WHICH ISOSORBIDE MONONITRATE?
TWICE DAILY STANDARD TABLET OR ONCE A DAY SLOW RELEASE?

Prepared jointly by TPCT Prescribing Team and Drug Information Service

The Accounts Commission for Scotland recently produced a report “Supporting Prescribing in General Practice” (September 99). The report provides information on prescribing patterns, identifying a range of areas where improvements in quality and cost-effectiveness are possible. One area identified, with regard to cost-effective prescribing, is that of “Premium Priced Preparations”. These are drugs that are produced in both a standard and a premium price form e.g. modified (slow, sustained) release formulations, combination drugs, inhaled drugs. The report highlighted that 72% of all isosorbide mononitrate (ISMN) prescribed in Tayside was as the modified release form, compared with a Scottish median of 63%. The Accounts Commission calculated that £600,000 per annum, potential savings, could be released if the standard formulation of ISMN was prescribed in Tayside. Within hospital, the standard is more expensive than the long acting formulation and thus this change would have minimal cost implications for the Tayside University Hospitals Trust.

Action and uses of the nitrates

Organic nitrates, which have been used in the treatment of angina pectoris for over 100 years, remain a first line treatment today. Nitrates reduce cardiac preload and improve left-ventricular emptying as a result of venodilatation but a reduction of cardiac afterload (associated with arteriolar dilatation) and increased myocardial O2 supply (with coronary vasodilatation) and possibly an antiplatelet action also contribute to the anti-anginal effect.1,2

The problem of nitrate tolerance …..

Continuous nitrate dosing is associated with reduced vascular reactivity and attenuation of the anti-ischaemic effect due to development of tolerance. Although nitrate tolerance has been recognised for many years, its clinical significance only came to light with the introduction and widespread use of GTN patches during the early 1980s.3,4 This led to a recommendation that the patch be removed overnight to permit a “low nitrate” period during which tissue sensitivity is re-established. The same principle applies to asymmetric (eccentric) dosing with standard ISMN tablets.

….. and its implications for choice of treatment and dosage

Nitrates have been available in a variety of forms but isosorbide mononitrate is now most often prescribed for regular oral prophylaxis. ISMN is almost completely absorbed after oral administration and is not appreciably removed by liver first pass metabolism. Conventional ISMN has a half life of about 4 hours and provides consistent, effective blood levels for up to 6 hours or longer. It is the nitrate of choice in the current edition of the Tayside Area Drug Formulary. ISMN may be administered twice daily as a standard tablet in an asymmetric dosing regimen (with 6-8 hours between tablets) or once a day in slow-release form.
Studies in patients receiving continuous nitrate dosing (GTN patches) or frequent daily oral dosing with ISMN at regular intervals have shown that clinically significant tolerance develops. When administered twice daily in an asymmetric dosing regimen, on the other hand, the development of tolerance was reduced and there was a corresponding increase in exercise duration after each dose of the day. Similar results have been reported with once daily formulations. Slow-release ISMN preparations (e.g. Elantan LA®, Imdur®) are designed to provide the appropriate “low nitrate” interval between doses.

Compliance with once daily versus twice daily oral dosing – the evidence

A search of the MEDLINE, EMBASE and COCHRANE databases reveals few conclusive studies that compare conventional release ISMN with once-daily formulations. The results from two studies do suggest that compliance is improved by once daily ISMN compared with standard ISMN in asymmetric dosage but the small numbers involved coupled with the problems of reliably measuring compliance make interpretation of the results difficult. Other studies have questioned the view that once-a-day equates with optimum compliance. A recent review concluded that no one ISMN preparation is superior to another (when taken as prescribed) and that the choice of formulation should be made on the basis of convenience, compliance and cost. Furthermore, the SIGN guideline “Management of Stable Angina” (currently in a draft form) recommends that “ISMN in an eccentric twice daily dosage is the preferred regimen”.

In conclusion

Following publication of the Accounts Commission’s report, the Tayside Area Drug & Therapeutics Committee issued the following advice in the Tayside Prescriber Supplement, No. 7, December 1999.

- Any patient to be commenced on ISMN, within either primary or secondary care, should be considered for standard ISMN prescribed twice daily as the first-line treatment.
- Any patient being admitted to hospital on an ISMN formulation (being either the standard or slow release formulation) should remain on that particular formulation for the duration of their hospital stay and at discharge, if clinically appropriate.

Indications for the use of once daily ISMN slow release capsules or tablets include cases where poor control of angina symptoms is thought to be related to compliance problems and where a once daily dose is considered to help. Where patients are prescribed the standard formulation, the need for careful patient counselling is further stressed. Patients should be advised to take a morning dose followed by a further dose 7 hours later i.e. during late afternoon and by teatime at the latest. Note that those with mainly nocturnal symptoms may require a night-time dose with the “low nitrate” interval during the following day.

It would now seem appropriate to prescribe ISMN as a standard formulation in a twice daily asymmetric dosage regimen in the majority of patients.

References