

Editorial**Evidence based treatment of arterial disease in the upper and lower limb****C D Forbes****Journal of the Ceylon College of Physicians, 1999, 32, 3-8*

In the last 10 years, there have been major changes in the use of evidence of efficacy of various treatments. Nowhere has this been better seen than in the SIGN Guidelines (Scottish Intercollegiate Guidelines Network). These Guidelines are generated by groupings of specialists, generalists and general practitioners in the search for optimum management of common disorders. SIGN Guideline No. 27 looks at drug therapy for peripheral vascular disease and this encompasses intermittent claudication and Raynaud's phenomenon¹.

Intermittent claudication

Intermittent claudication is so called because of the development of a limp in patients who have obstruction of their arterial supply to their lower limb on exertion and this is the commonest presentation of peripheral arterial obstructive disease. The patient may also complain of pain in the calf, aching muscle and stiffening and fatigue of the limb. In patients with more proximal occlusion in the aorto-iliac arteries, there may be buttock claudication as well as impotence due to arterial deficiency in the process of erection. It is usual for the pain or discomfort to disappear very rapidly on resting and this is the typical scenario in these patients. The walking time to pain is remarkably constant in individual patients if walking on the flat, but if additional exertion is undertaken, e.g. climbing stairs or running, the time is much shorter. In more severe disease, pain may come on at rest particularly during the night and is located in the

calf and thigh muscles and occasionally in the buttocks. There may in addition be night cramps in the calf muscle and occasionally paraesthesia due to neuropathy. Patients and their partners may complain of recurrently cold feet, even in bed at night and even when wearing bed socks. The prevalence of intermittent claudication is between 1-7 per cent. In all these patients a search must be made for risk factors and in particular smoking, hypertension, hypercholesterolaemia and diabetes should be excluded. Examination of the legs will often show decreased or absent pulses in one or both limbs. In addition, there may be coldness of the skin, cyanosis, deficient capillary reperfusion, and in later stages, atrophy of muscle, atrophy of skin and loss of skin appendages such as hair and nails. Later on, there may be changes in the skin with onset of gangrene, particularly of the toes. A simple clinical test in out-patients is to have the patient lying flat on the examination couch and raise the limb to 45°. The raised foot then becomes pallid if there is arterial obstruction. The patient is then made to sit-up with the leg dependent and the limb then becomes flushed. It is also possible to measure the ankle-brachial systolic pressure (ABPI). A value < 0.95 indicates a significant difference and points to the need for further investigation, i.e. angiography, if the patient has clinical symptomatology. The cause of the vast majority of patients having intermittent claudication is due to atheroma of the large and medium sized arteries. Occasionally patients with thromboangiitis obliterans or Raynaud's phenomenon will also be found. It is important to remember that patients who are diagnosed as having peripheral arterial disease will also have coronary artery disease (30-50%) and cerebral vascular disease (10-15%)^{3,4}.

This paper is based on a lecture given at the Ceylon College of Physicians in September 1998.

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Mortality

The five year cumulative mortality for males with intermittent claudication ranges from 5 to 20%, most of the mortality is associated with coronary artery disease or stroke and a smaller number have central arterial aneurysms.

Perhaps the most important part of management is the attention that is paid to the risk factors⁵. The most relevant is cigarette smoking and the usual slogan is "stop smoking, keep walking". Most patients find it very difficult to stop smoking suddenly but they should be given every encouragement to do so and attendance at an anti-smoking clinic is perhaps the most successful way of achieving this. Patients require long term counselling and motivating. Nicotine replacement may be of some value but has to be done in the context of counselling and supervision. Elevated blood pressure, elevated cholesterol, elevated blood sugar and changes in rheological factors such as the haematocrit and fibrinogen also require attention. Exercise must be encouraged.

Drug Therapy

Aspirin

There is now little doubt about the value of the use of acetyl salicylic acid as a prophylactic against arterial occlusion in coronary artery disease and stroke. It is also now proven in the prevention of intermittent claudication in the long term. The dose should be between 75-300mg per day and be continued life-long. Other antiplatelet agents may also be of value such as clopidogrel.

The other agents which have been used in peripheral arterial disease in the UK are Naftidrofuryl (Praxilene), oxpentifylline (Trental), inositol nicotinate (Hexopal) and cinnarizine (Stugeron forte).

Naftidrofuryl (Praxilene)

The exact action of this drug is not clear. It does improve tissue oxygenation increasing the ATP levels and reducing lactic acid accumulation. It may thus act by improving the consequences of

the anoxia. The drug is used orally in a recommended dose of 200mg three times per day. There are now nine double-blind, placebo controlled studies showing the potential value of this drug. It is to be noted that in all studies on intermittent claudication, a placebo is required as this may give benefit in pain free walking of up to 25% by itself. Meta analysis of these studies has also been carried out and suggests benefit⁶. Most physicians dealing with the problem would use this drug for a period of three to six months and evaluate whether any lasting benefit was apparent.

Oxpentifylline (Trental)

This is a drug which may change the rheological properties of blood, in particular may make the red blood cells more deformable and therefore reduce viscosity. There may also be a reduction in plasma fibrinogen which enhances this effect. The drug is given orally in a dose of 400mg three times per day. Seven double-blind, placebo controlled studies have been carried out but only two of these suggest benefit. Subsequent meta analysis of 10 randomised, double-blind, placebo controlled studies failed to show a consistent and significant clinical benefit¹. This drug is therefore not recommended.

Inositol nicotinate (Hexopal)

In inositol nicotinate (Hexopal), four double-blind, randomised, placebo controlled studies have been reported but none of them show a clear benefit over placebo and this drug is not recommended¹.

Cinnarizine (Stugeron forte)

There are six controlled studies evaluating cinnarizine⁽¹⁾. The results are not altogether compatible and therefore there is no recommendation on the use of cinnarizine in the treatment of intermittent claudication.

Much further research is therefore required on the development of new drugs in the treatment of intermittent claudication. Some patients will be referred early for angiography and if a local stenosis is shown, angioplasty may be of significant benefit in selected patients. In addition, if angiog-

raphy shows the possibility of benefit from surgical grafting, this may also be undertaken with quite dramatic benefit in individual patients. It is important that all patients who go for surgical intervention receive adequate lifestyle alteration management.

Raynaud's phenomenon

Maurice Raynaud in 1862 defined a syndrome which now bears his name². The symptoms suffered by patients, most of whom are female, are aware of the fingers being subject to recurrent episodes of coldness and colour change. Sometimes there is local pain. It is usual for the changes to be triggered by cold, change in temperature and also be associated with the use of tobacco³ and changes in oestrogen level, even during the normal menstrual cycle⁴. The changes in colour of the fingers often follow a triphasic pattern with colour, cyanosis and redness following in succession due to the episodic digital ischaemia. In addition to the fingers, the toes may be involved but also the earlobes, the tip of the nose and occasionally the coronary arteries, the lungs and the oesophageal arteries. Raynaud's phenomenon is common in Northernly populations and is said to affect between 20 - 30% of females in certain countries. It is usually present as a mild and non-progressive condition, but an occasional patient has severe symptoms which are a threat to individual digits, either fingers or toes.

Primary and Secondary Raynaud's phenomenon

In the past there has been a problem over the use of terminology. Raynaud's phenomenon is the blanket term used to describe the clinical consequences of vasospasm which is usually cold related. Primary Raynaud's is used to describe the features where there is no associated other disease. It has of course to be accepted that at the time of presentation, other disease may not have manifested and we have seen cases that have been labelled primary Raynaud's where only after a period of 20 plus years has the secondary disorder appeared or been diagnosed. Secondary Raynaud's phenomenon is the term given

when there is an associated disorder, usually of connective tissue, drug administration, occupation or of metabolic cause. In General Practice, the vast majority of patients are primary Raynaud's whereas in hospital, about 50% of the patients sent for an opinion have an associated other condition and are therefore secondary. Some of the secondary causes of Raynaud's phenomenon are shown in Table 1^{15,10}. Occupational disorders remain a very important cause of secondary Raynaud's, in particular in areas with heavy industry in which individual workers use vibrating tools for grinding and buffing metal castings, for cutting coal and chainsaws for cutting timber¹¹. This has become particularly important as compensation may now be claimed if it can be shown that there is negligence in terms of damping down the vibrations of the tool. The vasospasm induced by vibrating tools (vibration white finger) may also affect the toes and may become permanent after long term exposure. Other occupational clinical causes include exposure to polyvinyl chloride; people working with nitrates in the explosive industry may also be affected. This usually occurs away from work as the affect of the vasodilatory nitrates wears off. Various drugs have also been implicated in the causation and also in the duration of digital vasoconstriction. These include ergot derivatives which were widely used in the management of migraine, beta blockers, cytotoxics and cyclosporin¹⁰.

Connective tissue disorders are the commonest cause of associated disease. The conditions include systemic sclerosis (95%), systemic lupus erythematosus (10-45%), rheumatoid arthritis (10%), dermatomyositis and mixed connective tissue disorders (85%).

A variety of other conditions have been associated and in particular the obstruction from cervical rib or a fibrous cervical band, the presence of arterio-venous fistula, atherosclerosis of the upper limbs, especially in those over the age of 60 and Buerger's disease in those under 50. Hyperviscosity syndromes may also be implicated such as Waldenström's macroglobinaemia, polycythemia vera and cryoglobulinaemia.

Table 1.

Conditions associated with Raynaud's phenomenon (i.e. secondary Raynaud's)

Immune-mediated	Drugs
Systemic sclerosis	Anti-migraine compounds e.g. ergot
Systemic lupus erythematosus	Cytotoxic drugs
Mixed Connective Tissue Disease	Cyclosporin
Polymyositis/dermatomyositis	Beta-blockers (particularly non-selective)
Sjögren's syndrome	Nitrates
Rheumatoid arthritis	Obstructive
Cryoglobulinaemia	Atherosclerosis
Occupational	Micro-emboli
Vibration	Thromboangiitis obliterans syndrome
Cold	Thoracic outlet
Polyvinyl chloride exposure	

Non-drug treatment (SIGN Guideline No. 27)

It is always important to remember that general measures should be introduced before giving drugs and these involve stopping smoking, the removal of drugs which are known to precipitate Raynaud's phenomenon e.g. beta-blockers and ergot preparation. The question of employment should be considered and if any factor is implicated, then a change of occupation may be necessary. In addition, simple measures such as the use of chemical handwarmers, which are readily available in sports shops, may be of some value and if necessary electrical heated gloves and/or socks may be of value. There has been debate about the continuation of the contraceptive pill but this should only be stopped if there is a direct association between the onset of the condition and the starting of the contraceptive pill.

Drug Therapy for Raynaud's phenomenon (SIGN Guideline No. 27)

The above simple measures may be suitable for many patients, but some patients find the onset embarrassing or painful and accordingly, vari-

ous drug regimens should be started. The calcium channel antagonist, Nifedipine, is licensed for this use in the United Kingdom and is already widely used in the treatment of angina pectoris caused by coronary artery spasm. Other drugs in the same category have the potential to be used on a named patient basis as they are not specifically licensed as yet. This whole class of drug acts by lowering the intercellular calcium flux and limits the calcium dependent actin-myosin interaction resulting in smooth muscle relaxation. The dose of nifedipine ranges from 10 to 20mg three times per day and has been shown to reduce the number of vasospastic attacks and their duration. A slow release preparation is also available. Naftidrofuryl oxylate (Praxilene) has a slight vasodilatory effect due to a mild serotonin receptor antagonist action. Used in an oral dose of 100mg three times per day, it has an effect on the onset and duration of attacks of Raynaud's phenomenon. Inositol nicotinate (Hexopal) in a dose of 1 - 1.5g twice daily also has vasodilator properties. These latter two drugs should be used only if there is no effect from the calcium channel blockade. Drug therapy which has been widely investigated but is

not yet licensed is a range of prostacyclins e.g. iloprost which is a stable carbacyclin derivative of prostacyclin. Initial studies carried out in this Department suggests that this may be the drug of choice in the future once the trial data has been accumulated¹². The evidence is that it will facilitate the healing of digital ulceration when that has been established. It has a duration of clinical action that seems to be for several weeks after the infusions have been completed. The reason for this is not clear but may relate to stabilisation of cell membranes.

Patients who are referred for further investigation and management with Raynaud's phenomenon require a detailed history, especially to look for precipitating factors and associated diseases. A clinical examination is required to look at the

effects of the disease and this may include cold challenge. Laboratory tests are shown in Table 2 and some of these may differentiate primary from secondary RP.

Conclusion

This paper was written to highlight the importance of developing national guidelines. Much of the information given here is based on SIGN Guideline No. 27. These guidelines are important for the development of local guidelines so that all clinicians understand the objective, use of evidence and how it should be interpreted. SIGN Guidelines can be obtained from the SIGN Secretariat, Royal College of Physicians, 9 Queen Street, Edinburgh EH2 1JQ or may be found on the webpage - <http://show.cee.hw.ac.uk./sign/home.htm>.

Table 2.

Investigation of patients with Raynaud's phenomenon

Complete history - especially relevant work-history

Thorough Clinical - for consequences for Raynaud's phenomenon and related other diseases

Laboratory Investigations

- (a) Haematology - To define hyperviscosity syndromes
- (b) Biochemistry - Exclude hypothyroidism
- (c) Immunology - Autoantibodies

Vascular Lab Assessment

- Thermography
- Cold Challenge
- Laser Doppler flow
- Capillary microscopy

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