MALTA PRESCRIBERS REVIEW

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PRESCRIBING IN PERIPHERAL VASCULAR DISEASE

The spectrum of peripheral vascular disorders encompasses a variety of problems: arterial occlusion, arterial dilatation, arterial hypersensitivity and secondary cutaneous ulceration. The majority are surgical diseases and warrant surgical evaluation, full assessment and surgical intervention. In the aneurysmal and occlusive disorders in particular, surgery is often the mainstay of treatment. The number of drugs available on the market for occlusive disease attests to their overall inefficacy. These drugs are claimed to be effective by virtue of their vasodilator effect, their ability to increase tissue 0_2 delivery and their ability to enhance red blood cell deformability and therefore passage through narrow diseased vessels. Patients with intermittent claudication have a tendency to increase their claudication distance spontaneously by stopping smoking and exercising regularly within their claudication distance. All drug claims must therefore be judged in this light.

Vasodilators may shunt blood from where it is needed most, that is away from the muscle mass into healthier skin vessels. Thus by dilating healthy rather than diseased vessels they may even decrease blood flow in ischaemic areas. With the emergence of excellent vascular prostheses particularly double velour dacron and goretex grafts and the availability of surgical expertise, no patient with chronic peripheral vascular disease should be denied the possibility of being investigated with a view to reconstructive arterial surgery. It must be stressed that these patients can be helped surgically only as long as the distal pulseless vessels remain patent. Therefore excessive temporising and inappropriate drug therapy alone are likely to lead to thrombosis which renders such surgical reconstruction impossible.

In those cases deemed beyond surgical help and in those who have been investigated and found

to have early disease, a combination of regular exercise, cessation of smoking and either a vasodilator or an anti-platelet aggregatory agent may improve collateral circulation significantly. The ability of dipyridamole to decrease platelet adhesiveness and the ability of naftidrofuryl or oxpentifylline to increase oxygen delivery to the tissues are in practice more important considerations than vasodilatation. The thinning effect on blood afforded by dipyridamole enhances the easier passage of red cells through diseased atherosclerotic vessels where sludging is likely to occur. Smoking must be discontinued completely and not simply reduced in number. Exercising must be to the limit of claudication, as only by increasing the demand on vascularity can the collateral circulation be expected to improve.

Underlying conditions likely to predispose to and aggravate peripheral vascular disease such as diabetes, hypertension and hyperlipidaemia must be sought, investigated and treated appropriately. If dietary factors fail to achieve the desired effect in hyperlipidaemia, treatment with bezafibrate, clofibrate or cholestyramine alone or in combination may be indicated.

Skin ulceration of arterial origin is undoubtedly a difficult problem particularly in the presence of non-reconstructable arterial disease. In these cases vasodilator drugs and chemical sympathectomy are beneficial in that they improve skin blood supply.

Patients with vasospastic disorders of the hands such as primary Raynaud's disease and chilblains have been found to respond to treatment with nifedipine. It must be stressed here that patients with Raynaud's phenomenon must first be fully investigated to exclude an underlying cause before a diagnosis of primary Raynaud's disease can be made.

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PRECAUTIONS BEFORE PRESCRIBING THE PILL

Many millions of women have used oral contraceptives (OCs) since they became available in the 1960's. There has been a gradual, but significant reduction in both hormonal components which has led to decrease in adverse effects. Oral Contraceptives currently used are of two main types:

1. Combined oestrogen and progesterone pill.

2. The progesterone-only OC or mini-pill.

Like any other medical therapy, the oral contraceptive has both beneficial and adverse effects; thus OCs are contra-indicated in certain individuals. ABSOLUTE CONTRA-INDICATIONS include malignancy of the breast and genital tract, venous thrombo-embolism, cerebrovascular accident, undiagnosed abnormal vaginal bleeding, focal migraine and familial hyperlipidaemia. RELATIVE CONTRA-INDICATIONS include age over 40 years, smoking, mild hypertension or a history of hypertensive disease during pregnancy, epilepsy, diabetes mellitus, depression, recent oligomenorrhoea or amenorrhea in nulliparous women, and gall bladder or liver disease. In those situations an assessment of the risks and benefits should be made before starting OCs. The potential risks should be adequately explained, possible alternative contraceptive methods should be discussed, and the woman should be kept under medical supervision. Special situations may require careful use of OCs.

Drug interactions: A number of drugs reduce the efficacy of OCs; alternative methods of contraception should be used while taking these drugs. There are a few reports of pregnancies in OCs users treated with antibiotics (rifampicin, ampicillin, amoxycillin, tetracycline, chloramphenicol, neomycin, sulphonamides, griseofulvin), anticonvulsants (phenytoin, phenobarbitone) and laxatives.

Lactation: Both high and low dose combined OCs containing oestrogen adversely affect the quantity and quality of breast milk, and reduce the duration of lactation. If contraception is

needed during lactation, progesterone-only OC can be used. No deleterious effects have been reported so far from the transfer to the infant of small amounts of steroids in the milk even when the combined pill is used.

Impaired glucose metabolism is an important problem in the Maltese population. Changes in plasma insulin and glucose tolerance in OC users have been recognised for many years , and this may be a progesterone effect. While there is no evidence of an increased incidence of diabetes in OC users, patients with impaired glucose tolerance and diabetes mellitus need close supervision.

Selection of OC: It appears best to use a triphasic combination of oestrogen and levonorgestrol (varying dosages of each steriod three times during each cycle) as a first line OC. A shift to a monophasic (same dose throughout) combination of the same components is indicated if menstrual control is not achieved. The 30mcg oestrogen dose of the monophasic preparation is only increased if intermenstrual bleeding persists (provided pathological causes are excluded). OCs containing progestogens of the norethisterone group are more useful in the control of dysfunctional uterine bleeding. The progesterone-only pill may have a place as an OC when the oestrogen component is contra-indicated or not desirable, such as during lactation and the years before the menopause. However, this mini-pill is less effective with a relatively high incidence of ectopic pregnancy, and a higher incidence of menstrual disruption.

In women who are otherwise well, OC use may be continued for many years. There is **no** justification for the periodic withdrawal of the OC. Yearly follow-up must include a reassessment of the medical state of the patient to identify the development of contra-indications and provide an opportunity to screen for early signs of medical illness and early cervical neoplasia.

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KETOCONAZOLE

Ketoconazole (Nizoral) is now back on the market as per the CGMO's recent circular. This memo is meant to amplify warnings about its use and current indications. Most of the following information is taken from the manufacturer's own data sheet as used in the USA where stringent regulations make detailed information mandatory.

1. INDICATIONS

The drug is intended for:

a. **Systemic** fungal infections including candidiasis, chronic mucocutaneous candidiasis, histoplasmosis.
Comment — These indications will make it unlikely that this drug is given without the specific advice of a specialist.

b. **Severe recalcitrant** cutaneous dermatophyte infections which have not responded to adequate topical therapy or oral griseofulvin or in patients who cannot take griseofulvin.
Comment — These specific indications would strongly suggest that ketoconazole be strictly retained for specialist use within the above framework.

2. SIDE–EFFECTS

The major worry is hepatotoxicity, usually of the hepatocellular type and the data sheet specifies
"WARNING — Ketoconazole has been associated with hepatotoxicity including some fatalities. Patients receiving this drug should be informed of the risk and monitored closely".

The reported incidence has been about 1:10000 but has probably been under reported. The median duration of treatment before hepatic toxicity appeared has been 28 days and the hepatic injury has been usually but **not always reversible** on discontinuing the drug.

Other side effects:

i. potentiation of oral anticoagulants;

ii. increased blood levels of Cyclosporin A;

iii. can theoretically precipitate severe hypoglycaemia in patients on oral hypoglycaemic agents;

iv. rifampicin can decrease ketoconazole blood levels.

Ketoconazole is a valuable drug which is likely to be used far more frequently in the future as the number of immune compromised patients (be it due to medication following renal transplantation, treatment of malignancy, or HIV infection) under our care rises dramatically. In these situations there is no alternative and its use is more than justified. This is a very different situation, however, to the drug being prescribed as first line treatment in patients with banal cutaneous fungal infections or vaginal infections. This SHOULD NOT HAPPEN.

In conclusion, the usage of ketoconazole reminds us of some basics in drug prescribing which we all too often need to be reminded —

1. EVERY DRUG may have a serious side effect in some unfortunate patients;

2. The medication given should be the safest available for that condition;

3. Powerful drugs with known very serious side effects are best left to specialists experienced in their use. Even then these should be used ONLY for the specific indications mentioned above;

4. Although happily (?) malpractice suits are not yet in fashion in Malta, there is NO WAY that a serious side effect resulting from a drug used when it was not specifically indicated could be defended in a court of law;

5. In effect, this implies the doctor's responsabilty in 'knowing' the drugs he prescribes, rather than be quickly convinced by the 2-minute chat by the drug rep on the virtues of the very latest 'cures'. They are not responsible, WE are!

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Editorial Note: Drugs are discussed in the Review under their international non-proprietary names, but where appropriate the more common trade names are indicated in brackets. The drugs mentioned are generally those which are readily available in this country. Where relevant, certain drugs which do not appear in the Formulary, Government Pharmaceutical Services are discussed, but it should be borne in mind that the drugs listed in the Formulary are sufficient for all ordinary purposes.

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