Drug Therapy Management

Editorial

The purpose of drugs is to improve clinical outcomes and the patient's quality of life. However, evidence suggests that whenever drugs are given, a serious problem of drug-related morbidity and mortality exists which not only defeats the purpose of drug therapy but also entails considerable cost. It is predicted, that in future health care will relay even more heavily on drug therapy to improve patient outcomes, creating an increased risk of drug-related morbidity.

While we recognise the fact that drug misadventure will always occur, our aim as healthcare professionals should be to eliminate drug misadventure altogether. The one and only true focus of any healthcare professional is the patient's well being, and with that in mind it is unacceptable for us to allow the occurrence of drug-related morbidity and mortality especially when in many cases they could be prevented.

Today we form part of a society with increased expectations from health care; a society that expects accountability. This society primarily demands safe, appropriate and effective drug therapy. We are duty bound to make every effort possible to meet such demands. Undeniably, a multidisciplinary approach is necessary to deliver the best possible care to the patient. The constructive way forward is to identify the source of the problem and construct a plan to eliminate the likelihood of its future occurrence. A concerted effort to reduce drug-related problems would improve patient outcomes, enhance patient and professional satisfaction and decrease overall healthcare costs.

An interesting model currently practiced in the United States is collaborative drug therapy management (CDTM). CDTM requires a professional partnership between pharmacist and doctor whereby a pharmacist, within terms of professional agreement, may engage in activities which include initiating, modifying and monitoring drug therapy; ordering and performing laboratory tests, assessing patients' response to therapy; educating and counseling patients and administering medications. It has been found to be the most efficient and effective way to provide pharmaceutical care, as the pharmacist has a direct impact on patient care and clinical outcomes. It is also essential for CDTM to provide cost-effective drug therapy management.

Such a model should indeed be aspired to. ✶

Long Term Care for the Elderly

The Role for Pharmacists

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Consultant pharmacy represents a branch of the profession that has almost become synonymous with nursing homes in the USA. This is largely due to the legal framework that surrounds nursing home care in the USA and the requirement for pharmacy review of medication in this setting. However, consultant pharmacy has been in existence for almost 30 years and had its roots in community practice; today, a consultant pharmacist is defined as a practitioner who provides services to long-term care facilities on a contractual basis. This paper provides an overview of this type of pharmacy practice, the current delivery of consultant pharmacy services in the USA and lessons for the international pharmacy profession.

Development of consultant pharmacy in the USA

Consultant pharmacy developed from community pharmacy practice. Those based in community practice were providing a medication supply service to nursing homes with a number of these practitioners providing a more advanced service than basic dispensing. Legislation in the mid-1960's sought to improve the quality of nursing home care, but perhaps the most important development in nursing home regulation and legislation was the publication of the Institute of Medicine's (IOM) report on improving the quality of care in nursing homes in 1986[1].

One of the key recommendations from the report was that: "each resident is to receive high-quality care to meet individual physical, mental and psychosocial needs. The care should be designed to maintain or improve the residents' physical, mental, and emotional well-being".[1]

The Omnibus Budget Reconciliation Act of 1987 (OBRA 87)

Following the IOM report, legislation was enacted within the USA to improve care in nursing homes - the Nursing Home Reform Act which was embedded in the Omnibus Budget Reconciliation Act of 1987 (OBRA 87)[2] - and was implemented in October 1991.

As a first step to improve the quality of care in nursing homes, attempts have been made through the OBRA regulations to undertake a comprehensive assessment of the residents' needs, encompassing the following areas:

- Medically defined conditions and prior medical history
- Medical status measurement
- Functional status
- Sensory and physical impairments
- Nutritional status and requirements

- Special treatments or procedures
- Psychosocial status
- Discharge potential
- Dental condition
- Activities potential
- Rehabilitation potential
- Cognitive status
- Drug therapy

Such assessments must be carried out on patients no later than 14 days after admission, following a significant change in the resident's physical or mental condition and at least once every 12 months, with a partial reassessment every quarter.

As a means to assist in this standardisation of care, it was necessary to develop an instrument which could be used in the collection of patient data. The Resident Assessment Instrument (RAI) was produced by a research consortium in conjunction with the federal organisation that oversees the US government's health programmes-the Health Care Financing Agency (HCFA)[3]. It includes a set of central assessment items known as the Minimum Data Set (MDS) and 18 Resident Assessment Protocols (RAPs).

In terms of prescribing, the MDS contains a domain which embraces medication use; this specifically relates to the following elements:

- the number of medications used in the previous 7 days

- if any new medications had been initiated in the previous 90 days

- the number of days during which the resident had received injections of any kind in the previous 7 days

- the number of days (during the last 7 days) the resident received an antipsychotic, anxiolytic, antidepressant, hypnotic or diuretic medication.

Drug Regimen Review (DRR) is the means by which drug therapy in patients is evaluated in most long-term care facilities. Such reviews, under current legislation, are carried out on a monthly or quarterly basis by a consultant pharmacist.

The DRR should include at least an evaluation of the appropriateness of, and response to, each patient's drug therapy. The pharmacist must report any irregularities to the attending doctor and director of nursing.

Thus, specific justification is required in relation to prescribing of psychoactive drugs. The regulations state that "the resident has the right to be free from any chemical restraints imposed for purposes of discipline or convenience and not required to treat the resident's medical symptoms". Further regulations provide specific guidance on the use of unnecessary drugs and antipsychotic drugs.

An unnecessary drug is broadly defined as a drug that is used in excessive dose, for excessive duration, without adequate indications for its use or in the presence of adverse consequences which indicate the dose should be reduced or discontinued. For example, it is stated that specified long-acting benzodiazepines should not be used in residents unless an attempt with a shorter-acting drug has failed; these long-acting agents are listed in Table I.

However, exceptions to these guidelines are made in the case of diazepam being used for neuromuscular disorders or when long-acting benzodiazepines are being used to withdraw patients from shorter-acting drugs. Further guidance is given in relation to the use of short-acting

benzodiazepines and other anxiolytic/ sedative drugs, drugs for sleep induction (largely hypnotics) and miscellaneous agents such as barbiturates.

In the latter case, it is stated that the initiation of drugs such as amobarbital and secobarbital should not occur in any dose for any resident. Those patients already receiving these drugs should undergo a gradual dose reduction programme.

The regulations provide a wealth of information on the effective use of antipsychotic drugs. Guidance on drug dosage levels and monitoring for antipsychotic side-effects is given. It is specifically stated that, based on a comprehensive assessment of a resident, the facility must ensure that

Table I	
Long-acting benzodiazepines which should not be used in nursing home residents according to HCFA regulations[3]	- Flurazepam - Chlordiazepoxide - Clorazepate - Diazepam - Clonazepam - Quazepam - Halzepam

Table IIa
Medical conditions in which antipsychotic agents may be used as specifically governed by OBRA 87 regulations[2]
Antipsychotic drugs should not be used unless the clinical record documents that the resident has one or more of the following "specific conditions" - Schizophrenia - Schizo-affective disorder - Delusional disorder - Psychotic mood disorders (including mania and depression with psychotic features) - Acute psychotic episodes - Brief reactive psychosis - Schizophreniform disorder - Atypical psychosis - Tourette's disorder - Huntington's disease - Organic mental syndromes (called delirium, dementia and amnestic and other cognitive disorders by DSM-IV*) with associated psychotic and/or agitated behaviours. *   Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

residents who have not used antipsychotic drugs are not given these drugs unless antipsychotic drug therapy is necessary to treat a specific condition as diagnosed, and documented in the clinical record and those who receive these drugs, should also undergo gradual dose reductions and behavioural interventions (unless clinically contra-indicated) in an effort to discontinue these drugs; the medical conditions of note are detailed in Tables IIa and IIb. The aim of this particular regulation is that the use of psychoactive medication must be justified and documented. Therefore, it is permissable to prescribe in apparent contravention of the legislation provided clinical justification is given.

Lessons for the international pharmacy profession

Clearly, the provision of pharmaceutical services to nursing homes and other long-term care environments in the USA is markedly different to that in other parts of the world. Consultant pharmacy is generally perceived as a clinical speciality, and remuneration for

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Table IIb

Medical conditions in which antipsychotic agents should not be used as specifically governed by OBRA 87 regulations[2]

Antipsychotics should not be used if one or more of the following is/ are the only indication

- Wandering
- Poor self care
- Restlessness
- Impaired memory
- Anxiety
- Depression
- Insomnia
- Unsociability
- Indifference to surroundings
- Fidgeting
- Nervousness
- Uncooperativeness
- Agitated behaviours which do not represent danger to the resident or others

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services is very different to other national health systems. Perhaps most importantly, many countries do not have a legislative system in place which demands medication review by a pharmacist and justification of prescribing decisions.

Because of these pronounced differences, the import of a consultant pharmacy model into other countries requires considerable discussion and debate. Under the current United Kingdom system, the community pharmacist's involvement in clinical activities to nursing homes is limited to medication supply.

There is also the potential conflict of interest in that pharmacists are currently the main providers of medication to homes; as they are remunerated for the number of items they dispense, there is little incentive to rationalise medication. The current payment available to pharmacists providing advice to homes would not compensate for losses incurred through a reduction in dispensing.

It is also important to consider those who work within the nursing home sector. Although the pharmacy profession may view an extension of services and responsibility to be highly desirable, the views of nursing home managers and other health care professionals who work within this environment should also be sought. A recent survey carried out in all nursing and residential homes in Northern Ireland indicated that staff in these homes were highly supportive of further staff training by pharmacists in the recognition of medication-related problems, additional advice and guidance on missed doses and a pharmacist review of patient medication records to assess drug-drug interactions and possible adverse drug reactions[4].

Long-term care for the elderly is becoming a major issue within UK health policy. The Royal College of Physicians has commended the role of community pharmacists in medicines'

management as part of its report on "Medication for Older People"[5] and considers that the profession can contribute to the care of nursing home residents.

Most recently, the UK Department of Health has issued a document entitled "Care Homes for Older People. National Minimum Standards"[6]. This outlines national minimum standards expected under the Care Standard Act 2000 and one such standard states that the registered manager of a home should seek information and advice from a pharmacist regarding medicines policies within the home and medicines dispensed for individuals within the home.

The increasing elderly population represents major challenges for health care professionals in the new millennium and pharmacy is no exception. Pharmacists need to examine what they currently do within long term care and expand their services accordingly.

The American model is something from which we can learn, and perhaps by selecting those elements which are most adaptable to the other healthcare systems, we can start to move some way towards a more holistic approach of care to a highly vulnerable patient group. ✶

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Provision of Palliative Care in Malta

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The Malta Hospice Movement, within its young, fast-developing structure, is established as a Body within the Maltese Community that continues to expand its vision of Palliative Care, Palliative Medicine and Hospice Philosophy by increasing its human, structural and organisational resources. Through the multi-disciplinary team, it reaches out to cancer patients both as a voluntary, charitable organisation but more importantly as a professional one in a wide range of Hospice services.

What is Palliative Care?

Palliative Care, as defined by the World Health Organisation, is:

'The active total care of patients whose disease is not responsive to curative treatment. Control of pain and other symptoms, and of psychological, social and spiritual problems, is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.'

Thus, Palliative Care:

- affirms life and regards dying as a normal process

- neither hastens nor postpones death

- provides relief from pain and other distressing symptoms

- integrates the psychological and the spiritual aspects of care

- offers a support system to help patients live as actively as possible until death

- offers a support system to help the family cope during the patient's illness and in their own bereavement

The relief of suffering when cure is impossible has always been at the heart of all good medical practice, even before it was called palliative care. It was, and surely still is, what every patient hopes for - and has a right to expect - whatever his condition. It has never been, nor should ever be, regarded as a luxury, an optional extra available to the privileged few. To all of us is given the challenge and the chance to relieve suffering. This is Palliative Care.

My own personal philosophy is that dying is as important a part of life as being born. We believe that every person should be able to live until they die, free from pain and distressing symptoms, and receiving the emotional, psycho-social and spiritual support they require. How can we achieve this?

I would say that a partnership of patient, family, nurse, doctor and other health professionals is necessary. Each must nurture the other - in other words, a multidisciplinary team. Developing a multi-professional approach to management is highly desirable. It is unrealistic to expect one professional or individual to have the skills to make the necessary assessment, institute the necessary interventions, and provide ongoing monitoring. It ensures that the entire responsibility does not fall on just one individual and that patients' problems and needs are addressed from different perspectives. Nursing staff, in particular, make a major contribution to the success of the interdisciplinary team, mainly because they are continuous care givers - the 'nucleus' of the team. It is the nursing service that coordinates the diverse inputs of other health care professionals and services.

Nowhere is the multi-professional approach more essential than in response to the expressed and perceived needs of cancer patients and their families. The particular gifts and skills of doctors, nurses, social workers, counsellors, physiotherapists, priests and others, all contribute to providing a competent and compassionate service which addresses the whole person and not only the disease.

The Malta Hospice Movement works with other health care professionals to provide an optimum standard of care for those with advanced cancer and Motor Neuron Disease, using our expertise to advise on the alleviation of pain. We work from a multi-disciplinary approach making an ongoing assessment of the whole family's needs, coordinating and evaluating care. Most people want to stay in their own homes for as long as they can and our comprehensive home care package helps families manage this, with the specialist support enhancing the work of the patient's own general practitioners and district nurses. Continuity of care must and can be maintained but for this we need to ensure communication with all resources.

Our key objectives are therefore to:

- provide practical advice and support for patients and their families
- reduce distressing physical symptoms
- enable patients to choose the place of care and death
- identify those at risk in bereavement and refer to the appropriate bereavement service
- support patients and their families in their emotional and spiritual distress.

Our comprehensive range of facilities comprise:

- home care
- day therapy
- night nursing in the home
- hospital support
- loan of specialised equipment
- assisted bathing
- hairdressing
- family/group support
- bereavement support

Together we must aim at further enhancing palliative care in the hospital and in the community, emphasising a holistic approach to care. We should maximise the potential of our patients with good symptom control, enabling them to live until they die.

The essential components of palliative care are effective control of symptoms and effective communication with patients, their families, and others involved in their care. As a disease progresses, continuity of care becomes increasingly important - coordination between services is required, and information must be transferred promptly and efficiently between professionals in the community and in the hospitals.

The principles of palliative care are essentially about attitudes. They emphasise the human and humane aspect of medicine, of care when cure is no longer possible. They stress life-affirming values by recognising the dying person as a living person and as a whole person with a right to dignity, comfort and support up to and through the end of life.

Finally, serving the dying more effectively is not just a way of benefiting that special group of patients; it enriches and ennobles us all. ✶

Interactions of Grapefruit Juice with Drugs

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Interactions between grapefruit juice and oral drugs have been reported in the literature. The constituents of the juice that give rise to pharmacokinetic interactions have not been identified with certainty. It has been suggested that the mechanisms may involve inhibition of intestinal cytochrome P450 CYP3A4 isozyme and of drug efflux transporters. There are several variables that may influence the clinical significance of the drug-food interactions. In the pharmacy practice setting, the major concern is the increased bioavailability of drugs having a narrow therapeutic index.

Introduction

An interaction may occur in the body when a drug is taken concomitantly with other drugs or foods or in the presence of environmental chemical agents. The outcome of an interaction is a change in the effect that a drug exerts on the body. While this effect may at times be beneficial if it enhances the therapeutic benefit of the drug it may, at other times, prove to be harmful if toxicity ensues or if efficacy is reduced[1].

Drug-food interactions are often associated with changes in the absorption of a drug when in the presence of specific foods. A common example is the reduced intestinal absorption of tetracycline in the presence of dairy products. However other pharmacokinetic mechanisms, such as the influence of drug metabolism on the bioavailability of drugs and on the serum level of active drug substances, should not be excluded.

An important drug-food interaction that is receiving increasing attention occurs between grapefruit juice and drugs belonging to several therapeutic categories. The common factor that links these interactions with grapefruit juice appears to be a drug metabolising enzyme that plays a fundamental role in the detoxification of many drugs.

Cytochrome P450 metabolising enzymes

The metabolic routes by which drugs are biotransformed in the body are divided into two phases. Phase I reactions prepare a drug for the subsequent Phase II reactions that are the true detoxification pathways which result in products that are generally water-soluble and easily excreted[2].

The mixed-function oxidase (MFO) reaction catalysed by cytochrome P450 dominates Phase I metabolism.

Hundreds of structurally diverse drugs and chemicals are substrates for the MFO system found in microsomes (endoplasmic reticulum) of cells primarily of the liver, kidney, lung and intestine[2].

The enzyme, cytochrome P450 (CYP), is a haemoprotein and consists of a family of closely related isozymes embedded in the membrane of the endoplasmic reticulum[2]. Of the many isozymes isolated from human liver tissue, only a few subfamilies are responsible for about 90% of the metabolism of commonly used drugs. The predominant isozymes are designated as CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4[1]. The CYP3A subfamily is the most abundant in human liver microsomes. Of these, the isozyme CYP3A4 appears to be found in all human livers and is also expressed in extrahepatic tissues such as the small intestine[3]. Table I lists examples of drugs that are substrates for CYP3A4.

Grapefruit juice and CYP3A4

The interactions between grapefruit juice and drugs are believed to be the result of inhibition of CYP3A4 by substances present in the juice[1]. Since the isozyme is located both in the intestinal wall and in the liver, the drug-food interaction could influence absorption of an oral dose of a drug and its hepatic first-pass metabolism. The resultant effect of enzyme inhibition is manifested as an increase in plasma drug levels due to an increase in absolute bioavailability[4].

The drug-food interaction involving grapefruit juice is not known to occur when the fruit is eaten as opposed to drinking its juice[5]. Neither have similar interactions been seen with orange juice[4]. It appears that flavonoids found in grapefruit juice but not in orange juice may inhibit the CYP3A4 isozyme.

The major flavonoid found in grapefruit juice, the glycoside naringin, does not appear to affect human cytochrome P450 enzymes. However, naringin may be hydrolysed in the intestine to naringenin, a potent inhibitor of enzymes such as CYP3A4 and CYP1A2[4]. In fact, the increase in bioavailability of several calcium channel blockers, ethinyloestradiol, oral cyclosporin and benzodiazepines when taken with grapefruit juice may be due to inhibition of the CYP3A4 isozyme by naringenin[1].

The furanocoumarin[6,7] Dihydroxybergamottin is another inhibitor of CYP3A4 that is found in grapefruit juice[6,7]. It has been shown to be the major furanocoumarin responsible for a decrease in CYP3A4 activity and a reduction in cellular concentrations of the enzyme as a result of accelerated degradation[6].

Inhibition of CYP3A4 does not appear to be the only mechanism that accounts for the drug-food interactions. Constituents of grapefruit juice that are different from CYP3A4 inhibitors are known to enhance drug absorption by inhibiting intestinal drug efflux transporters such as P-glycoprotein[8]. This is an ATP-dependent membrane transporter known as multidrug resistance protein[3] which extrudes drug molecules from epithelial cells of the villi into the intestinal lumen thus reversing the process of absorption.

Table I
Examples of drugs metabolised by cytochrome P450 CYP3A4 isozyme (adapted from Klaassen, 1996 and Stockley, 1999)

Pharmacological/ Therapeutic Class	Drug Metabolised by CYP3A4
Analgesics	Alfentanil • Paracetamol
Anti-arrhythmics	Amiodarone • Lidocaine • Propafenone • Quinidine
Antibacterials	Clindamycin • Dapsone • Erythromycin • Troleandomycin
Antidepressants	Amitriptyline • Clomipramine • Imipramine • Nefazodone • Sertraline • Venlafaxine
Antiepileptics	Carbamazepine • Clonazepam • Zonisamide
Antihistamines	Astemizole • Loratadine • Terfenadine
Antihypertensives	Losartan
Antivirals	Indinavir • Nelfinavir • Nevirapine • Ritonavir • Saquinavir
Anxiolytics and/or Hypnotics	Alprazolam • Diazepam • Midazolam • Triazolam • Zolpidem
Bronchodilators	Theophylline
Calcium-channel blockers	Diltiazem • Felodipine • Nifedipine • Nimodipine • Nisoldipine • Verapamil
Cardiac glycosides	Digitoxin
Corticosteroids	Budesonide • Dexamethasone • Hydrocortisone
Cough suppressants	Dextromethorphan
Cytotoxic drugs	Cyclophosphamide • Etoposide • Ifosfamide • Paclitaxel • Teniposide
Gastric motility stimulants	Cisapride
Hormone antagonists	Flutamide • Tamoxifen • Toremifene
Immunosuppressants	Cyclosporin • Tacrolimus (FK-506)
Lipid-regulating drugs	Lovastatin • Simvastatin
Oral anticoagulants	Warfarin
Proton pump inhibitors	Lansoprazole • Omeprazole
Sex hormones	Ethinyloestradiol • Testosterone

Table II
Examples of the outcome of studies on the effects of grapefruit juice on drugs (Adapted from Stockley, 1999)

Drug	Effect of Grapefruit Juice	Outcome
Acenocoumarol (nicoumalone)	• No significant effect detected	• No clinically relevant interaction • Grapefruit juice need not be avoided
Astemizole	• No effect detected	• No clinically relevant interaction • Grapefruit juice need not be avoided
Benzodiazepines	• Increased bioavailability of midazolam, triazolam and diazepam probably due to inhibition of metabolism by CYP3A4	• Interactions of minor importance
Calcium channel blockers	• Increased bioavailability of felodipine with increase in drug effects and in side effects • Increased bioavailability of amlodipine, nicardipine, nifedipine, nimodipine, nisoldipine and nitrendipine without adverse haemodynamic effects • Increase in bioavailability likely to be due to inhibition of metabolism by CYP3A4 • Bioavailability of diltiazem is unaltered	• Grapefruit juice to be avoided with calcium channel blockers (other than amlodipine and diltiazem)[5]
Cilostazol	• Increase in drug activity is likely due to metabolism by CYP3A4	• No serious interaction is likely to occur • Recommended that grapefruit juice be avoided
Cyclosporin (Ciclosporin)	• Increase in bioavailability probably due to inhibition of metabolism by CYP3A4	• Interaction is clinically important • Grapefruit juice to be avoided unless serum cyclosporin levels are monitored
Ethinyloestradiol (Ethinylestradiol)	• Increased bioavailability possibly due to inhibition of metabolism	• No clinically relevant interaction • Grapefruit juice to be avoided
Indinavir	• Reduced bioavailability	• No clinically relevant interaction • Grapefruit juice to be avoided
Lovastatin	• Increased bioavailability likely due to inhibition of metabolism by CYP3A4	• Interaction is clinically significant • Grapefruit juice to be avoided
Prednisone and Prednisolone	• No significant effect detected	• No clinically relevant interaction • Grapefruit juice need not be avoided
Quinidine	• Delayed absorption • Inhibition of metabolism by CYP3A4	• No clinically relevant interaction • Grapefruit juice need not be avoided
Saquinavir	• Increased drug bioavailability and serum drug level	• No clinically relevant interaction • Drug dose adjustment not required in the presence of grapefruit juice
Tacrolimus (FK-506)	• Increased serum drug level probably due to inhibition of metabolism	• Interaction is clinically significant • Grapefruit juice to be avoided unless serum tacrolimus levels are monitored
Terfenadine	• Increased serum drug levels leading to drug accumulation in the body and potentially life-threatening cardiotoxicity • Metabolism by CYP3A4 of the parent drug to the active metabolite is inhibited	• Interaction is clinically important • Grapefruit juice to be avoided
Theophylline	• No interaction detected	• No clinically relevant interaction • Grapefruit juice need not be avoided

Clinical relevance of the interactions

Altered pharmacokinetic parameters are observed when an oral drug interacts with grapefruit juice. The increase in drug bioavailability is attributed to an increase in the maximal plasma concentration (C_{max}), the time to reach maximal concentration (t_{max}) and the area under the plasma concentration-time curve (AUC). No changes have been observed in total body clearance (Cl), elimination half-life ($t_{1/2}$) and volume of distribution (V_D)[4].

Studies conducted under controlled conditions and using standardised grapefruit juice can only give an indication of the significance of the drug-food interactions. In clinical practice the situation may be rather different due to several variables that can be identified[1,4,9,10].

These include:

- the amount of juice co-administered with the drug;

- the concentration of the juice preparation (regular versus double strength);

- the brand of juice and the proportion of specific constituents (differences exist between commercially available preparations and between preparations and freshly squeezed juice);

- the time/duration of administration of the juice (interactions do not occur solely with concurrent administration of the drug and juice; a decrease in intestinal CYP3A4 has been shown to occur within 4 hours of ingestion of a single glass of juice[6]; the duration of inhibition can last 24 hours and repeated juice consumption may result in a cumulative drug increase in the body[10]; it is unclear how long the interval between drinking the juice and taking the drug should be in order to limit the possibility of an interaction[5]);

- the regularity of juice intake during a course of drug treatment (occasional ingestion of juice as opposed to regular intake could lead to fluctuations in the plasma drug concentration with altered drug effects/toxicity);

- the variability in first-pass metabolism in the population;

- the extent to which a given drug is susceptible to first-pass metabolism;

- the extent of variability in intestinal CYP3A4 activity in the population (due to differences in CYP3A4 protein expression);

- the extent to which a drug is metabolised at the intestinal wall;

- the variability in bioavailability in the population for any given drug (this may be greater than the increase in bioavailability seen as an interaction with grapefruit juice); and

- the variability in serum drug levels in the population for any given drug.

Although there are many drugs that are metabolised by CYP3A4 (Table I) the clinical significance of an interaction with grapefruit juice depends on the beneficial or detrimental effect that this may have on the individual and on the extent of that effect. The examples shown in Table II demonstrate that, while there may be evidence of an interaction, the resultant effect may not be of significance and therefore is not of concern for the safety of the patient. The major concern arises with drugs having a relatively narrow therapeutic window, since an increase in drug toxicity at a given dose is more probable given the higher bioavailability[9]. In decreased hepatic or renal function, where drug clearance and elimination are reduced, an increase in drug effect or in toxicity may become more evident depending on the pharmacokinetics and the therapeutic index of the drug.

Drug-grapefruit juice interactions could be of benefit when a drug has low oral bioavailability. The beneficial effect is seen when bioavailability and plasma concentration increase without the need for an increase in the dose, the dosing frequency or the cost of drug therapy[4]. Cyclosporin has low oral bioavailability because of significant intestinal metabolism. The drug is not rapidly metabolised by CYP3A4 but has a long absorption phase (lasting up to 8 hours in some patients) that increases exposure of the drug to the enzyme[11]. Enzyme inhibition results in an increase in bioavailability of cyclosporin that may lead to increased nephrotoxicity. However, in cyclosporin therapy, CYP3A4 inhibitors such as diltiazem or ketoconazole are administered concurrently with the immunosuppressant in order to raise the bioavailability of cyclosporin so that the dose of the drug can be reduced while still achieving therapeutic plasma concentrations. In real terms, this proves to be advantageous because of the lower cost of therapy. It has been suggested that grapefruit juice could be used to achieve this effect because it is inexpensive, nutritious and lacks the systemic effects of diltiazem or ketoconazole[1]. However the variables discussed above would preclude this approach. Furthermore, the variability in enzyme inhibition may lead to an increase in the cost of laboratory monitoring of plasma drug concentrations that could offset the decrease in the cost of cyclosporin therapy[4].

Conclusion

The importance of drug-grapefruit juice interactions should be judged on the basis of the therapeutic index, pharmacokinetics and the increased effect or toxicity of the drug and the variables that influence the interactions. Where the negative effects of an interaction have been shown to occur with a substantial exposure to grapefruit juice that is not likely to be encountered in normal diets, the clinical significance of a potential interaction becomes limited[9]. In the pharmacy practice setting, the dietary habits of the patient should be taken into account when dispensing drugs that may potentially interact with foods. In the case of interactions with grapefruit juice, more attention should be afforded to drugs having a narrow therapeutic index that may potentially interact with the food. ✶

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Websites of Interest

thechronic✶ill

Journals

With the expansion of the Internet, an ever-increasing number of medical and pharmaceutical journals are making their contents available on-line. The level of free access to these journals varies widely: some are limited to tables of contents, others to article abstracts and the occasional journal allows full-text access. The following are some leading journals that allow at least access to the abstracts of articles.

Annals of Allergy, Asthma, & Immunology
http://allergy.edoc.com/

Journal of the American Medical Association
http://jama.ama-assn.org/

British Medical Journal (BMJ)
http://www.bmj.org

Medical Care
http://www.medicalcare.org/

Diabetes Care
http://care.diabetesjournals.org/

Morbidity and Mortality Weekly Report
http://www.cdc.gov/mmwr/

Free Medical Journals
http://www.freemedicaljournals.com

New England Journal of Medicine
http://www.nejm.org

Hypertension
http://hyper.ahajournals.org

The Lancet
http://www.thelancet.com/journal

Miscellaneous

A number of other web sites provide useful information with links to latest updates and even more journals. The following sites offer updated drug information.

Drug Infonet
http://www.druginfonet.com

Pharmweb
http://www.pharmweb.net

Drug Information Association
http://www.diahome.org

Rx List
http://www.rxlist.com

E-medicine.Com
http://www.emedicine.com

Health Gate
http://www.healthgate.com

Helix
http://www.helix.com

Medscape
http://www.medscape.com

Mayo Clinic
http://www.mayohealth.org

The Synapse
http://www.thesynapse.net

Prescribing Errors
What's the Story?

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Keywords: prescribing errors, medication errors, adverse drug events

Although prescribing errors are one of the most common causes of preventable iatrogenic injury, there have been relatively few studies of their incidence and causes. The majority of the studies that have been carried out have been based in secondary care. This paper reviews what is currently known about prescribing errors. It is suggested that prescribing errors occur in at least 1-2% of all medication orders written, cause harm in about 1% of admissions, and have a wide range of causes. Organisation-wide interventions and cultural changes are likely to be required to prevent them. However, useful first steps suggested include reporting prescribing errors identified, formally reviewing pharmacists' interventions and developing increased 'error awareness' amongst all health care professionals.

Introduction

Medical errors and the harm they can cause are receiving increasing attention. In the UK, the Department of Health recently issued two reports highlighting this problem[1,2] and an entire issue of the British Medical Journal has been devoted to the subject[3]. In the US, the Institute of Medicine report 'To err is human: building a safer health system'[4] has received worldwide publicity. It is clear that medical errors are causing concern amongst patients, health care professionals and governments alike.

Medication errors are one of the most common types of medical error[5]. It has been estimated that 1-2% of patients admitted to US hospitals are harmed as a result of medication errors[6], and that each error that results in harm costs an additional US$5000 excluding legal costs[7]. In the UK, it has been recommended that serious errors in the use of prescribed drugs should be reduced by 40% by 2005[1]. In a landmark US study, the majority of the preventable adverse drug events (mediation errors that result in harm) were specifically attributed to prescribing, rather than dispensing or administration[8,9]. It is therefore surprising that there have been few studies of prescribing errors and their causes. This paper reviews what we do know about prescribing errors and suggests some ways forward. It is based on a literature search carried out using Medline and Embase databases to identify studies of prescribing errors published between 1980 and April 2001. Studies of standards of prescription-writing, rather than prescribing errors, are excluded.

Studying prescribing errors

A word of caution - the prescribing error literature can be difficult to interpret! The results of many studies do not distinguish between the different types of medication error such as prescribing, dispensing and administration errors[5,10-12]. Others do not differentiate between medication errors and adverse drug reactions[13-15]. There are also wide differences in the definitions and data collection methods used[6], although a standard practitioner-led definition has now been developed[16].

How often do prescribing errors occur?

Studies of the prescribing error frequency generally fall into two groups, those based on pharmacist review of medication orders and those based on the identification of patient harm. Each of these will be considered in turn. Most research into prescribing errors has taken place in US hospitals, although more recently studies have also taken place elsewhere.

Pharmacists' Review of Medication Orders

In the US, pharmacists reviewing medication orders in the course of their prescription monitoring duties have identified (and prevented) prescribing errors in 0.3 to 1.9% of all medication orders written[17-20]. However, careful examination of these studies reveals some variation in the definitions of an error used and comparisons amongst them should be made with caution.

The most prolific authors in this area are Lesar and colleagues, based in a teaching hospital in New York State. In their first study, an error was identified in 0.3% of all medication orders written[17]. The most common category of error was 'wrong dose' errors. When 'problem orders' (errors without toxic potential, errors

concerning doses that were unlikely to be given, and missing information) were excluded, the 'significant' error rate was 0.2%. As a result of these findings, an ongoing prescribing error monitoring programme was initiated. A total of nine years' data were later published[21], which suggested that the rate of significant errors had increased from 0.2% to 0.4%. However, as the authors point out, these error rates are likely to be an underestimate of the true error rate, as many errors will go undetected by dispensary-based pharmacists.

In a further study, the same authors examined a series of significant errors to explore the most likely contributing factors[18]. The contributory factors were assigned by the investigators rather than the prescribers involved. Nevertheless, the results suggest that the most common factors involved knowledge about drugs and knowledge about patient characteristics that affect drug handling. Analyses of data for specific groups of drugs such as antimicrobials have also been published[22].

There have been far fewer studies outside of the US. Twenty-five years ago, Tesh and Beeley[23] carried out a retrospective review of 455 patients' drug charts in a UK hospital. These investigators examined errors in drug use and errors in prescription writing such as prescribing by brand name. It was concluded that more than 30% of all medication orders contained an error of prescription writing. The medical notes were also reviewed for 385 patients to identify any contra-indications to the drugs prescribed; it was concluded that overall, 3.6% of all medication orders were associated with an error in drug use.

More recent UK studies have focused on pharmacists' clinical interventions. For example, Hawkey et al.[24] recorded interventions in six hospitals. It was found that pharmacists made interventions in about 2.9% of all prescriptions, and that the majority concerned drug doses. In the former North Thames Region of England, hospital pharmacists record all interventions made during one week each year. These data are then collated and analysed centrally. For example,

Barber et al.[25] reported that 3501 interventions were made for 10,478 occupied beds during a one-week period, equivalent to 33 interventions per 100 beds per week. However, such studies do not allow firm conclusions to be drawn regarding the frequency of prescribing errors, as pharmacists' interventions also include advice-giving, formulary issues and patient counselling.

In a more recent UK study, pharmacists recorded details of all prescribing errors identified in non-obstetric inpatients during a four-week period[26]. The number of medication orders written was estimated from a 1 in 5 sample of inpatients. An error was identified in 1.5% of all prescriptions written, of which one quarter were judged to be potentially serious. As in other studies, the majority (59%) were associated with choice of dose.

In studies of this type, the errors reported are those that pharmacists identify and draw to the prescribers' attention. The medication orders concerned are usually corrected before the patient receives the medication. There are therefore no adverse patient outcomes. In contrast, studies based on the identification of harm include only the subset of errors that reach the patient and result in injury.

Identification of harm

Such studies usually include iatrogenic injury of many different kinds, but depending on how the data are presented, the frequency of medication-related events can usually be identified. The US Harvard study[5] is probably the most well known study of iatrogenic harm and was based on the retrospective review of more than 30,000 medical records. This study suggested that a medication error caused harm in 0.7% of inpatients. A similar study in Australia identified a figure of 1.8%[27]. However, these figures include both prescribing and administration errors and the results do not allow differentiation between them. The Adverse Drug Event (ADE) Prevention Study Group examined medication-related harm in more detail[8]. This six-month study included all adults admitted to a stratified sample of wards in two large hospitals.

A medication error that resulted in harm ('preventable ADE', in the authors' terminology) was identified in 1.8% of admissions. Prescribing accounted for the majority of these, representing 1.0% of all admissions. The staff involved were also interviewed to obtain details of the circumstances surrounding each error[9]. As in Lesar et al's study[18], the most common causes were lack of knowledge about the drug and lack of knowledge about the patient. More recently, a similar study was carried out in two paediatric hospitals; a preventable ADE was identified in 0.4% of admissions[28].

Why do prescribing errors occur?

Surprisingly, there has been little research into the reasons why prescribing errors occur. While many health care professionals have their own hypotheses about the causes of prescribing errors, there is little evidence on which to base these theories. There is, however, a growing body of research concerning human error in other fields.

Theories of human error have been used for some time to analyse errors in high-risk environments such as aviation and nuclear power, and have more recently been applied to medicine[29,30]. There are many different approaches to the study of human error[31], but Reason's accident causation model[32] is the most widely used. This model is based on the assumption that 'active failures' on the part of front-line individuals are largely the result of the conditions in which they work, often termed 'error producing conditions'. These in turn are the result of fallible decisions at an organisational level, known as 'latent conditions'. There is therefore less focus on the individual who makes the error and more on pre-existing organisational factors. The advantage of using this approach is that it aids the identification of relevant latent conditions, the primary focus of intervention[33]. Reason's model has now been used to investigate and analyse incidents in obstetrics[34], mental health[35] and other clinical settings[29]. It has also been used to develop a protocol for the routine investigation of adverse incidents in hospitals[36].

However, this approach has only recently been applied to prescribing errors[37]. In this UK study, forty-four interviews were conducted with prescribers making potentially serious errors. It was found that active failures were usually slips in attention or mistakes such as not applying relevant rules. Doctors identified many error-producing conditions; these included work environment, workload, whether or not they were prescribing for their own patient, communication within their team, physical and mental well-being, and lack of knowledge. Latent conditions included lack of training, low perceived importance of prescribing, a hierarchical medical team, and a lack of self-awareness of errors. It was concluded that amongst other things, we need to create a culture in which prescription writing is seen as important and to sensitise health care professionals to situations in which errors are most likely to occur.

Conclusions

The literature suggests that prescribing errors are a major source of iatrogenic injury in hospitals. While little is known about the incidence of errors in primary care, there is no reason to suppose that prescribing errors are any less frequent. Careful study of the literature also reveals that there is wide variation in the definitions of a prescribing error used, and that little is known about their causes or how they can be prevented. Human error theory has been helpful in the investigation of adverse incidents in medicine, and has more recently been applied to prescribing errors. Large-scale studies of interventions to reduce prescribing errors are now required. However, useful first steps suggested include reporting prescribing errors identified, formally reviewing pharmacists' interventions and developing increased 'error awareness' amongst all health care professionals. Any successful intervention to reduce prescribing errors is likely to require the involvement of all health care professionals. *

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The Importance of Education in Diabetes Care

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Diabetes is a condition that cannot be cured but can be controlled. It has been shown that people with controlled diabetes are less liable to develop the complications of the disease. Education is important because one cannot have good control without education in the management of diabetes.

There is a high prevalence of diabetes in Malta. 10% of the Maltese population over the age of 18 years suffer from this condition. Unfortunately, in spite of all the efforts done to promote education, there still exists a lack of awareness among the diabetics and the general public.

As the Deputy Nursing Officer in charge at the Diabetes Clinic and as a member on the Council of the Maltese Diabetes Association, I consider education as a priority in the treatment of diabetes. Controlling diabetes means keeping the blood sugar level as close to normal as possible.

It is very important that a diabetic keeps himself/herself well informed about his/her condition. Here are some ways how such information could be obtained.

• Education programs are held monthly at the Diabetes Clinic outpatients Department, at St. Luke's Hospital. All newly diagnosed diabetics are invited to attend. Those who have never attended such lectures can contact the reception desk at the Diabetes Clinic, and will be invited to attend these sessions.

2. Monthly lectures on diabetes are held at the Malta Diabetes Association in Valletta for members of the Association.

The Maltese Diabetes Association was set up in January 1981 with the aim of setting up a support group for those suffering from diabetes. The Association has a current membership of 900 persons. In spite of the high incidence of diabetes in Malta the response on the part of the public is very low. This may be due to the fact that those affected by this condition do not appreciate the possible long-term effects of diabetes. The Maltese Diabetes Association is a member of the International Diabetes Federation, with whom we exchange ideas and up to date information on new methods and technologies to fight and control the condition. Committee members, including lay members, attend conferences abroad where they are able to compare and contrast the local situation with those of other countries with a view to improving the conditions of people suffering from diabetes.

The Association publishes a magazine *(Id-Dijabete U Saħħtek)* once every four months wherein local specialists and other health care personnel write articles on matters of interest to those suffering from diabetes. A monthly meeting is held for all the members of the Association and the general public. Specialists in various fields related to diabetes are invited to deliver talks on a specific topic, such as, home monitoring care of the feet.

The Juvenile Support group has recently been revived to cater for the needs of young people with diabetes. Parents and their diabetic children are urged to attend to discuss their problems and learn how to deal effectively with various situations which may arise.. A summer camp is organised once a year for the diabetic children. The children are given the opportunity to learn how to cope with their condition without the over protectiveness of their parents. Throughout the camp continuous indirect education is given to the children.

The Diabetes Association is a philanthropic organisation run with the help of specialists in the field of diabetes and lay volunteers.

The Association's premises can be found at 111 Melita Street, Valletta. Council members are available for any assistance every Wednesday morning between 9.00 and 11.30 am. Any further information can be obtained by writing to the Association at P.O. Box 414 Valletta or telephone 221518. ✴

Back to Basics

Diabetes Mellitus and its Management
An Introductory Overview

Part 1 **Pathophysiology, Classification, Diagnosis and Complications**

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Key words: diabetes mellitus, insulin, type I diabetes, type II diabetes,
impaired glucose tolerance,

Diabetes is one of the most prevalent chronic disorders worldwide. By 2010, the number of people with diabetes is expected to exceed 350 million[1]. Diabetic complications cause considerable morbidity in 5-10% of these patients, with diabetic complications accounting for 4% of hospital admissions[2]. Malta is no exception with statistics gathered in 1987 indicating that 10% of adults aged 35 and over had diabetes while another 13% had impaired glucose tolerance (IGT).

This problem is found in other Mediterranean island communities (Cyprus, Sardinia, Sicily, Pantelleria) where a prevalence of 5% is found[3]. Opportunities for interacting with the diabetic patient are numerous and the pharmacist is ideally positioned to intervene with the aim of optimising patient treatment. This review will deal with a brief pathophysiology of diabetes and its complications, a good knowledge of which is fundamental since it leads to a clear understanding of the factors to be considered when choosing the appropriate therapy for the individual patient.

Definition of diabetes

Diabetes mellitus may be defined as a clinical syndrome characterised by hyperglycaemia due to absolute or relative deficiency of insulin[4]. If not treated, diabetes may lead to acute hyperglycaemia (diabetic ketoacidosis (DKA) or non ketotic hyperosmolar coma) and, if long-standing, to late complications leading to a reduced life expectancy.

How does insulin maintain a normal blood glucose?

Following food intake, a homeostatic mechanism comes into play which ensures that food is appropriately stored for later use. In response to food ingestion and the ensuing direct stimulatory effect of glucose and amino acids on pancreatic ß cells, insulin is secreted. This promotes carbohydrate uptake by the liver and muscle for glycogen synthesis, carbohydrate uptake by adipose tissue for triglyceride synthesis, amino acid uptake into liver and muscle and triglyceride uptake by adipose tissue. Throughout, insulin acts as an 'anabolic' hormone, that is, it promotes synthesis of protein, glycogen and triglycerides and prevents their breakdown into the respective subunits.

In the fasting state, mobilisation of stored energy is necessary and this is accomplished by:

1. reduced insulin secretion resulting in the release of glucose from glycogen stores in the liver and muscle

2. increased lipolysis during which triglycerides are broken down into free fatty acids. This is enhanced by glucagon and other counter-regulatory hormones.

What happens if there is a lack of insulin?

When insulin secretion is lacking, one observes:

1. a breakdown of stored triglycerides and proteins resulting in catabolism and the characteristic weight loss seen in uncontrolled diabetes

2. an excessive production of ketone bodies leading to metabolic acidosis. This results in DKA - an acute decompensated state which should be treated as a medical emergency[4,5].

Classification of diabetes.

The following is an overview of the classification of diabetes :

A. Primary diabetes: implying that no underlying disease is present

- Type I: previously known as insulin dependent diabetes mellitus (IDDM) or juvenile diabetes

- Type II: previously known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes

- MODY: maturity onset diabetes of the young

B. Gestational diabetes: defined as hyperglycaemia which is first diagnosed during pregnancy (that is, not in a previously known diabetic)

Diagnosis and treatment are important since the excess maternal glucose crossing the placenta may result in excess foetal insulin secretion. This, in turn, may cause foetal macrosomia and increase the risk of birth trauma, may necessitate Caeserean section and may lead to neonatal hypoglycaemia. Women with gestational diabetes often develop diabetes within five years post partum[4].

C. Secondary diabetes: implying diabetes secondary to an underlying pathology

- Malnutrition related diabetes

- Secondary to pancreatic disease - for example, chronic pancreatitis: a common cause is alcoholism where beta cell mass is destroyed[6]; cystic fibrosis; neoplastic disease

- Secondary to endocrine disease - often involves excess endogenous production of hormonal antagonists to insulin[4,6]: for example, phaeochromocytoma; acromegaly; Cushing's syndrome; 'stress hyperglycaemia' following severe burns, acute myocardial infarction and other life threatening illnesses (due to endogenous release of glucagon and catecholamines)

- Drug induced - for example, corticosteroids, loop and thiazide diuretics; phenytoin

- Insulin receptor dysfunctionality - hyperglycaemia occurs due to quantitative or qualitative defects in the insulin receptor or to antibodies directed against it[1,6].

- Inherited disorders - (diabetes plus) for example, muscular dystrophies; Down's syndrome; Turner's syndrome[7].

- Non-endocrine disorders - for example, renal failure and hepatic failure

Type I and Type II diabetes are the most commonly encountered forms of diabetes and consequently, this review will focus mainly on these two types. Since the approach to management and

Table I
Characteristic Features of Type I and Type II diabetes[(2,6)]

Feature	Type I diabetes	Type II diabetes
Prevalence	• 5-10% of diabetic population	90% of all diabetics
Age of onset	• usually less than 30 years	• usually over 40 years
Pancreatic function	• no residual or very little pancreatic function	• retain some pancreatic function
Aetiology	• though exact aetiology is unknown, presence of islet cell antibodies indicate an autoimmune function	• involves defects in insulin secretion, resistance to insulin, hepatic glucose output
Family history	• generally not strong	• strong family history
Obesity	• commonly not obese	• commonly obese
Onset	• usually sudden and patients present with ketoacidosis	• insidious and diagnosed during routine examination

treatment is somewhat different, an understanding of the main features of each one and the differences between the two is crucial.

Table 1 summarises the main characteristic features of Type I and Type II diabetes[1,6]:

What are the signs and symptoms of diabetes?

It is of primary importance that the pharmacist has a good understanding of commonly presenting signs and symptoms of diabetes since patients may present at the community pharmacy with such ailments.

In the Type I patient, the onset of the disease is sudden with profound weight loss (despite increased intake of food), severe fatigue, polydipsia (thirst) and polyuria (frequent urination)[5,8]. Such patients should be referred immediately since acute metabolic decompensation is imminent and patients normally require hospitalisation.

Patients with Type II present with less severe symptoms - fatigue, polyuria and vaginal and urinary tract infections. However, the onset of Type II is often a gradual process and very often the 'classic' symptoms are not apparent. Therefore, patients may present when complications of diabetes have occurred[8]. It is therefore very important to encourage patients at high risk to undergo screening tests with emphasis on fasting and random blood glucose levels.

The World Health Organisation criteria for the diagnosis of diabetes mellitus are[5,9]:

1. A fasting blood glucose of >7.8 mmol/l preferably obtained on two repeated occasions or a random blood glucose of >11.1 mmol/l on two repeated occasions

2. A two hour glucose level of 11.1 mmol/l or more during an oral glucose tolerance test. When the two hour value is between 7.8 and 11.1 mmol/l, the patient is diagnosed as having IGT. This implies that the patient is:

- at an increased risk of developing diabetes

- at an increased risk of developing atherosclerotic disease.

When IGT is diagnosed, management is directed toward avoidance of diabetes and arterial disease - follow up with blood glucose tests is imperative. At this point, it is appropriate to mention urine testing for glucose.

Unfortunately, there is a popular local belief that urine testing for glucose is "THE TEST" to use to diagnose and monitor diabetes. Urine glucose concentrations correlate poorly with blood glucose concentrations and therefore should only be used for patients who cannot or refuse to test blood. In the healthy individual, a blood glucose of 15 mmol/l or over is required for a urine glucose test to be positive. Besides, the renal threshold for glucose may be decreased, as in pregnancy or when other sugars are present in the urine, or increased in the elderly. This results in false positive or false negative tests implying that urine testing is not a reliable method[5].

Why is it important to maintain normal glucose levels?

The main aim of trying to achieve euglycaemia (normal blood glucose levels) is to prevent development of acute complications and to delay progression of the disease. Published studies have provided evidence that tight glycaemic control is associated with reduced complications both in Type I and Type II. The Diabetes Control and Complication Trial (DCCT) has clearly shown this in Type I diabetes[10] while the UK Prospective Diabetes Study (UKPDS) has shown this in Type II diabetes[11]. The latter is the longest and largest study in the history of diabetes and has clearly shown that tight control

produced a 25% reduction of macrovascular complications[9].

The main chronic complications of diabetes

A. **Macrovascular disease:** This leads to an increased risk of coronary heart disease and is the major cause of increased mortality in diabetic patients accounting for about 70% of all deaths[4]. Risk factors for coronary heart disease (for example, smoking, hypertension and hypercholesterolaemia) have to be minimised in a diabetic patient since risk factors are additive[5].

B. **Diabetic microangiopathy:** This is a disease of the small vessels specific to diabetes. It is the main cause of morbidity in the diabetic patient. Diabetes first induces a structural abnormality in the blood vessel with an increase in basement membrane thickness. This consequently leads to a functional abnormality with increased permeability of the blood vessels to fluid and molecules such as albumin[10]. Though all blood vessels are affected, three specialised regions are at particular risk:

- the kidney, leading to diabetic nephropathy

- the eye, leading to diabetic retinopathy and blindness

- the nerve sheath, leading to diabetic neuropathy in turn leading to a loss of sensation and increased risk of injury.

The acute complications of diabetes

A. **Diabetic ketoacidosis (DKA):** a metabolic acidosis which occurs due to excess synthesis of ketone bodies as a result of insulin deficiency. As already explained above, an insulin deficiency results in a catabolic state where triglycerides are broken down into free fatty acids. These are taken up

by the liver together with alanine, lactate and glycerol to synthesise acidic ketone bodies, acetoacetate and 3-hydroxybutyrate. Accumulation of these substances leads to a metabolic acidosis. The patients normally present with profound dehydration, hyperventilation, vomiting and sometimes abdominal pain. Management involves:

• Fluid replacement in the form of 0.9% normal saline

• Electrolyte replacement

• Insulin replacement usually in the form of a continuous intravenous infusion[5].

Within the local state hospital, all DKA patients are admitted on wards M5 and M6. A written protocol for the treatment of DKA is present on the wards and ensures that management is standardised.

B. Non-ketotic hyperosmolar coma: This usually occurs in older patients and normally affects patients with Type II. It occurs when uncontrolled hyperglycaemia leads to dehydration, increased osmolality and ultimately coma. However, ketosis does not develop since some residual insulin activity inhibits the peripheral lipolysis occurring in DKA and ketone production is therefore suppressed. Patients normally

present with profound dehydration and a reduced level of consciousness. Management is similar to that for DKA with the exception of the following :

• Fluid replacement is in the form of 0.45% Normal saline

• Insulin replacement is usually less

• Due to the high risk of thrombosis, heparin treatment is instituted[12].

C. Hypoglycaemia: This fall in blood glucose is often related to treatment issues in Type I and Type II patients. This will be discussed in detail later on in the series. ✶

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1. Withrow R, Roberts L. The videodisc: Putting education on a silver platter. Electronic Learning 1987: 1(5):43-4.

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2. Author's surname Author's first name or initial. Title of the Book. Edition [if not first]. Place of publication: Publisher's name; Year of publication.

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3. Blaxter P. Social health and class inequalities. In: Carter C, Peel J, editors. Equalities and Inequalities in Health. 2nd ed. London: Academic Press; 1976.

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