends higher doses, a loading dose of at least 30 mg/kg pralidoxime salt followed by 8 mg/kg infusion for a period of 7 days. But a clinical trial done in Sri Lanka provided evidence that routinely following the WHO recommended high-dose pralidoxime regimen in all patients with WHO Class II poisoning (as seen in Sri Lanka) does not improve survival.

There is no consistent clinical trial evidence for the use of pralidoxime in OP poisoning. A Randomized Controlled Trial (RCT) conducted in Baramati, India, found that high doses of pralidoxime (1 g of iodide salt, or 0.52 g of active pralidoxime cation per hour) for the first 48 h after a loading dose were beneficial. Two other studies done in Vellore, India, compared a low-dose infusion with a single bolus or placebo and found low-dose infusion to be harmful. However, clinical practice evidence suggests pralidoxime may be effective in certain types of OP poisoning such as with chlorpyrifos.

Further trials are required to assess the risk/benefit of oximes, and to explore using lower or shorter dosing regimens or different oximes. In the meantime, bolus doses of pralidoxime for two days may offer benefit to some patients and are recommended here. Recurrence of toxicity after stopping pralidoxime may warrant careful restarting of pralidoxime administration for a further 24-48 hours.

**Recurrences of cholinergic crisis**

Patients should be monitored at frequent intervals initially to detect recurrence of cholinergic symptoms and for features of atropine toxicity. Too little atropine leaves the patient in cholinergic crisis, whereas too much atropine causes atropine toxicity. Recurrences of cholinergic toxicity could be managed with bolus doses of atropine and an increase in the rate of infusion.

If atropine toxicity occurs (tachycardia, dry hot skin, absence of bowel sounds, agitation, delirium), the atropine infusion should be stopped until patient is stable without signs of atropine toxicity and the infusion could be restarted at a lower rate. In addition to reviewing the atropine dose, agitation may be treated by providing adequate sedation with benzodiazepines. Physical restraint of agitated patients in warm conditions risks severe hyperthermia, which is exacerbated greatly by atropine because it inhibits normal thermoregulatory responses including sweating.

A combination of careful monitoring and adequate sedation is important after initial resuscitation and management. Monitoring could be done less frequently as the patient becomes stable; reducing the atropine infusion should be done slowly - it may take days to completely stop the atropine infusion. Patients may not develop an early severe acute cholinergic crisis following ingestion of very fat soluble OPs such as fenthion. It is extremely important to keep such patients under observation for at least 24 hours for incipient toxicity or muscle weakness. Patients who have been completely asymptomatic for 24 hours can be considered for discharge with advice to return to hospital if any clinical features develop.

**Early and late respiratory failure**

Respiratory failure is a significant cause of the high morbidity and mortality from acute OP poisoning. Respiratory failure occurs with two relatively distinctive clinical patterns. An early form occurs at or soon after admission in patients with impaired level of consciousness and marked muscarinic features. Early and rapid atropinisation may reduce the incidence of early respiratory failure; however, it should be anticipated and detected early. If respiratory failure

occurs, the patient should be intubated and ventilated and adequately atropinised.

Late respiratory failure may occur in conscious patients whose muscarinic symptoms are controlled, or in unconscious patients, and is attributed to weakness of the respiratory muscles due to the intermediate syndrome (IMS). Before developing respiratory failure the patients classically develop weakness of the flexors of the neck, proximal muscles and muscles supplied by the motor cranial nerves. Patients are unable get up from the bed and are unable to raise the head off the bed. Although proximal muscle weakness is usually obvious, cranial nerve motor weakness may not be prominent.

Clinical evidence suggests that more than 50% of the patients developing severe muscle weakness (MRC grade 3 or less) require intubation and mechanical ventilation. Thus, if facilities are not available to ventilate, patients should be transferred to an institution where such facilities are available. A patient who develops late respiratory failure and the intermediate syndrome should be intubated and ventilated until patient recovery, which may take days. Early detection of development of the intermediate syndrome is of utmost importance as it can save lives. Monitoring neck flexion and proximal muscle power and tidal volume is mandatory especially after 24 hours (although there had been cases of patients developing intermediate syndrome before 24 hours and later than 5 days post-ingestion). Patients should be checked every 4 h if there is any evidence of muscle weakness. Tidal volume values less than 5 mL/kg suggest a need for intubation and ventilation.

**Complications**

Seizures are uncommon; however, those that do occur can be managed with benzodiazepines. Aspiration pneumonia is commonly a complication of pre-hospital unconsciousness and of gastric lavage, and should be treated with careful nursing care and, if signs of pneumonia develop, broad spectrum antibiotics.

**Further reading**

1. Eddleston M, Buckley NA, Eyer P et al. Management of acute organophosphorus pesticide poisoning. *Lancet* 2008;**371**:597–607.

2. Eddleston M, Buckley NA, Checketts H. Speed of initial atropinisation in significant organophosphorus pesticide poisoning—a systematic comparison of recommended regimens. *Journal of Toxicology Clinical Toxicology* 2004; **42**:865–75

3. Eddleston M, Dawson A, Karalliedde L. Early management after self-poisoning with an organophosphorus or carbamate pesticide—a treatment protocol for junior doctors. *Critical Care* 2004;**8**:R391–7

4. Buckley NA, Eddleston M, Li Y et al. Oximes for acute organophosphate pesticide poisoning. *Cochrane Database of Systematic Reviews* 2011;**(2)**:CD005085

5. Eddleston M, Eyer P, Worek F, et al Pralidoxime in acute organophosphorus insecticide poisoning: a randomised controlled trial. *PLoS Medicine.* 2009;**30**;e1000104

6. Abedin M J, Sayeed AA, Basher A, et al. Open-label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. *Journal of Medical Toxicology* 2012;**8**:108-17

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## Naming of Western medicines – is there a method?

We cannot disregard the fact that some of the generic names of new medicines are really difficult to write and pronounce. On the contrary the corresponding trade names are 'smooth' and easy to pronounce. For example, two new drugs have the generic names as dexmedetomidine and boceprevir and the corresponding trade names are Dexdor and Victrelis. One begins to wonder whether there is a secret attempt to dissuade the use of generic names. Against this background, let us look at the process of giving generic names.

Although we have used the term generic name so far, the experts recommend use of the term International Nonproprietary Name (INN). Hence we will use that. Presently a single pharmaceutical substance is designated with one INN.

**History, responsibility and method**

The INN programme developed as an extension of the WHO programme for unification of pharmacopoeias and preparation of the International Pharmacopoeia. A WHO Expert Committee on unification of pharmacopoeias drew up general rules for nomenclature that were adopted by the World Health Assembly in 1950. Consequently, the programme on International Nonproprietary Names (INN) for pharmaceutical substances was officially initiated in 1953 and the first list of INNs for pharmaceutical substances was published [1].

Now the INN programme is administered by the WHO Secretariat in Geneva, under the purview of the Expert Committee on Nonproprietary Names for Pharmaceutical Substances [2]. This expert group consists of representatives from national nomenclature groups and experts from different countries (i.e. France, Indonesia, Japan, Nigeria, Poland, Spain, UK and USA). INNs are taken up for discussion at consultations that are held biannually and 96 names have been selected for publication during the 58th consultation held in April 2014 alone [3]. All these are compiled into a cumulative list of INN that is published every two years and the most recent one has over 8500 names [4].

A request for an INN is submitted on a form to the appropriate section of the WHO [2]. Very often this request will be from the pharmaceutical industry although it may come from other sources also. Certain countries have their own national nomenclature commissions and the request for the INN is made through such an authority. For example in the USA, the request will come through the United States Adopted Names (USAN) Council. The request will include information on the chemistry, pharmacology, use and suggestions for an INN [5]. Next, all members of the Expert Committee designated to select INNs have to agree to this name. Each name proposed by the originator of such request is examined and a name selected [2].

Such a name is first published as a proposed INN and a period of 4 months is allowed for comments or objections [2]. If there are no issues after this 4 month period the name will get published as a recommended INN [6]. The proposed and recommended INNs are published in the journal titled WHO Drug Information. These INNs are intended to be used in scientific literature, drug regulation, pharmacopoeias, as product names (eg. for generic medicines), labelling and advertising [1].

Committees selecting the INN go for words which are (i) distinctive in sound and spelling (ii) not too long (iii) not liable to confusion with other names in common use [1]. Usually INNs have a random prefix and a common stem. This stem may appear anywhere in the INN. Substances belonging to a group of pharmacologically related substances will show their relationship by use of a common stem. Sometimes substems are included. For example the stem cef will be a common stem for cefalosporanic acid derived antibiotics. The stem grel is common for platelet aggregation inhibitors and this stem may appear at the end of the INN (eg. Clopidogrel, Prasugrel) or in the middle of the INN (eg. Ticagrelor, Anagrelide etc.). The letter 'e' is used instead of 'ae' or 'oe'; 'i' instead of 'y' and 't' and 'f' instead of 'th' and 'ph'. Hence now we write cefalexin (instead of cephalexin); amoxicillin instead of amoxycillin; estradiol instead of oestradiol [7].

**Problems**

It has been increasingly noted that common stems from the INN are included in trade names [8,9]. This causes difficulty in selecting new INNs and more importantly causes confusion among practitioners and pharmacists, leading to serious errors in prescribing and dispensing. The WHO has recommended member countries and the medicine manufacturers and traders

to take steps to safeguard the INNs [1].

The Committee deciding on INN names has faced increasing difficulty from various sources. Difficulty has arisen in deciding whether the mechanism of action of a compound under consideration is a 'new action' or is incorporated in an action that is already recognized [1]. Biotechnology generates a large number of compounds with similar actions but with minor differences. Sometimes the difference is in a single amino acid or a few amino acids [10]. In such instances do we need to give separate INNs? When drugs are generated through molecular modelling or when a 'new action' is identified to one such compound, is that compound taken off the related series of similar compounds? Policy decisions with explicit guidelines on selecting INNs for different classes of pharmaceutical substances (e.g. biologics, biosimilars, and biological qualifiers) have been made by the Committee to deal with such difficult matters [11]. However, the Committee will continue to face such challenges with the rapid advancement of technology and the advent of many complex pharmaceutical substances.

Prescribing and dispensing based on INNs also becomes a problem in certain situations. Due to variations in bioavailability it may be advisable to adhere to one brand, in medicines with a narrow therapeutic index, modified release preparations and for chronic prescriptions. Moreover, some patients must avoid certain excipients due to contra-indications, risk of interactions or known allergy. In these cases prescribing by a brand name may be safer [12].

**Conclusions**

It is reassuring to note that there is an international organization entrusted with the task of giving generic names, and that they follow some method. The names given are more than mere identifiers. The unattractive jaw-breaking names are designated for medicines with a purpose; as an indicator of its chemical structure and its pharmacological action, and not due to a conspiracy to discourage the use of such INNs.

**References**

1. World Health Organization. *Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substance.* 1997

2. World Health Organization. *International Nonproprietary Names: revised procedure-Report by the Secretariat.* 2004

3. World Health Organization. *Executive Summary of World Health Organization Programme on International Nonproprietary Names (INN).* [internet] 2014. Available at http://www.who.int/medicines/services/inn/58th_executive_summary.pdf (Accessed on December 2014)

4. World Health Organization. Publications [internet] 2015. Available at http://www.who.int/goe/publications/en/ (Accessed on December 2014)

5. World Health Organization. Request of an International Non-proprietary Name [Internet] 2015. Available at https://extranet.who.int/tools/inn_online_application/INN_online_application_files/INNFORM_072010.pdf (Accessed December 2014)

6. World Health Organization. *International nonproprietary names (INN) for pharmaceutical substances: lists 1-105 of proposed INN and lists l-66 of recommended INN: cumulative list no. 14.* 2011.

7. World Health Organization. *The Use of Stems in the Selection of International Nonproprietary Names (INN) for Pharmaceutical Substances.* 2011

8. Gopakumar KM, Syam N. International Nonproprietary Names and Trademarks: A Public Health Perspective. *Journal of World Intellectual Property* 2008;**11**:63–104

9. Grogan CM. Prescription Drugs and Administrative Costs. *Journal of Health Politics, Policy and Law* 2013;**38**:475–77

10. World Health Organization. *International nonproprietary names (INN) for biological and biotechnological substances; a review.* 2013

11. World Health Organization. *WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products.* 2006

12. International Society of Drug Bulletins Newsletter. INN: an essential tool 2006;**20**:1–17.

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# Self-assessment questions
## Select the best response in each question

**Question 1**

A 76 year old female with diabetes mellitus and hypertension, is on warfarin for a non-valvular atrial fibrillation. The warfarin dosage has been titrated to maintain a stable INR of 2.5 (range 2.0-3.0). Subsequently, she is prescribed clarithromycin for an atypical pneumonia. In addition to monitoring PT/INR, which of the following actions should the physician take to maintain adequate anticoagulation?

A. Stop warfarin and administer vitamin K

B. Reduce the dose of warfarin

C. Make no alterations in warfarin dose

D. Stop warfarin and change over to low-dose aspirin

E. Increase the dose of warfarin

**Question 2**

A 39-year old male has been taking warfarin for 2-months after suffering from a below-knee deep vein thrombosis. He presents with gum bleeding of two days duration. He has a blood pressure of 120/90 mmHg and a resting heart rate of 76/min. ECG reveals a normal sinus rhythm. The subsequent blood tests reveal an INR of 8.5, haemoglobin of 14 g/dl, and a platelet count of 225,000/mm3. What is the most appropriate treatment for this patient?

A. Stop warfarin only and monitor the PT/INR.

B. Stop warfarin and administer fresh frozen plasma.

C. Stop warfarin and administer factor VII.

D. Stop warfarin and administer 1mg vitamin K1 by slow IV injection.

E. Administer 1mg oral vitamin K1, while continuing a reduced dose of warfarin.

**Question 3**

Features of organophosphate insecticide poisoning includes all of the following, EXCEPT;

A. Increased salivation.

B. Convulsions.

C. Mydriasis.

D. Muscle weakness.

E. Rhonchi.

**Answers to self-assessment questions**

Question 1:   The best response is B. Clarithromycin inhibits warfarin metabolism (through cytochrome P450 enzymes), potentiating its action. This increases the risk of bleeding. Hence the dose of warfarin should be reduced to maintain adequate anticoagulation.

Question 2:   The best response is D. For patients on warfarin with evidence of minor bleeding, as in this patient, it is advisable to stop warfarin and administer vitamin K1 1-3mg orally or as a slow IV injection. This could be repeated if INR continues to remain high after 24 hours. Warfarin can be restarted at a lower dose when bleeding has stopped and when the INR is <5.0.

Question 3:   The best response is C. All other features are seen in organophosphate poisoning, except mydriasis. The pupils will actually constrict (miosis).

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