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Hypertension: New Aspects of an Old Problem

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Elevated arterial pressure is a major cause of cardiovascular morbidity and mortality worldwide[1]. Despite its importance, blood pressure control rate is poor in most countries including the USA[2] despite guidelines. Through publication of large-scale randomised controlled clinical trials, it is becoming increasingly clear that the magnitude of blood pressure reduction is of paramount importance. Indeed, the threshold of blood pressure target has been reduced from 160/90 mmHg to 140/90 mmHg and this target should be even lower in at risk patient populations such as those with diabetes and/or chronic renal disease. Usually, combination anti-hypertensive therapy is required to achieve blood pressure target.

Current discussion on the management of hypertension is not so much about what is the best anti-hypertensive drug to initiate, but rather what is the best combination to achieve blood pressure target. The Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA) study goes a long way in addressing this issue[3]. In this large-scale randomised controlled trial of over 19,000 hypertensive patients (with > 3 other risk factors), it has been shown that for only marginally superior levels of blood pressure reduction(2.7/1.9mmHg), amlodipine with added perindopril as required (amlodipine-based regime) was superior to atenolol with added bendroflumethiazide as required (atenolol-based regime) in reducing cardiovascular events and total mortality over a period of 5.5 years. The results of this landmark hypertension trial suggest that new drug combination (Calcium channel blocker (CCB) plus angiotensin-converting enzyme (ACE) inhibitors) may be superior to old drug combination (beta-blockers plus thiazide). While the outcome of this study is well known, the mechanism underlying this beneficial effect is not fully appreciated. In the recently published ASCOT sub-study, The Conduit Artery Function Evaluation (CAFE) study, over 2100 patients were included from the ASCOT cohort[4]. Central aortic pressures were assessed using pulse wave analysis. Intriguingly, despite similar brachial blood pressure reduction between groups, there was substantial reduction in central aortic pressure with the amlodipine-based regime compared to the atenolol-based regime. Central aortic pressure is largely determined by conduit vessel stiffness and pressure wave velocity. It is likely that CCB in combination with ACE inhibitors have favourable effects on arterial stiffness and pressure wave velocity shifting to more distal site through vessel remodelling as supported by experimental studies. This mechanism may contribute to the superior cardiovascular outcome observed among those allocated the amlodipine-based regime in the ASCOT study.

One limitation of all existing hypertension trials comparing different drug classes is the relative short study duration. Most studies do not exceed 5 years. Hence it does not take into account of the impact of new-onset diabetes, new-onset albuminuria and new-onset atrial fibrillation which are important risk factors or predictors for cardiovascular disease. There is accumulating evidence that treatment

with ACE inhibitors or angiotensin receptor blockers (ARBs) is associated with a substantial reduction in new-onset diabetes (by 23-27%)[5], compared with beta-blockers and CCBs. This metabolic benefit may be translated into even greater reduction in cardiovascular mortality over much longer time for a life-long condition. The recent updated recommendations for management of hypertension issued by the UK's National Institute for Health and Clinical Excellence (NICE) in collaboration with the British Hypertension Society (BHS) suggests ACE inhibitors (or ARB) (A) is more likely to produce benefit in young hypertensives (age < 55 years) whereas CCB (C) or diuretics (D) should be considered for older hypertensives (age > 55 years) with A+C or A+D as a next step and then with A+C+D as the subsequent step-up treatment[6]. Beta-blockers are relegated to step 4 given their lack of efficacy in terms of stroke prevention seen in a recent meta-analysis[7].

In this modern era of medical advances with vast research evidence and therapeutic excellence, prevention of cardiovascular complications from poorly controlled hypertension should be largely achievable. It is time to identify the obstacles!

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Angiotensin Receptor Blockade and New-onset Atrial Fibrillation: Beyond Blood Pressure, Beyond End-organ Protection

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Pharmacological interruption of the renin-angiotensin system (RAS) has emerged over the last few years to be an important therapeutic strategy in the management of hypertension in the presence of compelling indications such as left ventricular hypertrophy (LVH), albuminuria and diabetic nephropathy[1-5]. The notion that blockade of the RAS provides end-organ protection above and beyond blood pressure reduction is well established although it has been challenged by a recent meta-analysis[6]. Additional benefits in using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) include a reduction in new-onset diabetes and more recently, new-onset atrial fibrillation[7]. These additional metabolic and anti-arrhythmic benefits are likely to result in much greater reduction in cardiovascular morbidity and mortality in the long-term management of hypertension. This article specifically focuses on the effects of ARBs in prevention of new-onset AF.

New-onset atrial fibrillation: clinical trial evidence

Atrial fibrillation (AF) is the commonest arrhythmia observed in clinical practice and hypertension is a major risk factor[8,9]. The development of AF in subjects with hypertension significantly increases the risk for stroke and myocardial infarction[10]. Prevention of new-onset AF in hypertensive individuals is therefore an important intermediate goal in reducing cardiovascular disease. Four important clinical trials using different ARBs have provided some evidence that this class of anti-hypertensive therapy (and ACE inhibitors) may provide additional benefits beyond blood pressure reduction and beyond end-organ protection.

Irbesartan - Madrid et al., 2002

Early evidence came from a Spanish group who studied patients with pre-existent AF (n=154)[11]. All patients were previously converted to sinus rhythm by cardioversion. Approximately 42% of these individuals had hypertension. These patients were subsequently randomised to amiodarone or amiodarone plus irbesartan (150/300mg titrated against blood pressure). Concomitant medication was similar between groups with the exception that more patients were on beta-blockers in the irbesartan group (15 v 7, P=0.086). Over a period of 254 days (median, range 60-710 days), patients treated with irbesartan had a greater probability of remaining free of AF (79.5% vs 55.9%, P=0.007)[11]. This study is limited by a relatively small sample size and very wide range of follow up period. Nevertheless, it has provided early clinical evidence that ARBs might prevent AF.

Valsartan - Val-HeFT, 2005

In this study[12], the occurrence of AF was evaluated based on adverse event reports in patients (n=4395) with heart failure enrolled into the Val-HeFT study. Over a mean follow up period of 23 months, patients randomised to valsartan therapy had significantly reduced risk (relative risk reduction =37%) in development of AF than those randomised to placebo (5.12% vs 7.95%, P=0.0002). Interestingly, brain natriuretic peptide (BNP) level at baseline was the strongest independent predictor of AF development. Furthermore, the occurrence of AF during follow up significantly worsened the prognosis in patients with heart failure[12]. One weakness of this study was the fact that the effect of valsartan on incidence of AF was not pre-specified in the study protocol.

Candesartan - CHARM, 2006

In the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program, 7601 patients with symptomatic CHF and reduced or preserved left ventricular systolic function were randomised to candesartan (target dose 32 mg once daily, mean dose 24 mg) or placebo[13]. Unlike Val-HeFT study, the incidence of new AF was a prespecified secondary outcome. There were 6446 patients (84.8%) who did not have AF on their baseline electrocardiogram. Over a median follow-up period of 37.7 months, 392 (6.08%) developed AF, 177 (5.55%) in the candesartan group and 215 (6.74%) in the placebo group (odds ratio 0.812, 95% CI 0.662-0.998, P = .048). Thus this study provides strong evidence that candesartan reduced the incidence of new-onset AF in a large population of patients with symptomatic CHF.

Losartan - LIFE, 2005

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study 9,193 hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy were randomised to once-daily losartan- or atenolol-based antihypertensive therapy[10]. Electrocardiograms were Minnesota coded centrally, and 8,851 patients without AF by electrocardiogram or history, who were thus at risk of developing AF, were followed for 4.8 years. New-onset AF occurred in 150 patients randomised to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, P < 0.001) despite similar blood pressure reduction. Significantly, patients with new-onset AF had two-, three- and fivefold increased rates, respectively, of cardiovascular events, stroke, and hospitalisation for

heart failure[10]. Thus new-onset AF and associated stroke were significantly reduced by losartan-compared to atenolol-based antihypertensive treatment with similar blood pressure reduction. Like the Val-HeFT study, new-onset AF was not a pre-specified endpoint during study design and hence its validity is not as strong as a pre-specified prospective study. Nevertheless, the above study collectively showed that ARBs may have potential anti-arrthymic properties.

Potential mechanisms

In the LIFE study, patient treated with losartan had significantly greater LVH regression than those on atenolol. This greater LVH regression with losartan may have led to reduced left atrial overload and dilatation, thereby reducing stimuli to new-onset AF. In addition, animal studies have shown that ARB therapy reduces atrial fibrosis, a structural change that predisposes to the development of AF[14]. An important mechanism in AF induced by atrial pacing is shortening of the atrial effective refractory period (AERP). This phenomenon of electrical remodelling increases the inducibility of AF[15]. There is experimental evidence that the ARB, candesartan, prevents AERP shortening during rapid atrial pacing[16] thereby may contribute to the prevention of new-onset AF. Hence, RAS blockade appears to have beneficial effects on both electrical and structural remodelling which leads to prevention of AF.

Future directions

There is now emerging evidence from animal and human studies that ARB therapy prevents new-onset AF. Although results obtained from the few clinical studies were mostly post-hoc analysis, the findings are encouraging and appear to be most beneficial in patients with LVH and heart failure. Future prospective clinical studies and mechanistic studies are required to elucidate the pharmacological mechanisms responsible for such beneficial effects, the optimal doses of therapy required and to define the appropriate patient population who would benefit most from RAS blockade.

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Treatment of Elderly Hypertensive Patients with Angiotensin Receptor Blockers

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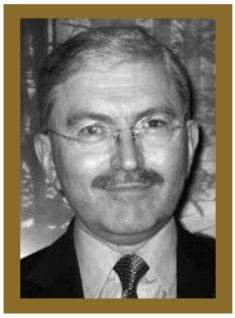

Prof. Brian Tomlinson

Hypertension in the elderly

In most developed populations, hypertension is common and the prevalence increases with age so that in people over 65 years usually at least two thirds will have hypertension, and it is a major independent risk factor for vascular disease. The relationship between increasing systolic blood pressure and the relative risk of stroke, particularly haemorrhagic stroke, is steeper than that for coronary events.[1-4] A recent meta-analysis of data from one million (40-89 years) adults showed that at all ages, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.[5]

Although trials in the elderly have shown that antihypertensive therapy can reduce the risk of vascular events, there has been continued debate over which type of antihypertensive agent is most appropriate for first line therapy. However, the realisation that most patients will require combination therapy[2] and the recent recommendation that if the blood pressure is >160/100 mm Hg or >20/10 mm Hg above the goal, then therapy should be initiated with a combination of two agents [1] makes the choice of combinations just as important as single drug first line therapy. Furthermore, the elderly represent a special group because of a higher frequency of concomitant conditions and organ damage related to hypertension and a greater requirement for multiple drug therapies that increase the risk for adverse drug reactions and problems with drug compliance.

The renin-angiotensin-aldosterone system (RAAS) is integrally involved in maintaining normal haemodynamic status, and angiotensin II contributes to atherogenesis and end-organ damage. Blockade of the RAAS with angiotensin-converting enzyme inhibitors (ACEIs) has proved useful in the treatment of hypertension and related vascular disorders. However, limitations, have been found with these agents, particularly the high incidence of cough, due in part to bradykinin or prostaglandin accumulation, and in rare cases, angio-oedema.[6,7] The angiotensin receptor blockers (ARBs) act at the final step of the pathway selectively inhibiting the angiotensin II type 1 receptor subtype. The role of the ARBs in treating high blood pressure and end-organ damage in older patients is summarised briefly below. A more detailed summary can be found in the review by Thomas et al.[8]

Relative blood pressure lowering efficacy amongst ARBs

Comparisons between different ARBs have generally been small short term studies with inconsistent findings. Meta-analyses of randomised, placebo-controlled trials involving over 12,000 patients treated with losartan, valsartan, irbesartan and candesartan found a mean absolute reduction of systolic/diastolic blood pressure of 10.4-11.8/8.2-8.9 mm Hg and there was no significant difference in blood pressure-lowering efficacy between any of these agents when used as monotherapy.[7] Despite the reduced activation of the circulating RAAS in the elderly, overall reductions in blood pressure with ARBs are similar to those with other classes of antihypertensive agent in both young and elderly patients.[7] When the hypotensive effect of these agents is not sufficient, the addition of a low dose of a thiazide diuretic will have an additive or possibly synergistic effect reducing blood pressure by 16.1-20.6/9.9-13.6 mm Hg.[7]

ARB trials in the elderly

Few studies have evaluated the effect of ARB on elderly subjects. The Study on Cognition and Prognosis in the Elderly (SCOPE) examined the double-blind effects of the ARB, candesartan, compared to placebo in 4,964 patients, aged 70 to 89 years, who also received open-label antihypertensive therapy, predominantly thiazide diuretics to help control blood pressure.[9] Candesartan insignificantly (p=0.19) reduced first vascular events by 10.9%, but did not reduce myocardial infarction and cardiovascular mortality, nor did the treatment reduce significant cognitive decline or developed dementia. However, candesartan reduced non-fatal stroke by 27.8% and all stroke by 23.6% (p=0.056). Similar observations were recorded in a subgroup analysis in those patients with isolated systolic hypertension, with a significant reduction in stroke events, but not other vascular disease events.[10] This beneficial effect in stroke reduction observed in the SCOPE study is likely to be due to differences in blood pressure reduction (in favour of the ARB arm). Hence it remains unclear from this trial whether ARBs have a class effect in CVD protection.

In the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) secondary prevention study of 1405 patients

with a mean age of 68 years, blood pressure reductions in those randomised to eprosartan or nitrendipine were similar, but those receiving eprosartan had 21% less primary events, and 25% less cardiovascular and cerebrovascular events.[11] Hence there is some evidence that ARBs might have a class effect in secondary stroke prevention. Clearly, more ARB clinical trials are required to establish its efficacy in CVD event reduction particularly in the elderly.

Clinical trials in type 2 diabetic patients with albuminuria

The prevalence of diabetes is rapidly increasing worldwide, particularly in the elderly. Furthermore, approximately 50% of diabetics from the general population have hypertension, with rates increasing in the elderly, for whom renal disease is a major cause of morbidity and mortality. The benefits of ACEIs in the treatment of Type 1 diabetic patients with albuminuria have been recognised for some time, and more recently studies have highlighted the renoprotective effect of the ARBs, which have influenced recent guidelines. The European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommend that ARBs should be used as a first line therapy for hypertension in those patients with Type 2 diabetes and proteinuria who may be controlled with monotherapy or they should be included as a component of combination therapies.[3] Similarly, the JNC-7 guidelines state that albuminuria is a compelling indication for the use of ARBs.[1] Overall, it has been recommended that ARBs should be added in patients with continued hypertension or proteinuria despite ACEI therapy in diabetic and non-diabetic renal disease.[12]

ARBs and new-onset diabetes mellitus

Hypertensive patients are at increased risk of developing diabetes. Inhibition of the RAAS appears to reduce the risk of developing diabetes. This has been seen in a number of trials using ACEIs and with ARBs and may represent an additional benefit which would only be seen with trials extending over a longer period than is usual in studies comparing antihypertensive drugs.[8,13-18] This issue is particularly relevant in the elderly who are at increased risk of developing diabetes as the function of pancreatic beta-cells declines with age.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an important independent predictor for vascular disease and the prevalence increases dramatically with age. A meta-analysis of treatment effects on LVH found that left ventricular mass index (LVMI) decreased by 13% with ARBs, 11% with calcium antagonists, 10% with ACEIs, 8% with diuretics, and 6% with beta-blockers.[19] The effects of beta-blockers were significantly less than ARBs, ACEIs and calcium antagonists. In the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial in patients with essential hypertension and LVH, losartan-based therapy induced greater reduction in LVMI than atenolol-based treatment and this was thought to contribute to the better clinical outcome particularly with regard to stroke with the ARB-based therapy.[20] In a subgroup of the LIFE study with isolated systolic hypertension with a mean age of 70 years, losartan similarly significantly reduced cardiovascular and cerebrovascular mortality more than in those receiving atenolol.[21] Additionally, in a subgroup of diabetic patients with LVH and nephropathy, with a mean age of 60 years, losartan was found to have reduced mortality levels to those inpatients without LVH.[22]

ARBs in heart failure

Heart failure is a common consequence of hypertension in elderly patients. Activation of the RAAS and sympathetic nervous system are important in the pathogenesis of progression of chronic congestive heart failure. In patients with heart failure who are not taking ACEIs, treatment with ARBs improves mortality and morbidity.[1,3] Most patients with moderate or severe heart failure do not have hypertension but in patients with both conditions, ACEIs are the preferred treatment because of their well established efficacy.[23] The use of ARBs in addition to ACEIs is also supported in some studies. For instance, in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) patients with chronic heart failure on ACEIs (CHARM-Added) also showed a significant (p=0.021) reduction of 16% in cardiovascular death with candesartan compared to placebo, but this benefit was not seen with the combination of valsartan and captopril in patients with left ventricular dysfunction after acute myocardial infarction.[24]

Adverse effects of ARBs

The rate of adverse events with ARBs is similar to that seen in the placebo groups and significantly lower than in those groups receiving ACEIs and this may result in improved compliance.[8,13-18] Common side effects include headache, dizziness or fatigue and the dry cough found with ACEIs, which seems more common in some Asian populations,[6] is no more frequent with ARBs than with placebo.[8,13-18] The side effects of most concern involve renal function deterioration, hyperkalaemia and hypotension. With both ARBs and ACEIs slight increases in plasma creatinine up to 20% can be expected; but greater increases may be indicative of volume depletion or renal artery stenosis.[8,13-18] ARBs have been used without adverse effect in renovascular hypertension secondary to unilateral renal artery stenosis but ARBs should be avoided in patients with bilateral renal artery stenosis. It is always advisable to check the renal function and serum potassium soon after starting ARBs treatment, particularly in the elderly to check for deterioration in renal function or changes in plasma potassium. The ARBs may be less likely than ACEIs to cause an acute reduction in glomerular filtration because ARBs appear to increase renal blood flow more than ACEIs in hypertensive patients.[25,26]

Despite the finding that most of the ARBs show somewhat higher plasma concentrations in the elderly compared to younger people, the ARBs generally do not require a dose-adjustment for elderly patients per se, partly because the elderly are slightly less responsive to drugs which inhibit the RAAS. However, in patients with moderate hepatic impairment generally all the ARBs except irbesartan and eprosartan require a reduction or limitation in dose, and in patients with severe renal impairment olmesartan should be used at a maximum dosage of 20 mg but the dosage of other ARBs does not have to be reduced.

Very few drug interactions of clinical significance have been seen with the ARBs, but telmisartan increases median trough digoxin levels by 20% so digoxin doses may have to be adjusted.[17] Concomitant use of ACEIs, spironolactone, the other potassium-sparing diuretics, or potassium supplements may lead to increases in serum potassium, especially in the presence of declining renal function in the elderly. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors decrease the antihypertensive effects of ACEIs and ARBs and may interact resulting in renal insufficiency and hyperkalaemia. The risk of this may be less with ARBs than with ACEIs but this combination should be used with caution.

Drug selection considerations

The ARBs represent one of the classes of drugs which can be used to treat hypertension in the elderly as either monotherapy or in combination with other classes of anti-hypertensive drugs.[2,3,8,13-18] Some guidelines suggest diuretics or calcium channel blockers may have advantages in the elderly because of their efficacy in reducing systolic blood pressure and the evidence that they improve cardiovascular outcomes.[2,3] In patients with hypertension and concomitant heart failure, ACEIs are still considered the first line therapy and ARBs should be reserved for those patients that do not tolerate ACEIs or as an additional treatment if considered appropriate. The most recent guidelines recommend that ARBs should be considered as first line therapy or as part of a combination in diabetics with microalbuminuria or overt nephropathy.[1-3] ARBs should also be considered for elderly patients with hypertension and LVH as they have been shown to be superior to beta-blocker based regimens in such high risk subjects and are especially useful in preventing stroke. Their excellent tolerability with few side effects and effectiveness in once daily dosing, offer distinct advantages over many of the older drugs and should improve compliance. This is particularly useful in elderly patients who are more likely to have concomitant diseases or be taking other drug treatments.

The ARBs appear to be a useful treatment for both uncomplicated hypertension and when hypertension is associated with complications in older patients, particularly those who have side effects when taking ACEIs. Although, the higher cost of the ARBs is a disadvantage, this may be offset when the costs related to side effects and non-compliance are taken into account.

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Endocrine Hypertension- Strategy for Screening and Workup

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2006.

Hypertension is one of the common chronic diseases affecting one fourth of the population worldwide.[1] Recent epidemiology studies showed that worldwide hypertension contribute around 20% of the risk in myocardial infarction.[2] Traditionally, less than 5% of hypertension was thought to be due to secondary causes and there has been much controversy in whether it is worthwhile to screen for secondary causes of hypertension.[3,4] However, recent studies showed a much higher prevalence of secondary causes, although different studies yielded different results due to different target populations, different settings and different methodologies in detection of secondary causes.[5,6] The importance of diagnosing secondary hypertension lies in the fact that it may convert an incurable disease into a potentially curable disease. Even if the underlying disease may not be curable, being able to offer disease specific treatments will often make blood pressure control much easier. Furthermore, the underlying diseases often confer damages beyond effect of high blood pressure alone and hence need specific treatment by itself. This article will discuss endocrine causes of hypertension and the strategy for screening.

Common causes of endocrine hypertension are listed in Table 1. Running through the list of causes, it is not difficult to notice that most of the causes either affect the adrenal or the pituitary gland. The most common causes of secondary hypertension is primary hyperaldosteronism.[5,7] The renin-angiotensin-aldosterone(RAS) system is an important system in the regulation of intravascular volume as well as the blood pressure. RAS system will be activated in the case of intravascular volume depletion such as dehydration and acute blood loss. The activated system will cause vasoconstriction and resorption of Na. There will be urinary loss of potassium due to exchange with Na during the resorption process. However, in patients with primary hyperaldosteronism, there is partial/complete autonomous secretion of excess aldosterone. This will cause hypertension, hypokalaemia and alkalosis. The signs and symptoms of primary hyperaldosteronims are mostly non-specific, although some patients may present with symptoms of severe hypokalaemia such as paralysis or muscle ache.[8] Quite often, the only clue to the diagnosis is unprovoked hypokalaemia in the presence of hypertension. Spot renin or aldosterone has limited value due to their diurnal variation in level, change in respond to posture and interference by concomitant antihypertensive drugs.[9-11] With recent advances in the screening method using renin-aldosterone ratio, which is less affected by concomitant anti-hypertensive medications, we gain much deeper understanding of primary hyperaldosteronism. There has been a number of studies trying to address the prevalence of primay hyperaldosteronism using renin-aldosterone ratio alone or in combination with aldosterone concentration as a screening tool. However, it should be noted that these studies were conducted in quite different settings, using different methodologies and using different cut-off points in the ratio. Some studies were done at primary care settings,[15,18,19] while more were done in referral centres.[12,14,16,17] Some studies standardised the anti-hypertensive medications,[13] while others have the renin-aldosterone ratio checked without any change in anti-hypertensive medications.[12,17] Different cutoff points have been adopted in different studies, mostly ranging from 20-30(ng/dl)/(ng/ml/hour).[13,17] Lastly, different methods have been adopted to confirm the diagnosis. Due to large differences in methodology, we would expect a large variation in the prevalence of hyper-aldosteronism. However, taking a glance at the studies, it is not difficult to realize that the prevalence of primary hyperaldosteronism is around 5-13%, which is much higher than previous reported.

Take the study by Loh et al as an example,[17] using renin aldosterone ratio of 20 (ng/dll)/(ng/ml/hour) with aldoterone concentration greater than 15 ng/dl as cutoff points, it detected a prevalence of primary hyperaldosteronism as 4.6%. Similar cutoff points have also been adopted by the Mayo Clinic. It should be noted that anti-hypertensive medications were not changed at the time of screening and that the initial screening yielded a high rate of 18% suspected primary hyperaldosteronisms although only 4.6% were confirmed eventually, a relatively low positive predictive rate. Using similar methodology but with adjustment of antihypertensive drugs to minimise possible interference with screening, study by Stowasser M et al at referral settings found a high prevalence of confirmed primary hyperaldosteronism up to 18%. One interesting point is that the initial screening rate is 19.6%, therefore a much high positive predictive rate.[13] The differences in these two studies

can be due to difference in prevalence in primary hyperaldosteronism in the respective population, or more likely, due to lower specificity in the absence of adjustment in concomitant medications. Furthermore, it should be noted that around half of the confirmed primary hyperaldosteronism patients have normal potassium level and therefore serum potassium level is not a sensitive enough tool for detecting hyperaldosteronism.[13, 17]

Methods for confirming the diagnosis of primary hyperaldosteronism also vary with different centres. The more commonly adopted methods include the saline suppression test, oral salt loading test, and fludrocortisone suppression test.[20-22] Recent studies showed that the saline suppression test may be as reliable as fludrocortisone suppression test and is more convenient to be conducted at out-patient setting.[22] After biochemical confirmation of the diagnosis, we need to find out the exact aetiology of primary hyperaldosteronism. The main issue is to differentiate adrenal adenoma from bilateral adrenal hyperplasia. The exact aetiology will be further differentiated using CT scan, MRI scan and iodocholesterol scan. Postural response of aldosterone also gives hint to the underlying aetiology.[23-27] CT scan is the most often arranged investigation because of its wide availability and reasonable accuracy,[23] although some studies showed a rather low sensitivity.[26] The main problem in imaging is that there is significant proportion of adrenal incidentaloma, and therefore, the presence of adrenal mass even in the presence of hypertension does not necessarily point to primary hyperaldosteronism.[27] On the other hand, normal adrenal imaging does not exclude primary hyperaldosteronism since bilateral adrenal hyperplasia may not be well shown on imaging and small adenoma may not be detected by CT alone.[24, 28] In difficult cases with high suspicion of adrenal adenoma but normal CT, we may have to resort to adrenal venous sampling.[13, 24, 28] Some authorities even suggested that venous sampling should be done in all cases with confirmed hyperaldosteronism.[28] For confirmed cases of aldosterone producing adenoma, the best treatment is adrenalectomy.[29] With recent advances in the technology of laparascopic adrenalectomy, the operation has been made much less invasive and hospital stay has been much shortened.[30] For patients with bilateral adrenal hyperplasia or who refuse surgery, they should be treated medically with aldosterone receptor antagonist, aldosterone.[31, 32] However, aldosterone may be limited by its side effects, namely gynaecomastia, decreased libido and menstrual problems.[33] With surgical excision of adrenal adenoma, there is around 60% chance that the patient can be taken off antihypertensive medications. Other patients can usually have the number or dose of anti-hypertensive medications decreased. Hypokalaemia is often cured. The blood pressure control is usually improved in those receiving medical treatment.[13, 34]

With the wide spread use of renin-aldosterone ratio as a screening tool, there is increased prevalence of primary hyperaldosteronism over the last few decades. The pattern of disease seems to change as well. Before 90s, the predominant lesion of primary hyperaldosteronism was aldosterone-producing adenoma. However, after 90s, bilateral adrenal hyperplasia accounted for a much higher proportion.[35] Furthermore, we now realize that only around 50% of patients with primary hyperaldosteronim have hypokalaemia.[35, 13, 17] All these raise the possibility that we are now detecting milder cases which do not need specific intervention and raise the question of cost-effectiveness in screening. Looking at the previous series, non-selective screening only yielded about 2-5% of potentially curable adenoma among all subjected screened.[13, 17] However, the screening strategy led to an improvement in blood pressure control in 16% of the subjects with the disease specific treatment, a much lower and more acceptable number needed to be treated from a screening perspective.[13] Furthermore, aldosterone receptors present not only in the kidney, but also in the heart, brain and blood vessels. Presence of excess aldosterone leads to myocardial fibrosis. Therefore, hyperaldosteronism may have deleterious effects beyond hypertension and hypokalaemia.[36] All these speak for more aggressive screening for primary hyperaldosteronism. However, large scale randomised trials are needed to answer the question of cost-effectiveness in the screening strategy of primary hyperaldosteronism more definitively.

The presence of excess glucocorticoid is known as Cushing's Syndrome. The clinical features of Cushing's Syndrome almost involve all parts of the body; the more commonly found clinical features include central obesity, facial plethora, hypertension, easy bruising, glucose intolerance, etc.[37] Although hypertension is a known feature of Cushing's Syndrome, the prevalence of Cushing's Syndrome in hypertension is only 1%.[5,6] Furthermore, unlike primary hyperaldosteronism, patients with Cushing's Syndrome are often symptomatic, therefore mass screening for hypertension subjects are often not needed. The difficulty in diagnosing Cushing's Syndrome lies in that most of the clinical features are commonly found in subjects without the disease, such as people with obesity, as well. Previous studies showed that bruising, plethora, and myopathy have highest differential value among all the clinical features.[38] Furthermore, we should never forget that the one of the common causes of Cushing's Syndrome is exogenous Cushing's.[39] Therefore, a careful medical history is mandatory, especially for those with skin and joint problems. Over the counter drugs is another possible source of steroid apart from doctor's prescriptions. If exogenous Cushing's is suspected, short synacthen test should be performed to assess adrenal cortisol reserve and proper physiological glucocorticoid replacement is important[40]. For endogenous Cushing's Syndrome, the commonly employed screening tests are overnight dexamethasone suppression test and 24 hour urinary cortisol excretion.[41, 42] A morning cortisol level greater than 54 nmol/l after taking 1 mg dexamethasone at midnight or urinary cortisol excretion greater than normal range raises the suspicion of Cushing's Syndrome. In our experience, overnight dexamethasone suppression is much more convenient as the patient does not need to comply with complete collection of urine sample over 24 hours, which can be quite cumbersome. However, one should be aware of concomitant medications such as anti-epileptic or anti-tuberculosis drugs which will affect the validity of tests.[43, 44] Endogenous Cushing's Syndrome can be confirmed with low-dose dexamethasone suppression test with CRH stimulation.[45, 46] A base line ACTH is often done at the same time of low dose dexamethasone suppression. A suppressed ACTH points to the underlying cause as adrenal in origin while a normal or raised ACTH points to ACTH dependent Cushing's

Syndrome, which is usually pituitary in origin or due to ectopic ACTH. The underlying disease is usually further localised with imaging of the respective site, namely CT adrenal or MRI pituitary.[47] It should be noticed that MRI pituitary can only pick up less than 70% of pituitary Cushing's,[48] and therefore a normal MRI pituitary does not rule out the disease. On the other hand, pituitary incidentaloma can confuse the clinical picture.[49] The treatment of Cushing's Syndrome usually aims at cure by resection of the tumour. However, the details of treatment are beyond scope of this article.

Phaeochromocytoma is a rare cause of hypertension. It is estimated to occur in less than 0.2% of hypertensive population.[50] It originates from the chromaffin tissues of sympathetic nervous system. It is a disease which is very difficult to diagnose. Post-morten series showed that around one third of patients who die from phaeochromocytoma have their disease unsuspected during lifetime.[51] Although it is a very rare disease, proper diagnosis and management is very important. With correct diagnosis and proper management, phaeochromocytoma is potentially curable. However, misdiagnosis and improper management can be potentially fatal.[52] Most of phaeochromocytoma are sporadic cases. However, a small proportion are associated with genetic diseases such as MEN IIa and IIB, von-Hippela Lindau Sydrome and neurofibromatosis.[53,54] Around 90% of phaeochromocytomas are unilateral and found within adrenal gland. However, around 10% of phaeochromocytomas are extra-adrenal and bilateral. The most typical clinical features of phaeochromocytomas are hypertension, headache, palpitation and paroxysms.[51, 55] However, none of these features are specific and can mimic anxiety. Therefore, the correct diagnosis often relies on a high index of suspicion. Methods of screening for phaeochromocytoma differ between different centres. The often-employed methods include urinary cateholamine, plasma catecholamine, urinary metanephrine and plasma fractionated metanephrine. So far, plasma fractionated metamephrine seems to be the most promising method, but is limited by local availability.[56, 57] It should be realised that some drugs such as methydopa and labetalol, acute sepsis or obstructive sleep apnoea may either interfere with the assay or cause acute rise in sympathetic activity and affect the accuracy of the biochemical diagnosis. Phaeochromocytomas are often localized by CT and MRI examination. Both CT and MRI have very high sensitivity, but the specificity is limited by incidentaloma as previously discussed. In this regard, MRI is more specific tool but is limited by its cost. MIBG scan is especially useful in detecting extra-adrenal involvement of phaeochromocytoma.[58] The definitive treatment for phaeochromocytoma is surgical excision. The mortality of operation was very high in the old days, up to 24-50% in some old series. With introduction of alpha and beta blockade before operation, the survival of the operation has rise up to 97-100%. Agents used for alpha and beta blockade include phenoxybenzamine, prazosin, propanolol, metoprolol, labetalol.[59] It should be remembered that unopposed beta-blocker in the case of phaeochromocytoma is very dangerous and can be fatal.[52]

Acromegaly, congenital adrenal hyperplasia, etc are rare causes of secondary hypertension and will not be discussed in detail in this article. Acromegly is characterised by coarse facial feature, spade like hand, protruded jaw, which can be recognised clinically. However, it has a slow disease course and hence the diagnosis is usually delayed. The diagnosis can be as late as 10 years after onset of symptoms.[60] Only the rare type of congenital adrenal hyperplasia including 11-OH and 17-OH congenital adrenal hyperplasia will cause hypertension due to excess activity of 11-deoxycorticosteroid. The hint is usually hypertension at very young age, hypokalaemia and is associated with problems of sexual characteristics.[61, 62]

Table 1. Endocrine causes of hypertension

Primary hyperaldosteronism
Cushing's Syndrome
Phaeochromocytoma
Acromegaly

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Endocrine Hypertension-Strategy for Screening and Workup" by Dr Wing-bun Chan and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2006. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. What is the estimated attributed risk of hypertension to myocardial infarction worldwide?
a. 5%
b. 10%
c. 20%
d. 30%

2. What is the prevalence of hypertension worldwide?
a. 5%
b 15%
c. 25%
d. 35%

3. Which of the following is not an endocrine cause for hypertension?
a. Cushing's Syndrome
b. Renal artery stenosis
c. Hyperaldosteronism
d. Phaeochromocytoma

4. Which of the following is the most common causes of endocrine hypertension?
a. Primary hyperaldosteronism
b. Cushing's Syndrome
c. Phaeochromocytoma
d. Acromegaly

5. Which of the following is the clinical feature of hyperaldosteronism?
a. Hypertension
b. Hyperkalaemia
c. Alkalosis
d. All of the above

6. Which of the following is the best screening method for primary hyperaldosteronism?
a. Young onset hypertension
b. Hypokalaemia
c. PAC/PRA ratio
d. CT adrenal

7. After successful resection of adrenal adenoma in primary hyperaldosteronism, what proportion of hypertensive subjects can be taken off anti-hypertensive medication?
a. 10-20%
b. 20-30%
c. 50-70%
d. 90-100%

8. Which of the following is not a good differential clinical characteristics in the diagnosis of Cushing's Syndrome?
a. Menstrual disturbance
b. Easy bruising
c. Myopathy
d. Plethora

9. Which of the following drugs can interfere with overnight dexamethasone suppression test?
a. Rifampicin
b. Carbamazepine
c. Phenytoin
d. All of the above

10. Which of the following drugs cannot be used alone to control the blood pressure of patients with phaeochromocytoma?
a. beta-blocker
b. calcium channel blocker
c. thiazide diuretic
d. ACEI

ANSWER SHEET FOR OCTOBER 2006

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2006 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Endocrine Hypertension-Strategy for Screening and Workup

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Answers to September 2006 issue

Comparison of Various Biological Agents in the Treatment of Psoriasis

1. A 2. D 3. D 4. D 5. E 6. A 7. D 8. C 9. D 10. C

Reaching Target Goals in the Treatment of Dyslipidaemia

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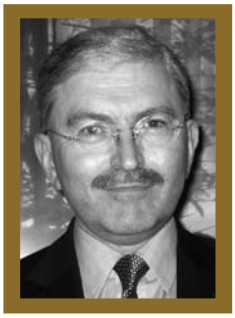

Prof. Brian Tomlinson

Dr. G Neil Thomas

The large clinical trials of LDL-cholesterol lowering conducted over the past decade have demonstrated that therapy with various statins (3-hydroxy-3-methylgluatryl coenzyme A reductase [HMG CoA] reductase inhibitors) is a highly effective and well tolerated treatment for reducing cardiovascular morbidity and mortality. These studies have consistently shown that there is a direct relationship between the magnitude of the reduction in LDL-cholesterol levels and the reduction in CHD risk and furthermore, the clinical benefits of statin therapy are largely independent of the baseline levels of LDL-cholesterol.[1,2] Thus, significant reductions in the relative risk of cardiovascular events have been observed among patients whose baseline concentrations of total and LDL-cholesterol were close to or within the so-called normal range. Based on these results there has been a revision of treatment guidelines to reduce CHD risk in patients with dyslipidaemia or other risk factors for cardiovascular disease. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommended modifications to the earlier treatment algorithm so that for very high risk persons, an LDL-cholesterol goal of <1.8 mmol/L (70 mg/dL) is a therapeutic option, and this therapeutic option extends also to patients at very high risk who have a baseline LDL-cholesterol <2.6 mmol/L (100 mg/dL).[3] For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-cholesterol goal is <3.4 mmol/L (130 mg/dL), but an LDL-cholesterol goal <2.6 mmol/L (100 mg/dL) is now a therapeutic option on the basis of recent trial evidence. In the European Joint Task Force guidelines, target LDL-cholesterol levels in patients with clinically established cardiovascular disease and/or diabetes mellitus were reduced from <3.0 mmol/L (115 mg/dL), recommended in their 1998 publication[4] to <2.5 mmol/L (100 mg/dL) in their current guidelines.[5]

Even before these more aggressive lipid treatment guidelines, surveys in the USA showed that many high risk patients did not achieve LDL-cholesterol target levels.[6] Similar results were found in the European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE II) study, which showed that approximately 50% of high-risk patients in Europe were not achieving the goal for LDL-cholesterol set in the previous European Guidelines in 2001.[7] Some of the explanations for the shortfall in LDL-cholesterol goal attainment include selection of lipid-modifying therapy with inadequate efficacy, poor patient compliance, and reluctance to titrate to higher doses.[8-10] In light of the clear evidence that CHD risk reduction is contingent upon effective reduction on LDL-cholesterol there is a need to educate both physicians and patients in this respect.

Statins and efficacy in LDL reduction

Considering that the starting dose of statin should be sufficiently effective to achieve the lipid goal in the majority of patients, rosuvastatin is the most effective of all the statins in reducing LDL-cholesterol across the dose range as shown in the STELLAR study.[11] Furthermore, the Measuring Effective Reduction in Cholesterol Using Rosuvastatin therapy (MERCURY I) study found that significantly more patients treated with rosuvastatin 10 mg/day achieved the European goal (2003) for LDL-cholesterol compared with those receiving atorvastatin 10 mg/day, and this difference was particularly marked among those patients considered to be at greatest risk for coronary heart disease.[12] In a meta-analysis of pooled data from 6743 patients included in five studies from the DIrect Statin COmparison of LDL-C Values: an Evaluation of Rosuvastatin therapY (DISCOVERY) programme, rosuvastatin 10 mg was confirmed to be significantly ($p<0.001$) more effective than atorvastatin 10 mg in achieving 2003 European goals for both LDL-cholesterol and total cholesterol.[13] Rosuvastatin had a safety profile comparable with those of other statins in these and other studies.

Rosuvastatin in Asian patients

There has been some concern that the plasma concentrations and systemic exposure to rosuvastatin were found to be approximately 2-fold higher in Japanese subjects living in Japan compared with white subjects in Western Europe or the United States. Similar findings were reported in Chinese, Malay, and Asian-Indian subjects living in Singapore compared with white subjects.[14] The reason for this difference in

pharmacokinetics has not been fully established and did not appear to be related to polymorphisms in one of the drug transporter proteins studied[14] but may be related to another one known as breast cancer resistance protein (BCRP).[15] It should be noted that the variations in plasma levels and systemic exposure to rosuvastatin are greater between individuals within any ethnic group than between ethnic groups[14] so the advice to restrict the dose to a maximum of 20 mg daily in Asian patients is not entirely rational.

Despite these differences in pharmacokinetics between Asians and western subjects there does not appear to be any difference in efficacy or safety with rosuvastatin. Studies in Japanese patients with hypercholesterolaemia have shown a similar dose-response relationship to that in western patients, with reductions in LDL-cholesterol levels of 49.7% to 66.0% with rosuvastatin 10-40 mg.[16] Similar results were reported with rosuvastatin 10-40 mg in an open-label study of 37 Japanese patients with heterozygous familial hypercholesterolaemia, with significant ($p<0.0001$) reductions from baseline in LDL-cholesterol of 49.2% to 56.7%.[17] The safety of rosuvastatin is well established with a similar safety profile to that of comparator statins in data from 12,400 patients included in the multinational rosuvastatin phase II/III programme[18] and a retrospective observational study using an administrative managed care claims database covering 9 million members in the USA.[19]

Clinical implications

The benefits of aggressive lipid lowering with high doses of atorvastatin were established in the Treating to New Targets (TNT) study in in patients with stable coronary heart disease[2], the clinical endpoint study in 4162 patients who had been hospitalised for an acute coronary syndrome in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study[20] and in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study using intravascular ultrasound to measure progression of atherosclerosis[21] The REVERSAL study showed that on average a reduction in LDL-cholesterol of 50% was needed to prevent the progression of atherosclerosis. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial has now shown that high-intensity statin therapy using rosuvastatin 40 mg daily achieved an average LDL-cholesterol of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis measured by intravascular ultrasound in patients with coronary disease and this treatment was well tolerated.[22]

Clinical outcome studies with this very high-intensity LDL-cholesterol lowering are awaited. As a monotherapy for LDL-lowering, rosuvastatin is a suitable therapeutic option for reaching target lipid goals and reducing CHD risk.

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Management of Childhood Short Stature

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" The boy lives next to us is much taller than my son although they are in the same class. What happened to my son, doctor?" This is not an uncommon complaint from parents.

Short stature is actually not a disease by itself. It is only a statistically defined height threshold. It can be broadly defined as real or perceived impairment of linear growth which may result in physical, psychological or social difficulties. Medically, it is defined as height less than the 3rd percentile for age on the growth chart derived from local data.

Physiology of growth

Normal linear growth can be divided into three phases after birth: infancy, childhood and pubertal growth. They are under different regulatory mechanisms. During infancy, the growth is rapid, approximately 25cm gain in body length is achieved in the first year. However the growth rate shows a marked decrease during this period from 38cm/year in the first 2 months to 28cm/year at 4 months of age and 12cm/year at 1 year of age. In this period, nutrition plays an important role. In the second year, the height velocity is about 10cm/year. It drops to 7cm/year at 3-4 years and 6cm/year at 5-6 years. It then remains at 4-6cm/year until puberty occurs.[1,2] During childhood period, nutrition becomes less important and hormonal changes, especially growth hormone, becomes the principal regulating factor. Normal thyroid status is also important to maintain growth.

The growth accelerates again in puberty. Girls have their peak height velocity at early puberty, 9cm/year. Boys reach their peak height velocity during mid-puberty, with growth rate of about 10cm/year.[2] Activation of the hypothalamic-pituitary-gonadal axis, especially a significant increase in growth hormone secretion, is responsible for the pubertal growth spurt.

Causes of short stature

In general practice, most short stature patients have familial short stature, constitutional growth delay or a combination of both. Some have short stature following intrauterine growth retardation. Other important differential diagnoses include dysmorphic syndromes, endocrine disorders, chronic diseases and psychosocial deprivation. (Table 1)

Genetic short stature/Familial short stature

This is probably the most common cause of short stature. These patients are short throughout life and are short as adults. However, they characteristically grow at normal rates in their own percentile. It is usually obvious that one or both parents or occasionally, a more distant relative is short. Their bone age is normal. and there is no endocrine abnormalities.

Consititutional growth delay

This is characterised by a retarded linear growth occurring during the first 3 years of life, followed by normal growth that parallels the normal curve throughout the rest of the prepubertal years and a catch-up growth or growth spurt after the usual expected time of pubertal spurt. It usually occurs in boys, only occasionally in girls. Late menarche of mother or delayed pubertal spurt in father occurs in 60-90% of the cases.[3] They are normal on examination apart from slight delay in pubertal development. The bone age is characteristically delayed. The mechanism of the delay is unclear. In most patients with constitutional growth delay, there are no abnormalities in endocrine function.[4] It is easy to diagnose when there is positive family history or when the pubertal spurt starts. But it may lead to extensive investigations in some cases.

Short stature following small for gestational age (SGA)

Small for gestational age can result from foetal, placental or maternal aetiologies. Usually the symmetrical foetal growth retardation is related to early growth failure while the asymmetrical growth failure, with preservation of head growth, occurs because of late deprivation of nutrients related to placental insufficiency. For the latter group, potential for postnatal catch-up growth is reduced. Follow up studies on non-dysmorphic SGA infants indicate that all but 10-15% show catch-up growth by the age of approximately 5 years.[5] There is increasing evidence to suggest that there is an association between metabolic syndromes, adult cardiovascular disease and small for gestational age. The definition of SGA can be variable. Most people use birth weight less than 10th centile for gestation, but some would use less than the 3rd centile. Unless there is obvious reason for their low birth weight, such as chromosomal abnormalities or intrauterine infection etc, they are usually endocrinologically normal.

Dysmorphic syndromes

Every now and then, we might encounter short child

with dysmorphic features. The most common ones are Turner and Noonan Syndrome, others include Russell-Silver, Williams Syndrome etc. Children with other dysmporphic syndromes such as Down's Syndrome may also have short stature. They are often diagnosed prior to referral for short stature.

For Turner Syndrome, it is caused by complete or partial absence of one of the X chromosomes. It occurs in about 1 in 2500 liveborn girls. It is characterised by three main features: abnormal external appearance and abnormality of certain internal organs, ovarian failure and short stature. Among the three, short stature is always present, irrespective of the karotype and may be the only clinical feature. The following dysmorphic features are helpful for picking up Turner Syndrome: low hairline, web neck, wide carrying angle of arms, short 4th /5th metacarpals, and nail hyperconvexity. The diagnosis is made by karyotyping and in girls of pubertal age, elevated FSH and LH will give a clue.

Noonan Syndrome can occur in both boys and girls. It shows some of the dysmorphic features of Turner Syndrome together with ptosis, hypertelorism and low-set ears. The diagnosis is usually made clinically but about 50% showed mutation in PTPN 11 gene. Studies have shown that growth hormone injections can increase the final height of about 2 inches in Turner patients on average. It also increases growth velocity in cases of Noonan Syndrome.[6]

Endocrine disorders

Growth hormone insufficiency is the most common endocrine disorder presenting with short stature. It can be congenital due to structural defects such as septo-optic dysplasia, genetic due to GH-1 mutation or acquired secondary to CNS tumors, head injury or even transient due to psychosocial deprivation. For severe GH deficiency, it can present before 3 years old with hypoglycaemia, micropenis and obvious short stature. Usually, what we see in clinic are those mild cases who present as short stature in early primary school age. They are short with subnormal growth velocity. They typically have delayed bone age and growth hormone stimulation test showed peak GH value of <15mIU/l. One needs to be aware that GH deficiency can be isolated but it can be part of panhypopituitarism. Therefore, other hormonal axis need to be assessed before starting growth hormone therapy.

Hypothyroidism if untreated may lead to severe stunting of growth. But because of the introduction of neonatal screening, we seldom see short stature due to hypothyroidism only.

Other causes

Cushing's Syndrome is another cause of short stature. The patient is usually obese and short. There might be history of chronic illness and steroid intake. There might be physical signs such as moon face, buffalo humps, skin striae and hypertension. An overnight dexamethasone test is a useful screening test for cortisol excess.

Skeletal dysplasias such as achondroplasia, hypochondroplasia can present as short stature. Chronic paediatric diseases such as SLE, congenital cyanotic heart disease, chronic renal failure are often associated with short stature. These patients are usually managed by paediatric specialist or even followed in hospitals. One important factor needs to be considered is psychosocial deprivation. Although it is not a common cause for short stature and it is seldom severe enough to cause short stature alone, one should bear in mind during history taking because it is a reversible condition once the underlying psychological stress is removed.

Management of children with short stature

Clinical assessment of growth

Accurate measurement is of crucial importance for growth assessment. For measurement of height, a stable wall-mounted device that has been accurately installed and is regularly calibrated should be used by a well trained person. The patient is asked to stand with heels (without shoes and socks), buttocks and shoulder blades against the backplate. The measurer then applies pressure on the mastoid processes and the reading is taken at maximum extension without the heels losing contact with the baseboard. For neonates and toddlers, the measurement is often difficult. The use of supine table and neonatometer, consisting of a flat surface with a fixed headboard and moving baseplate can reduce the measurement error. Two people are necessary to get a reliable measurement. The shoulders should be pinned down and the legs are straightened. The measurement is taken when the head is still in contact with the headboard. Weight should also be taken with the subject wearing the minimum of clothing with the use of electronic bathroom-type scales.

In assessment of children with short stature, it is important to also measure the height of both parents with standiometer. After the initial measurement, the height and weight of patient are plotted on the local growth charts using decimal age. Both parents' heights are plotted on the chart as well.

History and Examination

Birth history should be asked in details including prenatal events, birth weight, gestation and any perinatal events. Parents should be asked when and how they notice their kid is short, any other family members are short and any past medical history. Family history, consanguinity, social history and school performance should be asked too, Mother's menarche and father's growth if he can remember is very important in diagnosing constitutional growth delay. Sometimes the height and pubertal history of extended family members are of help. It is then followed by systematic inquiry.

After the history, the patient should be examined for any dysmorphic features, any disproportion of body height with the help of sitting height or lower segment measurement. Neck should be examined for goitre. Pubertal development should be examined in details. Last but not least is the systematic examination.

Initial investigations

Various biochemical investigations can be performed depending on the history and examination. FSH and LH will be helpful in a girl at pubertal age to screen for ovarian failure which might be secondary to Turner syndrome. Renal function and blood count can be done if

chronic disease is suspected. Thyroid function should also be assessed. IGF-1 or growth hormone profile is usually performed once abnormal growth velocity is documented. Two growth hormone stimulation tests are required for the diagnosis of growth hormone deficiency unless there is obvious reason to account for it, such as post cranial irradiation, or post intracranial surgery in hypothalamic-pituitary region. Other dynamic tests are usually indicated when suspicion of a specific endocrine disease is strong. Bone age is essential for diagnosis of constitutional delay and growth hormone deficiency. MRI pituitary is mandatory if there are signs of hypopituitarism or confirmed growth hormone deficiency. Procedures to assess a child with short stature are summarised in Table 2.

Treatment

Most cases of short stature are due to genetic short stature and constitutional delay. Generally, they do not require any treatment unless their psychological well-being is affected. Detailed explanation and reassurance is usually enough for the patients and parents.Lots of attention is paid in paediatric endocrinology to treatment of short stature with different hormonal preparations. However, we have very limited choices of growth promoting therapies, namely growth hormones and sex hormones. And they need to be used properly to minimise their potential side effects.

In cases of severe constitutional delay, a short course of low dose of sex hormone can be used to promote pubertal development. It works well in both boys and girls. Nowadays, growth hormone is licensed for treatment of GH deficiency, Turner Syndrome, Prader-Willi Syndrome, short SGA children, short children with renal failure and lately idiopathic short stature. Before starting the treatment, detailed auxological assessment is essential to make sure that the child still has growth potential. The family must be fully committed after a detailed discussion. Growth hormone is given as a daily subcutaneous injection, usually in the evening. The dosage varies depending on the condition. For a growth hormone deficient patient, 0.5units/kg/week of growth hormone would be started initially and titrated clinically and biochemically with IGF-1 and IGFBP3. Higher dosage, 1 unit/kg/week is used in non-growth hormone deficient patients such as Turner Syndrome, SGA and idiopathic short stature. Regular assessment of height and bone age is essential for the timing of discontinuation of the treatment. After the use of recombinant GH, the complication of Creutzfeldt-Jakob disease has been wiped out. Leukaemia, once has been reported in association with growth hormone, has been demonstrated in number of epidemiological studies to have no greater incidence than general population[7-9]. Furthermore, there is no evidence that GH therapy stimulates tumour regrowth in children with cancer.[10-13]

Overall, the use of human growth hormone therapy in the management of short stature is safe with regular monitoring under a paediatric endocrine specialist.

Short stature is a common problem in our daily practice. Most of these cases need no therapy. If endocrine abnormalities are suspected, referrals to a paediatric specialist would be recommended.

Table 1. Causes of short stature

Genetic short stature
Constitutional growth delay
Combined genetic short stature and constitutional growth delay
Short stature following small for gestational age
Dysmorphic syndromes
Endocrine disorders
Skeletal dysplasia
Chronic diseases
Psychosocial deprivation

Table 2. Assessment of short stature

Height, weight, height velocity
Height of parents
Birth weight, gestation
History of short stature, past medical history
Family history of puberty, consanguinity, social history, school
performance
Systemic inquiry
Examination of dysmorphic features
Systemic examination
Pubertal development staging
Blood test if necessary (CBC, TSH, RFT, LFT)
Radiological examination if necessary (bone age)
Endocrine assessment (if indicated)

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Strontium Ranelate-An Innovative Agent for the Treatment of Osteoporosis

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Osteoporosis is one of the most prevalent health problems in Hong Kong. It has been estimated that one third of postmenopausal women and 20% of older men in Hong Kong suffer from osteoporosis.[1] Moreover, the incidence of hip fracture, which is the major complication of osteoporosis, increased by 2-3 folds in the Hong Kong population over the last 3 decades.[2]

Osteoporosis results when there is uncoupling of the functions of the Bone Metabolic Unit i.e. the activity of the osteoclasts exceeds that of the osteoblasts. Antiresorptive drugs, including the bisphosophonates and raloxifene, have been found to be efficacious in suppressing bone loss in osteoporotic patients. On the other hand, teriparitide injections could enhance bone formation and increase bone mass. A new compound-strontium ranelate-was recently shown to have both antiresorptive and bone forming effects. This could be a promising new breakthrough in the clinical management of osteoporosis.

The mechanism of action of strontium ranelate

The anti-resorbing and bone-forming effects of strontium ranelate have been demonstrated in several animal studies[3]. In mouse calvaria cultures, strontium ranelate inhibits bone resorption by around 30%.[4] Additionally, strontium ranelate decreases osteoclast activity by about 30%, as measured by pit assay in isolated rat cells.[5] Further studies indicate that strontium ranelate has positive effects on bone formation in vitro. In rat calvaria organ and cell cultures, strontium ranelate has been shown to enhance the replication of preosteoblastic cells, as well as the activity of funcational cells and bone matrix synthesis.[6]

The mechanisms of action of strontium are not fully understood, but several mechanisms are possible. Firstly, strontium was found to activate the calcium sensing receptor in some cell types, resulting in activation of inositol triphosphate production and mitogen-activated protein kinase signalling.[7] Strontium was also found to induce cyclooxygenase-2 expression and prostaglandin E2 production.[8]

Effects of strontium ranelate on bone mass

The in vitro effects of strontium ranelate are also observed in vivo. In adult mice and rats, treatment by strontium ranelate causes an increased bone mass at the vertebra and femur. [9,10] In normal adult monkeys, strontium ranelate caused a decrease in bone resorption and increased bone mineralisation in alveolar bone.[11]

Strontium ranelate was also found to be effective in preventing bone loss in osteoporotic animal models. In ovarectomized rats, strontium ranelate prevented bone loss induced by estrogen deficiency, as a result of decreased bone resorption.[12] In another study where bone loss was induced by immobilisation, strontium ranelate prevented the increased bone resorption and trabecular bone loss.

Clinical trial results on strontium ranelate

According to the principles of evidence based medicine, the results of randomised controlled clinical trials should be carefully scrutinised before drugs are recommended for use in clinical settings. The results of randomised controlled clinical trials confirm the effectiveness of strontium ranelate in increasing bone mass in osteoporotic women.

In the first clinical trial, a significant increase of 7.3% per annum was observed in women given 2g of strontium ranelate per day.[12] Moreover, the percentage of patients with new vertebral fracture was reduced by 44% in the second year of the study.

The antifracture efficacy of strontium ranelate was assessed in 2 large randomised controlled clinical trials, the Spinal Osteoporosis Therapeutic Intervention (SOTI) Trial, and the Treatment of Peripheral Osteoporosis Study (TROPOS). The SOTI Trial[15] involved 1649 postmenopausal women with osteoporosis and at least one vertebral fracture. Oral strontium ranelate (2g daily), or placebo, was given for 3 years. New vertebral fractures occurred in fewer patients in the strontium ranelate group than in the placebo group, with a risk reduction of 49% in the first year of treatment and 41 % in the 3-year period (relative risk 0.59, 95% CI 0.48-0.73). At the end of 3 years, the bone mineral density at the lumbar spine, adjusted for strontium content, showed an increase of 6.8% over the baseline.

In the TROPOS study,[16] 5091 postmenopausal women with osteoporosis were recruited. In the entire sample, relative risk was reduced by 16% for all nonvertebral fractures and 19% for major fragility fractures. In the high risk subgroup for hip fracture, the Relative Risk Reduction was 36%. The average difference between the strontium treated group and the placebo group at 3 years was

8.2% at the femoral neck and 9.8 % at the total hip. A 50% adjustment is recommended for the effects of strontium content on dual XRay densitometry measurements.

In both SOTI and TROPOS, strontium ranelate appeared to be well-tolerated, the most common side effects were nausea and diarrhoea, which disappeared after a few months.

Two clinical cases below illustrate the potential indications for using strontium:

Case 1

Mrs Cheung is a 64 years old lady with recently diagnosed established osteoporosis (According to Dual X Ray Densitometry, T score at the lumbar spine was -2.8 and T score at the hip was -2.5). She has had 3 episodes of upper gastro-intestinal bleeding, resulting from gastric ulcer, in the last 3 years.

Comments

Stronitum ranelate may be useful to treat her osteoporosis, for bisphosphonates are contraindicated due to the history of GI bleeding.

Case 2

Mrs Lee is a 59 years old lady with established osteoporosis diagnosed 2 years ago. According to dual X - Ray densitometry, her BMD was -3 at the spine and -2.5 at the hip at the time of the diagnosis. She was prescribed a bisphosphonate by her physician. Her BMD was -3.3 at the spine and -2.7 at the hip, at 12 months after drug treatment was commenced. A repeat BMD at 24 months showed a T score of -3.5 at the spine and -2.9 at the hip.

Comments

Sequential decrease in BMD may suggest that the patient is not responding to bisphosphonates. Strontium ranelate could be considered in this situation.

Conclusion

Strontium ranelate is a unique agent with both anti-resorbing and bone-forming effects. Although the exact molecular and cellular mechanisms for its mode of action remain to be established, it is useful in the treatment of osteoporotic patients.

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Anti-ischaemic Therapy in Diabetes: Focus on Trimetazidine

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Dr. Godwin TC Leung

Diabetes is a cardiovascular risk equivalent. Results from the East and West Study showed that non-diabetic patients who had a previous myocardial infarction (MI) have a similar risk of developing a future MI when compared with diabetic patients without previous MI[1]. Furthermore, diabetic patients who develop MI have a markedly higher mortality compared with patients without diabetes.[2] Diabetic patients also have a decreased awareness of myocardial ischaemic pain and hence many suffer from silent ischaemia which is associated with a reduced survival.[3,4] Because of the frequent presence of multi-vessel disease involving both the proximal and peripheral branches, diabetic coronary patients often develop heart failure. The severity of this diabetic ischaemic cardiomyopathy is strongly related to changes in energy metabolism of the myocytes. It has been demonstrated that ischaemic damage may be exacerbated by the excessive use of fatty acids by the diabetic heart.[5] This observation have led to the consideration of pharmacological manipulation of cardiac metabolism and optimising myocardial energy production as a promising approach to counteracting the deleterious consequences of myocardial ischaemia, particularly in coronary artery disease (CAD) patients with diabetes.

Metabolic dysfunction in the diabetic myocardium during ischaemia

Diabetes mellitus impairs glucose uptake and glycolysis of myocardial cells. In the case of myocardial ischaemia, glucose oxidation is reduced, and this reduction is more pronounced in diabetic hearts along with a more accelerated rate of free fatty acid (FFA) oxidation which is less efficient than glycolysis in energy production.[5] In the diabetic heart, the preferential increased uptake and utilisation of FFA during ischaemia causes not only a diminished energy production, but also an increase of intermediate metabolic products which are toxic to the myocardium and cause disturbances in calcium homeostasis which may lead to systolic and diastolic dysfunction.[6] Because of the altered metabolism in these patients, even a small reduction of myocardial oxygen supply may cause significant reduction of contractility. This may accelerate the development of overt heart failure in the presence of reduced coronary blood flow such as during acute myocardial ischemia or chronic CAD, or during increased myocardial energy requirement as occurs with hypertension.[7]

Trimetazidine: metabolic benefits beyond anti-ischaemia

Traditional anti-anginal drugs such as beta-blockers, nitrates and calcium channel blockers act either by reducing oxygen consumption or by increasing oxygen supply via increases in coronary blood flow. However, these agents do not address the myocardial metabolic abnormalities that are characteristically found in patients with diabetes. A new approach to treat myocardial ischaemia is to improve the efficiency of oxygen utilisation by cardiac tissues. Metabolic agents like trimetazidine that modify the use of energy substrates in the heart improve cardiac performance during ischaemia. This additional metabolic effect is particularly beneficial for diabetic patients. Trimetazidine is the first of a new class of metabolic anti-ischaemic agents know as 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors. Under ischaemic conditions, trimetazidine optimises cardiac metabolism by shifting from FFA to glucose oxidation, secondary to selective inhibition of the mitochondrial long-chain 3-KAT.[8] A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because energy production is greater when glucose, rather than FFA, is the preferred energy substrate. The beneficial effect of trimetazidine in patients with angina and diabetes has been attributed to the preservation of the intracellular levels of adenosine triphosphate, the reduction of cell acidosis and calcium overload, the reduction of free radicals, and the inhibition of oxidative phosphorylation. Due to its purely metabolic mode of action, trimetazidine provides benefits in angina patients without changes in hemodynamic parameters, such as heart rate, blood pressure, or rate-pressure product at rest or during exercise. Unlike beta-blockers, trimetazidine therapy has a favourable effect on lipid and glucose levels. It is generally better tolerated than calcium antagonist and beta-blockers.[9] There is also no evidence that long term therapy can lead to tolerance as observed with nitrate therapy. Mild gastrointestinal disorders such as heartburn are the most frequently reported adverse reactions, but their overall incidence is low.

Evidence-based efficacy in patients with diabetes and CAD

Trimetazidine is an effective anti-ischaemic agent in patients with angina.[10] It significantly improves symptoms and exercise tolerance in patients with stable angina when used either as monotherapy or when combined with beta-blockers or calcium antagonists. In a study of stable angina patients with diabetes whose angina remained uncontrolled with conventional treatment, four weeks of treatment with trimetazidine resulted in improved exercise capacity and exercise duration, and a significant reduction in the number of angina episodes.[11] It was well tolerated during the entire period of the study and no drug interaction was recorded. In another study of patients with ischaemic cardiomyopathy and depressed left ventricular function, trimetazidine produced significant improvements in left ventricular ejection fraction.[12] It has also been shown that trimetazidine improves left ventricular function and functional capacity in diabetic patients with ischaemic cardiomyopathy receiving background anti-ischaemic therapy.[13, 14] Given that diabetic patients are at risk of silent ischaemia, anti-ischaemic drugs with a long duration of action would be desirable to prevent cardiovascular events. It has been shown that the modified release formulation of trimetazidine (trimetazidine MR 35mg taken twice a day) offers a sustained anti-ischaemic and anti-anginal efficacy even at trough plasma concentration, twelve hours after the intake of the drug.[15] Randomised controlled trials with hard endpoints will be required to show its benefit over conventional therapy.

Patients with diabetes mellitus frequently have erectile dysfunction (ED) as a consequence of atherosclerosis, endothelial dysfunction and autonomic neuropathy. It is effective and safe for coronary patients to receive phosphodiesterase type 5 (PDE5) inhibitors. However, PDE5 inhibitors are contraindicated in patients taking nitrate therapy and beta-blockers may further worsen ED. Trimetazidine, because of its mode of action and an absence of negative effect upon ED, is the drug of choice for the treatment of patients with CAD and ED who require treatment with PDE5 inhibitors. It has also been shown that trimetazidine plus sildenafil are more effective than nitrates in the control of myocardial ischaemia during sexual activity in patients with CAD.[16] Putting the evidence together, trimetazidine may be a better therapeutic option over conventional anti-anginal therapies for CAD patients with diabetes complicated by ED.

Conclusions:

Modulation of cardiac energy metabolism has proved to be an attractive option for the treatment CAD, particularly in patients with diabetes, as reflected by the significant improvements obtained in exercise capacity, symptom relief, and left ventricular function. Due to its purely metabolic mode of action, trimetazidine does not affect hemodynamic parameters and is well tolerated. It is also a safe and effective treatment for diabetic coronary patients and those who have erectile dysfunction requiring treatment with PDE5 inhibitors.

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Clinical Quiz

Dr. Vanessa WS Ng
Prince of Wales Hospital

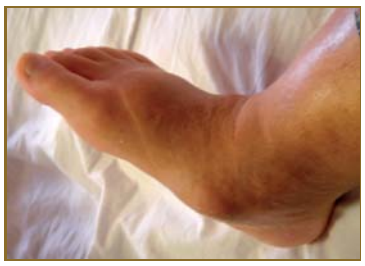

Figure 1

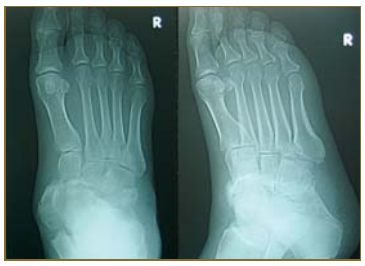

Figure 2

A 58-year old man with poorly controlled Type 2 diabetes (Hba1c 9.7%) presented with a 2-week history of painless progressive swelling over the medial aspect of his right foot (Figure 1). He also had retinopathy, nephropathy and peripheral neuropathy. X-ray of the right foot was performed (Figure 2)

Question:

1. What is the diagnosis?
2. What are the potential treatment modalities?

Answer to Clinical Quiz

Diagnosis:

Charcot neuroarthropathy

Potential treatment modalities

- Avoidance of weight bearing on the affected joint is recommended during the acute phase of treatment.
- Biphosphonate therapy with alendronate and pamidronate has been shown to provide symptomatic relief and to halt the progression of the disease.
- Podiatry care, a pair of well-fitting shoes and orthotic devices
- Foot and ankle reconstructive surgery in selected cases.

Dr. Vanessa WS Ng
Prince of Wales Hospital

Soccer Five Tournament 2006

Match results for 19 August 2006

	Score	
Pfizer	0 : 2	Janssen
AstraZeneca	1 : 1	GSK
IDS	1 : 3	Abbott
Bayer	3 : 3	Schwarz

Match on 19 August 2006
There were 4 exciting matches between pharmaceutical companies on 19th August 2006. All teams played well with support from their friends.


From left to right: Mr. Edwin Li (NobleApex), Mr. Nelson Lam (FMSHK), Mr. Lam Chi Ho and Mr Derrick Hui (HK Chinese Referees Association)

Match results for 27 August 2006

	Score	
Jacobson	5 : 1	P&G
HKDA	8 : 2	Schering-Plough
HKMA	5 : 1	AVC
HKOS	0 : 1	Boehringer Ingelheim

Match on 27 August 2006
There were 4 exciting matches between medical societies and pharmaceutical companies on 27th August 2006. There were impressive performances by HKDA and HKMA teams with 8 and 5 goals respectively.


Tossing the coin (from left to right): Dr Kingsley Chan (HKMA), referee, Mr. Patrick Chu (AVC Medical)

Match results for 3 September 2006

	Score	
Boehringer Ingelheim	0 : 1	Sanofi-Aventis
T. Mountain	0 : 2	Schwarz
P&G	3 : 0	AstraZeneca
Wyeth	0 : 4	Pfizer

Match on 3 September 2006
There were 4 exciting matches between pharmaceutical companies on 3rd September 2006. All teams played well with Pfizer scoring the most goals on the day.


The Sanofi-Aventis team (from left to right starting back row): Keith Lai, Alvin Ngai, Raymond Cheung , Daniel Kwan, William Lau (front row from left to right): Anthony Chang, Leung Lai-king, Patrick Lau

Society News

News from Member Societies

Hong Kong Orthoptists Association
New office-bearers for the year are as follows: Chairman: Mr. Shing-chin KWOK, Secretary: Ms. Lisa Wai-yin WONG, Council Representative: Ms. Lisa Wai-yin WONG.

The FMSHK would like to send its congratulations to the new office-bearers and look forward to working together with their society.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
★HKMA Tennis Tournament **1**	**2**	★Sixth Refresher Course on Colposcopy **3**	★Clinical Nurse Specialist Group Evening Forum (SCNSG-06-02) ★Post-Registration Certificate Course in Intensive Care Nursing **4**	★醫療護理英語基礎課程 (TC-FEC-0106) ★HKMA Council Meeting **5**	**6**	**7**
★HKMA Trailwalker Practice Session ★HKMA Tennis Tournament **8**	★Certificate Course for Development of Advanced Nursing Practice (TC-ANP-0106) ★醫療護理英語基礎課程 (TC-FEC-0106) **9**	★HKMA Newsletter Editorial Meeting **10**	★Hong Kong Neurosurgical Society Monthly Academic Meeting - Endoscopic Surgery of the Third Ventricle ★Everolimus with Low Dose Calcineurin Inhibitor (CNI) in Renal Transplantation **11**	★HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2006 (X) - Scar Management ★醫療護理英語基礎課程 (TC-FEC-0106) **12**	★Certificate Course on Quality Management (TC-CQM-0106) ★The Third Annual Training Program, HKSIEM "IEM in Hong Kong - Past, Present and Future" **13**	★Sixth Perinatal Symposium 2006 - Topics in Perinatal Medicine ★The Third Annual Training Program, HKSIEM "IEM in Hong Kong - Past, Present and Future" **14**
★HKMA Swimming Gala ★HKMA Structured CME Programme at Queen Elizabeth Hospital Year 06/07 (VII) - Neurosurgery & Pathology ★The Federation's Soccer Five Tournament 2006 ★HKMA Tennis Tournament **15**	★醫療護理英語基礎課程 (TC-FEC-0106) ★Certificate Course for Development of Advanced Nursing Practice (TC-ANP-0106) **16**	★HKMA CME Luncheon Lecture on Office Dermatology **17**	**18**	★HKMA Trailwalker 2006 Final Briefing Session ★醫療護理英語基礎課程 (TC-FEC-0106) **19**	★Scientific Symposium on Emergency Medicine: Meeting a Decade of Challenges ★The First Asian Pacific Symposium on Advanced Molecular Technologies (APSAMT) ★Certificate Course on Quality Management (TC-CQM-0106) **20**	★Scientific Symposium on Emergency Medicine: Meeting a Decade of Challenges ★The First Asian Pacific Symposium on Advanced Molecular Technologies (APSAMT) **21**
★The First Asian Pacific Symposium on Advanced Molecular Technologies (APSAMT) ★HKMA Structured CME Programme at Kwong Wah Hospital Year 06/07 (VII) - Paediatrics ★HKMA Trailwalker Practice Session ★HKMA Tennis Tournament ★2nd Certificate Course in Recent Medical Advances for General Practitioners **22**	★醫療護理英語基礎課程 (TC-FEC-0106) ★Certificate Course for Development of Advanced Nursing Practice (TC-ANP-0106) ★The First Asian Pacific Symposium on Advanced Molecular Technologies (APSAMT) **23**	**24**	**25**	★醫療護理英語基礎課程 (TC-FEC-0106) **26**	★Certificate Course on Quality Management (TC-CQM-0106) **27**	★14th Annual Scientific Meeting of Hong Kong College of Radiologists **28**
★Annual Scientific Meeting ★HKMA Tennis Tournament ★The Federation's Soccer Five Tournament 2006 **29**	**30**	**31**				

Medical Diary of October

Date / Time	Function	Enquiry / Remarks
1 SUN 7:30PM	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club, 113A Waterloo Road, Kowloon Tong, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285
3 TUE 7:00PM - 9:00PM	**Sixth Refresher Course on Colposcopy** Organised by: The Hong Kong Society for Colposcopy & Cervical Pathology Department of O&G PYNEH Baptist Hospital Chairman: Dr. Steven LO Speaker: Dr. Steven LO # Chapel, 9/F, Hong Kong Baptist Hospital, Kowloon	Mr. Phyllis KWOK Fax: 2855 0947 2 CME Points
4 WED 6:00PM - 9:00PM	**Clinical Nurse Specialist Group Evening Forum (SCNSG-06-02)** Organised by: College of Nursing, Hong Kong Speaker: Ms. Sylvia WONG & Ms. Camila LI	Sugar Tel: 2572 9255 Fax: 2838 6280 2 CME Points
	Post-Registration Certificate Course in Intensive Care Nursing Organised by: Department of Surgery, University of Hong Kong Medical Centre # Skills Development Centre, Department of Surgery, University of Hong Kong, Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong	Institute of Advanced Nursing Studies Tel: 2855 5836
5 THU 6:00PM - 9:00PM (9,12,16,19,23,26)	**醫療護理英語基礎課程 (TC-FEC-0106)** Organised by: College of Nursing, Hong Kong Speaker: Various	Sugar Tel: 2572 9255 Fax: 2838 6280
8:00PM	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association # HKMA Headquarter Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 SUN 7:00AM	**HKMA Trailwalker Practice Session** Organised by: The Hong Kong Medical Association Chairman: Dr. C YU # Tai Po Road (at the entrance of Kam Shan Road)	Ms. Dora HO Tel: 2527 8285
7:30PM	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club, 113A Waterloo Road, Kowloon Tong, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285
9 MON 6:00PM - 9:00PM (16,23)	**Certificate Course for Development of Advanced Nursing Practice (TC-ANP-0106)** Organised by: College of Nursing, Hong Kong Speaker: Various	Sugar Tel: 2572 9255 Fax: 2838 6280 35 CME Points
10 TUE 8:00PM	**HKMA Newsletter Editorial Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Headquarter Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Tammy TAM Tel: 2527 8941
11 WED 7:00AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting - Endoscopic Surgery of the Third Ventricle** Organised by: Hong Kong Neurosurgical Society Chairman: Dr. ZHU Xian Lun Speaker: Dr. LAW Hing Yuen Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon	Dr. Y.C. PO Tel: 2990 3788 Fax: 2990 3789 2 CME Points (College of Surgeons of Hong Kong)
	Everolimus with Low Dose Calcineurin Inhibitor (CNI) in Renal Transplantation Organised by: Hong Kong Society of Nephrology & Hong Kong Society of Transplantation Chairman: Dr. Alex YU & Dr. K.L. TONG Speaker: Prof. Laurence CHAN # Lecture Theatre M, Queen Elizabeth Hospital, Kowloon	Ms. Chloe WONG Tel: 2882 5222
12 THU 2:00PM	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2006 (X) - Scar Management** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. TUNG Man Kwong # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 1 CME Point
13 FRI 6:00PM - 9:00PM (20,27)	**Certificate Course on Quality Management (TC-CQM-0106)** Organised by: College of Nursing, Hong Kong Speaker: Various	Sugar Tel: 2572 9255 Fax: 2838 6280 35 CME Points
(14)	**The Third Annual Training Program, HKSIEM "IEM in Hong Kong - Past, Present and Future"** Organised by: Hong Kong Society of Inborn Errors of Metabolism Chairman: Dr. T.S. LAM Speaker: Various # HAHO	Dr. WONG Kar Yin Tel: 7306 9532 Fax: 2855 3334
14 SAT 12:30PM - 4:30PM	**Sixth Perinatal Symposium 2006 - Topics in Perinatal Medicine** Organised by: The Obstetrical and Gynaecological Society of Hong Kong & The Hong Kong Society of Neonatal Medicine Chairman: Dr. K.C. AU YEUNG, Dr. W.H. LEE, Prof. T.F. FOK, Dr. S.K. LAM Speaker: Various # Ballroom, 3/F, Sheraton Hong Kong Hotel and Towers, Tsimshatsui	Ms. Teresa CHAN Tel: 2510 6310 Fax: 2969 5511 2.5 CME Points (HKCOG) 3 CME Points (HKC Paediatricians)
15 SUN 1:30PM	**HKMA Swimming Gala** Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. M.H. IP # Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285
2:00PM	**HKMA Structured CME Programme at Queen Elizabeth Hospital Year 06/07 (VII) - Neurosurgery & Pathology** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Queen Elizabeth Hospital, Lecture Theatre, Block M, G/F., Queen Elizabeth Hospital, Kowloon	Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 3 CME Points
(29)	**The Federation's Soccer Five Tournament 2006** Organised by: The Federation of Medical Societies of Hong Kong & The Hong Kong Association of the Pharmaceutical Industry Chairman: Dr. Godfrey C.F. CHAN # Shek Kip Mei Park Sports Centre, 290 Nam Cheong Street, Shek Kip Mei, Sham Shui Po	Ms. Karen Chu Tel: 2821 3515 Fax: 2865 0345
7:30PM	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club, 113A Waterloo Road, Kowloon Tong, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285

Medical Diary of October

Date / Time	Function	Enquiry / Remarks
17 TUE 2:00PM	**HKMA CME Luncheon Lecture on Office Dermatology** Organised by: The Hong Kong Medical Association Chairman: Dr. T.C. SHIH # Conrad Hotel, Pacific Place, 88 Queensway, Hong Kong	Miss Dorothy KWOK Tel: 2527 8452 (Maximum Capacity: 150) 1 CME Point
19 THU 7:00PM	**HKMA Trailwalker 2006 Final Briefing Session** Organised by: The Hong Kong Medical Association # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road C, Hong Kong	Ms. Dora HO Tel: 2527 8285
20 FRI (21)	**Scientific Symposium on Emergency Medicine: Meeting a Decade of Challenges** Organised by: Hong Kong Society for Emergency Medicine and Surgery, Hong Kong College of Emergency Medicine & Hong Kong Emergency Nurses Association # Hong Kong Academy Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen	Ms. Lenora YUNG / Ms. Jessie CHOW Tel: 2871 8841 Fax: 2871 8898
(21,22,23)	**The First Asian Pacific Symposium on Advanced Molecular Technologies (APSAMT)** Organised by: Hong Kong Society for Molecular Diagnostic Sciences Ltd, The Hong Kong Polytechnic University (Department of Health Technology and Informatics) & Chinese American Association for Clinical Microbiology Chairman: Dr. TAM Chuen Chu Speaker: Various # The Hong Kong Polytechnic University, Hung Hom, Kowloon	Mr. HUI Wai Ting Tel: 9464 7392 Website: www.hksms.s.org
22 SUN 2:00PM	**HKMA Structured CME Programme at Kwong Wah Hospital Year 06/07 (VII) - Paediatrics** Organised by: The Hong Kong Medical Association & Kwong Wah Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Kwong Wah Hospital, Lecture Theatre, 10/F., Yu Chun Keung Medical Memorial Centre, Kwong Wah Hospital, Kowloon	Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 3 CME Point
7:00AM	**HKMA Trailwalker Practice Session** Organised by: The Hong Kong Medical Association Chairman: Dr. C YU # Pak Tam Chung (at the tuck shop)	Ms. Dora HO Tel: 2527 8285
7:30PM	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club, 113A Waterloo Road, Kowloon Tong, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285
	2nd Certificate Course in Recent Medical Advances for General Practitioners Organised by: The Family Medicine Unit, the University of Hong Kong and the Family Medicine Division, Hong Kong Sanatorium and Hospital Speakers: Various	Hospital Administration Department Tel: 2835 8800 Fax: 2835 8008 E-mail:hospadm@hksh.com Website: http://www.hksh.com/CME.pdf
28 SAT	**14th Annual Scientific Meeting of Hong Kong College of Radiologists** Organised by: Hong Kong College of Radiologists Speaker: Various # Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen	Secretariat Tel: 2871 8788 E-mail: enquiries@hkcr.org Website: http://www.hkcr.org
29 SUN 9:00AM - 4:00PM	**Annual Scientific Meeting** Organised by: Hong Kong Society of Nephrology Chairman: Dr. Alex YU Speaker: Various # Ballroom, Kowloon Shangrila Hotel, Kowloon	Ms. Joyce LO Tel: 2589 8586 Fax: 2858 7340
7:30PM	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club, 113A Waterloo Road, Kowloon Tong, Kowloon, Hong Kong	Ms. Dora HO Tel: 2527 8285

Calendar of Events

Meetings

5-9/11/2006	**7th Asian Congress on Oral and Maxillofacial Surgery Hong Kong** Organised by: The Hong Kong Association of Oral and Maxillofacial Surgeons Chairman: Prof. Nabil SAMMAN Speaker: International Speakers # Hong Kong Convention and Exhibition Centre Enquiry: Mr. Daniel CHOK Tel: 2871 8896 Fax: 2871 8898
11-12/11/2006	**HKOA Annual Congress 2006 - Knee Surgery 2006: In Pursuit of Excellence** Organised by: Hong Kong Orthopaedic Association Chairman: Dr. Wilson LI & Dr. W.M. TANG Speaker: Prof. L ENGEBRETSEN, Prof. A.B. IMHOFF & Prof. W.J. MALONEY # Cyberport Convention & Exhibition Centre Enquiry: Ms. Terry LEUNG Tel: 2632 3482 Fax: 2647 7432 Email: congress@hkoa.org
15-17/11/2006	**13th Hong Kong International Cancer Congress & 3rd Annual Meeting of Centre for Cancer Research** Organised by: Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital # Cheung Kung Hai Conference Centre, William MW Mong Block, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong Enquiry: Congress Secretariat Tel: 2855 4235 / 2818 0232 Fax: 2818 1186 Email: hkjcc06@hku.hk Website: www.hkicc.org
1-3/12/2006	**9th International Symposium on Thrombolysis and Acute Stroke Therapy (TAST 2006) & 19th Annual Scientific Meeting of The Hong Kong Neurological Society** Organised by: The Hong Kong Neurological Society, Chinese Society of Neurology & The Hong Kong Polytechnic University (Rehabilitation Sciences Department) Speaker: Various # Jockey Club Auditorium, The Hong Kong Polytechnic University Enquiry: Conference Secretariat Email: tast2006@icc.com.hk Website: www.tast2006.com
9-10/12/2006	**Hong Kong Ophthalmological Symposium 2006 - Theme: Glaucoma** Organised by: College of Ophthalmologists of Hong Kong, Euro Asia Congress Chairman: Prof. Clement C.Y. THAM Speaker: Prof. Robert STEGMANN Venue: Hong Kong Convention & Exhibition Centre Enquiry: Ms. Vicki WONG Tel: 2761 9128 Fax:2715 0089
25-27/01/2007	**International Colorectal Disease Symposium (ICDS) 2007** Organised by: Hong Kong Society for Coloproctology & Pamela Youde Nethersole Eastern Hospital (Department of Surgery) Chairman: Mr. Michael K.W. LI Speaker: Various # 2/F New Wing, Hong Kong Convention & Exhibition Centre Enquiry: Ms. Olivia HO Tel: 2595 6362 Fax: 2515 3195
2-4/02/2007	**Cardio Rhythm 2007** Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology # Hong Kong Convention & Exhibition Centre Enquiry: Secretariat, CMP Medica Pacific Limited Tel: 2559 5888 Fax: 2559 6910 Email: info@cardiorhythm.com Website: www.cardiorhythm.com
10-11/02/2007	**Cancer Imaging 2007 - Joint Meeting of the International Cancer Imaging Society & Hong Kong College of Radiologists** Organised by: International Cancer Imaging Society & Hong Kong College of Radiologists Chairman: Ms. Lilian LEONG Speaker: Various Venue: Hong Kong Academy of Medicine Jockey Club Building Enquiry: Mrs. Maureen WATTS Tel: 44 (0) 208 661 3420 Fax: 44 (0) 208 661 3901 E-mail: Maureen.Watts@icr.ac.uk or Ms. Diane LEE Tel: 2871 8788 Fax: 2554 0739 E-mail: enquiries@hkcr.org
13-17/06/2007	**The 21st Congress of International Association of Paediatric Dentistry IAPD** Organised by: Hong Kong Society of Paediatric Dentistry # Hong Kong Convention & Exhibition Centre Enquiry: Mr. Daniel CHOK Tel: 2871 8896 Fax: 2871 8898 Email: info@iapd2007.com Website: http://www.iapd2007.com

Courses

1,3,8,10,15,17,22,24,29/11/2006 1,6,8,13,15,20,22,27,29/12/2006 3,5,10,12,17,19,24,26,31/01/2007 2,7,9,14,16,28/02/2007 2,7,9,14,16,21,23,28,30/03/2007	健康服務助理員訓練課程 (TC-HCA-0306) Organised by: College of Nursing, Hong Kong Enquiry: Sugar Tel: 2572 9255 Fax: 2838 6280
2,6,9/11/2006	醫療護理英語基礎課程 (TC-FEC-0106) Organised by: College of Nursing, Hong Kong Enquiry: Sugar Tel: 2572 9255 Fax: 2838 6280
3,10,17,24/11/2006 1,8,15,29/12/2006	**Certificate Course on Quality Management (TC-CQM-0106)** Organised by: College of Nursing, Hong Kong Enquiry: Sugar Tel: 2572 9255 Fax: 2838 6280
6,11,20,27/11/2006 4,11,18/12/2006 8/01/2007	**Certificate Course for Development of Advanced Nursing Practice (TC-ANP-0106)** Organised by: College of Nursing, Hong Kong Enquiry: Sugar Tel: 2572 9255 Fax: 2838 6280
6,9,13,16,20,23,27,30/11/2006 4,7,11,14/12/2006	家務助理陪月服務訓練課程 (TC-PNC-0206) Organised by: College of Nursing, Hong Kong Enquiry: Sugar Tel: 2572 9255 Fax: 2838 6280
10&17/12/2006	**Pre-hospital Trauma Life Support (PHTLS) Provider Course** Organised by: Department of Surgery, University of Hong Kong and Hong Kong Chapter of the American College of Surgeons Enquiry: Course Secretariat, Department of Surgery, University of Hong Kong Medical Centre Tel: 2530 8016
12/11/2006, 17/12/2006 21/1/2007, 11/2/2007 18/3/2007, 22/4/2007 20/5/2007, 17/6/2007	**2nd Certificate Course in Recent Medical Advances for General Practitioners** Jointly organized by the Family Medicine Unit, the University of Hong Kong and the Family Medicine Division, Hong Kong Sanatorium and Hospital Speakers: Various, Enquiry: Hospital Administration Department Tel: 2835 8800, Fax: 2835 8008, E-mail:hospadm@hksh.com, Website: http://www.hksh.com/CME.pdf

Upcoming Certificate Courses of the Federation of Medical Societies of Hong Kong

Date	Course No	Course Name	Co-organiser	Target Participants
17 Oct 06 - 21 Nov 06 (Tue)	C97	Certificate Course in Ophthalmology	The Hong Kong Ophthalmological Society	Medical & health professionals
6 Nov 06 - 11 Dec 06 (Mon)	C106	Certificate Course on Sleep Health & Disorders	Hong Kong Society of Sleep Medicine	Public
8 Nov 06 - 13 Dec 06 (Wed)	C98	Certificate Course on the Diagnosis, Prevention and Management of Thalassaemia	Hong Kong Society for the Study of Thalassaemia	Medical & health professionals
3 Jan 07 - 7 Feb 07 (Wed)	C111	Certificate Course on Medical Genetics	Hong Kong Society of Medical Genetics	Medical & health professionals
9 & 16 Jan 07 (Tue)	C112	Certificate Course on Drug Safety in Old Aged Homes		Medical & health professionals