Journal of the Malta College of Pharmacy Practice

The Chronic*ill

Issue 10 Summer 2005
ISSN 1811-9514

Malta College
of Pharmacy Practice

www.mcppnet.org

Ensuring the appropriate use of medicines

Maria Cordina B Pharm(Hons), PhD(QUB)

Email: president@mcppnet.org

The safe and effective use of medicines requires the ongoing collaboration of the various health care professionals involved in patient care. Pharmacists are crucial in ensuring the appropriate use of medicines both in the community and in hospital. The large number of medicines available and the constant efflux of new information, be it safety or regulatory, makes it practically impossible for any one health care professional to be updated on all aspects.

Since our aim is the well being of the patient, it is our professional responsibility to proactively seek unbiased information about medicines and their appropriate use. We have, for some time now, realized that the choice of medication is not only based on the disease but we need to select the right drug for the patient with a health-related problem, bearing in mind that the patient has a particular life style, possibly has concomitant conditions, is treated with other medicines and/or self-medicates. The selected medicine must also be accepted by the patient. Our choice, therefore, needs to be by far more refined, making the process more demanding. Hence, appropriate drug use is not a simple issue.

The Malta College of Pharmacy Practice is committed to contributing to the appropriate use of medicines by facilitating the provision of medicines information to both pharmacists and medical doctors through its meetings and publications. Having access to the same information, communicated in the same style will help us speak the 'same language' in terms of medicines use and enhance inter-professional collaboration for the eventual

Journal of the Malta College of Pharmacy Practice

THE chronic*ill

Issue 10 Summer 2005

ISSN 1811-9514

The Official Publication of the Malta College of Pharmacy Practice
c/o Department of Pharmacy, University of Malta, Msida
Tel: (356) 2340 2899
Fax: (356) 2540 1157
Email: info@mcppnet.org
www.mcppnet.org

benefit of the patient. We have therefore formed an alliance with the Medicines and Poisons Service at St. Luke's Hospital and with the Medicines Authority to fulfill our aim of ensuring patient care through medicines use.

The paper by van Mill, a pioneer in research on drug-related problems (DRPs), gives us a well-defined and practical over view of DRPs. While some DRPs are unavoidable, others are preventable. The article clearly differentiates between a medication error and a DRP. These problems may originate when the drug is prescribed, dispensed or administered. It is the pharmacist's responsibility to identify any DRPs at the point of dispensing. Prescription verification should follow if there is reason to believe that a DRP, especially one which could lead to morbidity, may result from dispensing such a drug. This, however, may prove to be a rather monumental, unachievable task when the prescriber's name and registration number are not identifiable. Pharmacists are often faced with the problem of being unable to identify a prescriber due to an illegible signature and the absence of the prescriber's contact details, making it impossible to determine who is responsible for prescribing the drug and to verify the prescription. The pharmacist must practice in the best interest of the patient, and may be placed in a position to exercise the right to refuse dispensing (Medicines Act, Part III, 80).

The importance of pharmcovigilance and post marketing surveillance is highlighted by Zammit in the paper entitled 'The rise and fall of cyclo-oxygenase 2 (COX-2) inhibitors'. The paper outlines the identification of the problems associated with COX-2 inhibitors, the published studies leading to regulatory action and the emphasis on more cautious and appropriate use. When a drug is given a license for use in a particular indication/s, information would have been provided regarding its therapeutic and safety profile. However, it is only when it is used in the 'real' world that new and possibly unforeseen problems start to emerge, that could lead to drug related morbidity and mortality. Considering the significant problems emerging when drugs are used appropriately for an indication for which they have been licensed, the use of a medicine for an unlicensed indication should be a rare event, and ethical issues should be factored in to such a decision. It is therefore clear that *all* medicines should be used with caution and a risk/benefit analysis should be performed before their use. Monitoring of the patient to determine if the positive desired outcome has been achieved, to identify the emergence of any negative effects and to ascertain if the patient's expectations of the therapy are being met, is essential.

Vella focuses on the problem of drug induced peptic ulcer disease. The paper provides an evidence-based update on the main classes of drugs, which contribute to GI morbidity. Practical information as to how to reduce this type of drug-related morbidity has also been included. Preventing drug related morbidity not only contributes to enhancing patient care but also reduces the costs of treating these events.

At times it appears that medicines have become such an integral part of our lives that we tend to over look the fact that every time we introduce a xenobiotic into a person's system we are potentially also introducing a negative effect. Medicines have lost their 'mystical' powers and hence at times we tend to use them without due attention. We have also, unfortunately, transmitted this false sense of security to society, conveying the message that there is a 'pill for every ill' and introducing a quick fix mentality.

Our restricted ability of communicating to patients both the benefits and risks of medicines by using terms such as 'this is very mild' in order to enhance 'compliance' (as opposed to the current trend of concordance) is backfiring. Patients may either choose to believe these statements and take their medicines without a second thought, getting their refills without being monitored or procure information through various means including the internet and finding out that their medicine invariably does have negative effects. At this point they may loose faith in their health care professionals and choose to stop their medication on their own accord. Some may seek a solution through the less conventional means of alternative and complimentary medicine. Herbal preparations are a current favorite, as they are aggressively marketed as being perfectly safe and causing no harm since they are natural.

Another favorite approach is telling patients who have chronic disease that they have to keep taking 'THIS' medicine for the rest of their lives. What is actually meant by this statement is that the condition cannot be cured but can be managed on a long term basis by using medication. The medicine selected would be the most appropriate when taking into consideration the patient's condition, the current state of general health of the individual, the patient's response to therapy, the knowledge currently possessed regarding the management of the condition and about the medication itself, and the availability of medicines. When one or more of the above factors change it is very likely that the therapy may also need to change. Therefore the statement that any one particular medication must be taken for the rest of one's life is inaccurate and may lead to confusing the patient when the time inevitably arrives to alter therapy.

We should, once again, start to treat medicines with respect and transmit this to patients by providing correct information in a manner in which they can understand.

The College has recognised the importance of communication skills in forming and enhancing relationships with other health care professionals and with patients. We have therefore invited Juliet Higdon, an expert in communication and counseling skills to share her experience with us through an article in the Journal and an interactive session to be held as part of the Autumn professional development programme.

Pharmacists are the key health care professionals involved in the provision of safe and effective use of medicines. Inter-professional collaboration is essential to ensure appropriate medicines use. Pharmacists and medical doctors both at community level and in a hospital setting should seek constructive and effective ways to form a working relationship that will put the interest of the patient first and lead to the safest and most appropriate use of medicines.

Drug-related problems: a cornerstone for pharmaceutical care

Foppe van Mil Pharm D, PhD

Community Pharmacist
Pharmacy Practice Consultant
Secretary of Pharmaceutical Care Network Europe (PCNE)

Email: foppe@vanmilconsult.nl

Key words: Drug-related problem, pharmaceutical care, medication errors

Drug related problems are an essential term in the world of pharmaceutical care. Other terms can be used for the same concept, such as medication errors, but this term is different from drug related problems. The errors refer to the mistakes in the process that could lead to problems. Drug related problems can originate when prescribing, dispensing or taking/administering medicines. Drug use problems by the patient are probably the most frequent, but are not always noticed. There are several classifications for drug related problem, but in this article the classification of the Pharmaceutical Care Network Europe (PCNE) is used to clarify the concepts. Some of the known classifications seem difficult to be used in practice, and especially the reproducibility of the existing classifications should be researched further.

The concept of pharmaceutical care started developing in the early 1990s after the milestone publication of Hepler and Strand on this subject[1] and some years later Hepler depicted pharmaceutical care as a quality improvement process (a circle of Denning) in which the professional improves the outcomes of pharmacotherapy. During the quality improvement process, the causes that potentially lead to problems resulting from pharmacotherapy should be identified and corrected.[2] This philosophy around optimizing the outcomes of pharmacotherapy and pharmaceutical care lead to the concept of Drug Related Problems or DRPs, indicating some problem in the pharmacotherapy of the patients. DRPs therefore are defined as problems in the pharmacotherapy of the individual patient that actually or potentially interfere with desired health outcomes (definition PCNE 1999). The essential element of this definition is the impact of the problem on the health-outcome of the pharmacotherapy. If there is no potential impact, then there is no drug-related problem.

It would be much better to prevent drug related problems than to correct them, but this is not always possible because of the complexity of pharmacotherapy, lack of training and knowledge of health care providers and the behaviour of the medicine users. Also, some pharmacotherapy problems are the result of an unexpected reaction of the individual, like allergies, and cannot always be predicted. Therefore, even if one could analyse the medication and patient related factors during a medication review before a medicine is handed over to the patient, the evaluation of the pharmacotherapy after it has been initiated still remains necessary to detect DRPs and optimise outcomes.

A drug related problem is essentially different from a medication error. According to the NCC MERP a medication error is 'any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of a health care professional, patient, or consumer'.[3] A medication error is much more process orientated than outcome orientated. If something goes wrong in the prescribing or dispensing *process*, then it is automatically regarded as a medication error whether or not there is an impact on patient outcome. Additionally, errors in medication use by patients seem not to be included but such errors can be causes for drug related problems.

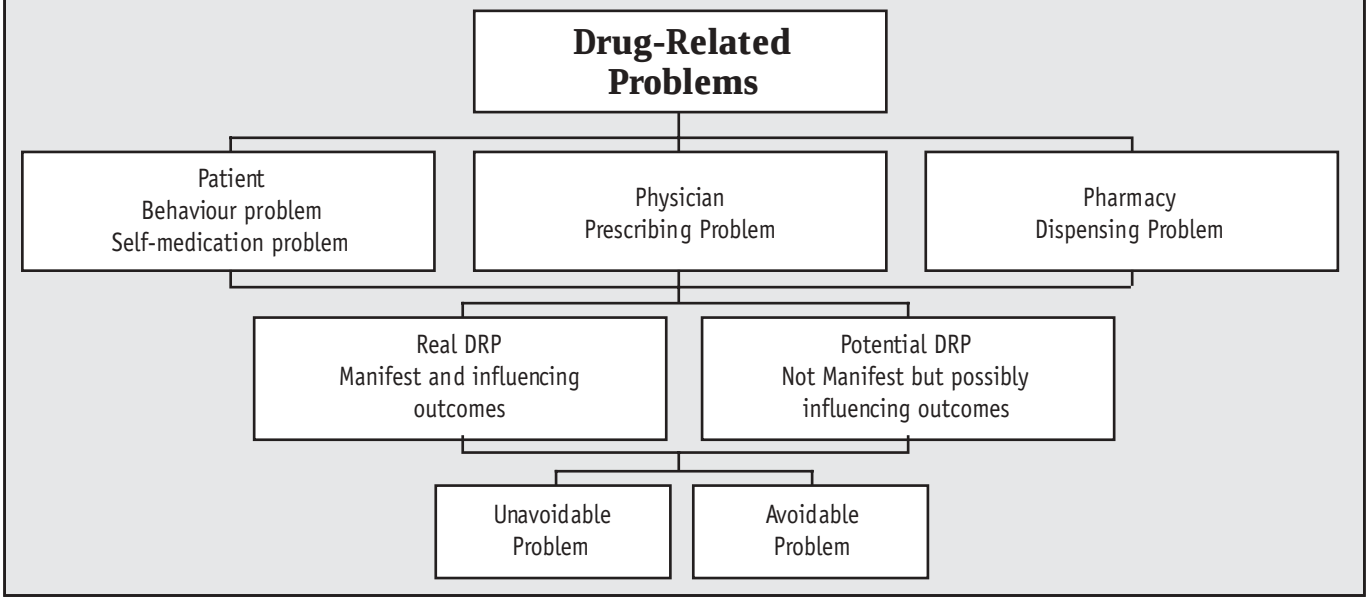
Terminology

The term 'Drug Related Problem' is not unique for a problem with pharmacotherapy. Other terms have been proposed. For instance 'drug-therapy problem' is often used too, and was introduced by the group of Cipolle, Morley and Strand.[4] Krska introduced the term 'Pharmaceutical Care Issue' in 2002. That term is sometimes used in the UK.[5]

Fernandez-Llimos *et al.* recently proposed 'pharmacotherapy failure', corresponding to negative clinical outcomes resulting from the use or the lack of use of medicines. Those pharmacotherapy failures then include necessity, effectiveness and safety problems.[6]

All these terms may stand for similar concepts as drug-related problems and therefore it remains important to define the concept properly before using it in research or publications.

Figure 1: The scenery of drug-related problems



How and where do DRPs originate

In the entire course of installing pharmacotherapy there are three main processes where a drug-related problem can be generated: the prescribing, dispensing and drug use process as illustrated in Fig.1

DRPs can also be split into real and potential DRPs. Additionally some of those problems cannot be avoided without reducing the effect of the pharmacotherapy, e.g. nausea as a side effect of oncolytic medicines, or interactions between different medications for AIDS.

Prescribing problems originate usually behind the physicians' desk, or sometimes at the bedside. Usually negligence or lack of knowledge may cause such problems, sometimes lack of information regarding the full therapeutic profile of the patient, and at times possibly also missing laboratory data. The physician can also be influenced by external entities, such as the pharmaceutical industry, and may not prescribe the most appropriate medicine. Nurses may also cause DRPs by wrongly copying the physicians' instructions on a chart or order form, or by not providing medication as intended.

Dispensing problems also are often a result of negligence. Misinterpreting the physicians' handwriting, not performing a drug use review, taking the wrong box or bottle may all cause DRPs.

Drug use problems by the patient probably occur very frequently, but are not always noticed. In general, half of the patients do not adhere to the pharmacotherapy. This leads to a significant amount of drug related problems, but only part of those problems are detected e.g. when the patient is taken to the emergency department of a hospital for not taking insulin.

Example of a Drug Related Problem - Case study

Mrs A, an 87 year old lady, has been taking digoxin 0.25 mg daily for her atrial fibrillation for 3 years. Recently you have noticed that she is getting increasingly frail and may have lost weight. On a Saturday morning she presents a new prescription for digoxin. While you prepare the prescription, she tells you that she has been having visual disturbance and wonders if she needs her glasses replaced. You recognise the possible side effect of the digoxin and tell her not to take the digoxin for one day and to go to her GP on Monday to explain her symptoms.

There clearly is a DRP, a problem with the pharmacotherapy, because the visual disturbance is most probably due to high plasma levels of the digoxin. The probable cause of the problem is too high a dose as a result of a lack of therapeutic drug monitoring.

If this problem must be documented or registered, a classification that is especially designed for DRPs can be used. The PCNE-DRP classification is an example of such a documentation tool. The global outline of this classification is illustrated in Table 1

In the case of the woman with the digoxin, P1 and C1 plus C2 would be the appropriate coding choices because the patient suffers from an adverse drug event, caused by an issue in the drug use process. However, this description does not provide much information. Therefore, in the PCNE classification, a second more detailed information level is available. Then the coding would read as P1.3, C2.4, I2.3 and I3.5 (see also Table 2).

One will also need some extra patient and drug data in order to document a drug related problem like gender and age and ATC-code.* A form to document drug related problems is illustrated in Figure 2.

* A coding system for medicines compiled by the WHO: the Anatomic Therapeutic Classification.

Table 1: The first level domains of the PCNE-classification V. 5		
	Code	**Domains**
Problems	**P1**	**Adverse reaction(s)** Patient suffers from an adverse drug event
	P2	**Drug Choice Problem** Patient gets or is going to get a wrong (or no drug) drug for his/her disease and/or condition
	P3	**Dosing problem** Patient gets more or less than the amount of drug he/she requires
	P4	**Drug Use/Administration Problem** Wrong or no drug taken/administered
	P5	**Interactions** There is a manifest or potential drug-drug or drug-food interaction
	P6	**Other**
Causes	**C1**	**Drug/Dose Selection** The cause of the DRP can be related to the selection of the drug and/or dosage schedule
	C2	**Drug Use Process** The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label)
	C3	**Information** The cause of the DRP can be related to a lack or misinterpretation of information
	C4	**Patient/Psychological** The cause of the DRP can be related to the personality or behaviour of the patient.
	C5	**(Pharmacy) Logistics** The cause of the DRP can be related to the logistics of the prescribing or dispensing mechanism
	C6	**Other**
Interventions	**I0**	**No intervention**
	I1	**At prescriber level**
	I2	**At patient (or carer) level**
	I3	**At drug level**
	I4	**Other**
Outcome of intervention	**S1**	**Problem totally solved**
	S2	**Problem partially solved**
	S3	**Problem not solved**

Table 2: PCNE V 5.01 codes for the example case		
	Code	**Description Subdomain**
Problems	**P1.3**	**Toxic effects suffered**
Causes	**C1.2**	**Inappropriate dosage selection**
	C2.4	**Therapeutic drug level not monitored**
Intervention	**I2.3**	**Patient referred to prescriber**
	I3.5	**Drug stopped**

Classifications

There are many classifications available to code drug related problems (see also Table 3) but not all those classifications are easy to use. Van Mil *et al.* published an overview of such classifications in 2004.[7]

A practical classification should at least have the following characteristics:

- Focus on the problem itself not on its cause or consequence;
- Problems should be clearly and uniquely defined;
- The classification should be valid and the coding reproducible

Some additional properties would make a classification extra attractive:

- Preferably enable coding for both practice and research;
- Suitable for the documentation needed for the remuneration of cognitive services;
- Open structure, enabling introduction of additional coding levels without the need to change the basic structure;
- Offer an option to classify the intervention.

Selection and validity issues†

The issue of definitions becomes once again important when choosing a valid classification for documenting DRPs. What does one consider a DRP to be? In a publication by Paulino *et al*, the uncertainty or lack of knowledge about the aim or function of the drug was considered to be a drug related problem.[8] For others it could be the cause (potential cause) of a problem, but not a problem in itself.

Not many DRP-classifications have been tested for validity and reproducibility. For both the PCNE Classification and Westerlund system testing is almost continuous. Some usability data are also available for the Revised Granada Consensus, in comparison with the PCNE classification.[9] But for other classifications such data cannot be retrieved.

† This section is partially based upon a document of the National Centre for Health Outcomes Development at the University of Oxford. Source original document: http://phi.uhce.ox.ac.uk/, last accessed 12-07-2004.

Table 3: List of DRP classifications[7]

ABC system
ASHP classification
Cipolle *et al.*
Granada consensus
Hanlon
Hepler/Strand
Krska *et al.*
Mackie
PAS
PCNE Classification
PI-doc
SHB-SEP
Westerlund classification

Figure 2: DRP-Registration Form V5.01 (PCNE Classification)

Patient number _____

Age of patient _____ ☐ Male ☐ Female

Name of medication _____ ☐ R_x ☐ OTC

Main active substance _____ ☐ New ☐ Refill
(ATC-Code(s))

N° of drugs taken _____ ☐ According to patient
☐ According to medication record

Problem discovered ☐ by patient ☐ by pharmacy ☐ by physician Date:_____

Description & comments: Time spent on evaluation and intervention: min _____

TYPE OF PROBLEM *(Code for max. 1 problem)*

CAUSE OF DRP *(Max. 3 codes)*

TYPE OF INTERVENTION *(Max. 3 codes)*

OUTCOME OF INTERVENTION *(Only one code)*

Like for other classification or instruments, for DRP classifications it is also important that users can consider different aspects of the instruments. There are eight criteria that should be considered in the selection of drug related problem classification and those criteria in the mean time also constitute criteria for validation.

Appropriateness: is the classification content appropriate to the questions which the application seeks to address?

Acceptability: is the classification acceptable to pharmacists and researchers?

Feasibility: is the classification easy to use and process?

Interpretability: how interpretable are the codes of the classification?

Precision: how precise are the codes of the classification?

Reliability: does the classification produce results that are reproducible and internally consistent?

Validity: does the classification document what it claims to measure?

Responsiveness: does the classification offer options to follow interventions and outcomes of interventions?

These criteria are not uniformly described in the literature; nor can they be prioritised in terms of importance, rather they should be considered in relation to the proposed application of a DRP classification.

Conclusion

The concept of drug related problems is essential for pharmaceutical care, and the pharmaceutical care process. Nevertheless, documenting DRPs systematically in practice or for research is difficult. There are a number of instruments available. But the available validation data for some instruments show poor reproducibility. There seems to be a difference in how different professionals assess the drug treatment process, and identify the problems. This difference in skills is enhanced by varying levels of actual knowledge.

Documentation systems for other professions also pose problems in practice. The quality and correlates of medical records in the ambulatory care setting are debatable too.[10]

It is certain that actual and potential drug related problems occur, and can be corrected in order to improve the outcome of pharmacotherapy. But there seems to be little agreement on how to name and classify these problems between both researchers and practitioners alike.

References

1 Hepler CD, Linda M. Strand LM. Opportunities and responsibilities in pharmaceutical care. Am.J.Hosp.Pharm. 1990; 47:533-543.

2 Van Mil JWF, Schulz M, Tromp TF. Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review. Pharm.World Sci. 2004;26:303-11.

3 National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). About Medication Errors.[Cited 17-04-05]. Available from http://www.nccmerp.org/aboutmederrors.htm.

4 Cipolle RJ, Strand LM, Morley PC. Pharmaceutical care practice. New York, McGraw Hill. 1998:78-79 (ISBN 0-07-012046-3).

5 Krska J, Jamieson D, Arris F, McGuire A, Abbott S, Hansford D, Cromarty J. A classification system for issues identified in pharmaceutical care practice. Int J Pharm Pract 2002;10:91-100.

6 Fernandez-Llimos F, Tuneu L, Baena MI, Garcia-Delgado A, Faus MJ. Morbidity and mortality associated with pharmacotherapy. Evolution and current concept of drug-related problems. Curr.Pharm.Des 2004;10:3947-67.

7 van Mil JWF, Westerlund LOT, Hersberger KE, Schaefer MA. Drug-Related Problem Classification Systems. Ann.Pharmacother. 2004;38:859-67.

8 Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm.World Sci. 2004;26:353-60.

9 Costa S, Santos C, Madeira A, Santos MR, Santos R. Using two different Classifications of Drug Related Problems in community pharmacies – the Portuguese experience. Seguim Farmacoter 2004;2:267-85.

10 Soto CM, Kleinman KP, Simon SR. Quality and correlates of medical record documentation in the ambulatory care setting. BMC Health Services Research 2002;2:22.

Multiple Sclerosis

Leslie Agius BPharm

President, Multiple Sclerosis Society of Malta

Email: lagus@onvol.net

Multiple Sclerosis (MS) is a condition about which one does not very often hear in Malta. This is understandable due to the low incidence of the disease in our islands, an incidence which is significantly lower than that of nearby Sicilian towns such as Enna, Agrigento, Acireale and Caltanisetta and, indeed, of the rest of Europe. Yet MS is the most common non-traumatic neurological disease in young adults in the world and afflicts some 2.5 million persons worldwide.

Until the advent of Magnetic Resonance Imaging (MRI), diagnosis of MS was very difficult and several cases of misdiagnosis are recorded. In a study of MS in Malta carried out in 1978 by Drs Dean and Elian, 14 persons with MS were identified. A second survey in 1999 by the same doctors, in conjunction with Maltese consultant neurologists, showed a significant increase but the prevalence in Malta remains very low. According to the records of the Multiple Sclerosis Society of Malta the current number of confirmed cases hovers around the figure of 100

As yet there is neither a cure for, nor a certainty as to the causes of MS which is an inflammatory demyelinating condition in which the myelin is attacked by the body's immune system itself. Myelin, the fatty substance insulating the nerve fibres, ensures that messages from the brain are transmitted speedily and efficiently to the rest of the body. In MS, the loss of myelin causes a disruption in the ability of nerves to conduct electrical impulses to and from the brain with the result that the different parts of the body fail to react to stimuli from the brain. The sites where myelin is lost appear as hardened scar areas (plaques) and they appear at different times and in different areas of the brain and spinal cord. Researchers do not know what triggers the immune system to attack myelin; one theory is that a dormant virus in the body (e.g. measles or herpes) may act as a trigger by activating the white blood cells, which enter the brain by rendering vulnerable the brain's defence mechanisms. Once inside the brain these cells activate other elements of the immune system in such a way that they attack and destroy myelin. The most common symptoms of MS are blurred vision, numbness or tingling of the limbs, fatigue and problems with coordination. There are four types of MS: relapsing – remitting (25%); secondary (20%); progressive (approx. 40%) and primary progressive (15%). The course of MS is unpredictable. Some people are minimally affected while others have rapid progress to total disability, with most people fitting between the two extremes.

There is considerable research all over the world about causes of and cures for MS. In their report following the 1999 survey, Dean and Elian suggested that the reason for the low prevalence of MS in Malta could be explained by environmental factors and, more importantly, by a different genetic make up of the Maltese people to the rest of Europe. Indeed, Dean and Elian suggest that Malta offers a unique opportunity for researchers to ascertain the relative importance of genetic and environmental factors responsible for MS.

Researchers come up with possible cures on a regular basis; goat serum, statins and cannabis have been indicated in recent months. More recently a major milestone was reached through the identification of 80 genes involved in MS. This is a significant step forward in building a complete inventory of genes involved in MS. The completion in 2006 of the MS Whole Genome Scan will lead to a comprehensive catalogue of potential MS drug targets, thus providing the basis for the future development of innovative MS therapies. The understanding of the disease's genetics will enhance the possibility of identifying proteins that can be used either as targets for drug development or directly as therapeutics. In addition, the knowledge of genetics in MS provides a basis for the better designing of safer and more effective drugs and for enabling physicians to address unmet needs and potentially match treatments to individual patients.

In Malta, the Multiple Sclerosis Society was set up in October 1997 at a meeting at St. Philip's hospital. The Society organizes monthly meetings for its members and their families and organizes a number of social events so that members have the chance to interact. Several members are wheelchair bound and have very limited opportunities for socializing. The Society provides physiotherapy services held at home at a subsidized rate; this service has proved very useful and there is increasing demand for it. Equally successful and popular are the group psychotherapy sessions held at the Hospice Movement, which has become the Society's regular meeting place. Ideally, the Society wishes to offer psychotherapy on an individual basis but its limited funds preclude it from embarking on this step as yet. The Society constantly offers advice to members, visits members who are house-bound, and acts as a lobby with government. It is very active on the international front with a seat on the Executive Committee of the MS International Federation and a very active participation in the activities of the European MS Platform (EMSP). The 2003 EMSP annual congress was held in Malta and the Maltese association is regularly invited to participate in seminars and workshops of the Platform. Last year EMSP provided the services of a Polish volunteer for a whole year to instruct members of the society on how to use computers.

Multiple Sclerosis Society Malta
PO Box 209
Valletta CMR 01, Malta
Email: **lagus@onvol.net**
Tel: **+356 2132 0612**

The rise and fall of the COX-2 inhibitors

Mark L Zammit, BPharm(Hons), MSc(Agr Vet Pharm), Pg Dip Med Tox(Cardiff)

Medicines and Poisons Information Pharmacist
In-Patients Dispensary, St.Luke's Hospital

Email: mark.l.zammit@gov.mt

Key words: Non-steroidal anti-inflammatory drugs (NSAIDs), Cyclo-oxygenase-2 selective inhibitors (COX-2 inhibitors), prostanoids, pharmacovigilance, market withdrawal

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed groups of medicines in clinical practice, their anti-inflammatory, analgesic and anti-pyretic properties making them central to the management of osteoarthritis and rheumatoid arthritis. Gastro-intestinal toxicity represents some of the most-serious adverse drug reactions of this class of drugs. In an attempt to minimize these side-effects, selective cyclo-oxygenase-2 (COX-2) inhibitors were developed. In light of increasing concerns regarding their safety, two COX-2 inhibitors – rofecoxib and valdecoxib were withdrawn from the market in September 2004 and April 2005 respectively. Various restrictions have been also imposed on all the other selective COX-2 Inhibitors.

COX-2 inhibitors were marketed aggressively and rapidly gained wide popularity among prescribing physicians based on the propagated belief that they had a better ADR profile; especially with regards to gastrointestinal side-effects when compared to traditional NSAIDs.

Two independent studies, the VIGOR-study (rofecoxib vs naproxen) and the CLASS-study (celecoxib vs ibuprofen or diclofenac) concluded that the intake of both rofecoxib and celecoxib was associated with a decrease in upper gastrointestinal toxicity when compared to other NSAIDs.[12,13] Both studies were extensively criticized regarding data analysis, publishing policy and study design.[14,15] From the beginning it was obvious that at least rofecoxib was associated with an increased risk of cardiovascular events and that the gastrointestinal benefits of COX-2 inhibitors were at best marginal and completely lost if the patient has to take aspirin.[12,16,17] The VIGOR trial in fact noted a five-fold higher incidence of myocardial infarction in the rofecoxib group compared with the naproxen group.[12,18] Naproxen inhibits the production of thromboxane and platelet aggregation, and the difference in cardiovascular risk was attributed to a cardioprotective effect of naproxen, rather than a cardiotoxic effect of rofecoxib.[12] This interpretation was reiterated in a 2001 meta-analysis of randomised trials of rofecoxib and three case-control studies of naproxen and myocardial infarction published in 2002. [19-22]

Regulatory action

The first global signal of a problem with COX-2-selective inhibitors came in October 2000 – six months after the launch of rofecoxib where evidence for high reporting odds ratio for cardiovascular ADRs with some fatalities and which occurred early in treatment with rofecoxib were presented for the first time at a WHO International Drug Monitoring Programme meeting in Tunis.[23,24] A cumulative meta-analysis of randomised controlled trials in 2001 indicated that an increased risk of myocardial infarction was evident from 2000 onwards; at the end of 2000, the effect was both substantial and unlikely to be a chance finding.[25] Concerns were shared with various regulatory authorities who implemented various labeling changes in 2002, which had as expected no impact on the prescription patterns of selective COX-2 inhibitors.

Data from a placebo-controlled trial with rofecoxib (25mg daily) for the prevention of adenomatous polyps (APPROVe study) proved unequivocally in September 2004 that (as indicated by VIGOR) there was a significant increase in the incidence of serious thromboembolic adverse events for patients taking rofecoxib for more than 18 months.[26] The trial was stopped and rofecoxib (available in Malta

Overview of NSAID Pharmacology

NSAIDs are a chemically diverse group of agents (although most of them are organic acids), that share similar pharmacological properties and adverse-drug-reactions. They are widely-used for the control of pain and inflammation but prospective studies have shown a significant risk of serious gastrointestinal complications and mortality associated with NSAID use.[1-5]

It is well known that both the therapeutic and toxic effects of NSAIDs are mediated by the inhibition of cyclooxygenase (COX) (of which there are three forms[6,7]) and consequent inhibition of prostanoids (a term which encompasses prostacyclins and thromboxanes). Prostanoids are released in the inflammatory process; predominantly PGE_2 but also PGI_2; both generated by local tissues and blood vessels; and PGD_2 released by mast cells.[6] PGE_2, PGI_2 and PGD_2 are powerful vasodilators and synergise with other inflammatory vasodilators such as histamine and bradykinin to dilate precapillary arterioles to contribute to the increased blood flow characteristic of acute inflammation.[6] They also potentiate the effect of bradykinin by sensitising afferent C fibres and thus produce pain.[6] The anti-inflammatory effects of NSAIDs thus result largely from the prevention of these actions of prostaglandins.

Prostaglandins have also a gastro-protective action. PGE_2 when acting on EP_3 receptors inhibits gastric acid secretion and increses gastric mucus secretion. Through COX inhibition there is also an inhibition of PGE_2, which explains why adverse gastrointestinal events are the commonenst unwanted effects of NSAIDs.[6]

There are three isoforms of COX; COX-1, COX-2 and COX3 which has recently been described.[6,7,8] COX are bifunctional having two distinct activities; the main action which gives PGG_2, and a peroxidase action, which converts PGG_2 to the unstable PGH_2 which is then converted into another prostaglandin.[6] According to the working hypothesis that constitutive COX-1 is responsible for the physiological production of prostanoids and inducible COX-2 for the elevated production of prostanoids at sites of inflammation, selective COX-2-inhibitors have been developed in the hope of a specific anti-inflammatory function and less gastrointestinal side-effects attributable to inhibition of COX-1. Most traditional NSAIDs in current use are inhibitors of both isoenzymes though they vary in their degree of inhibition of each.[9,10] Ketorolac, flurbiprofen, suprofen, ketoprofen, indomethacin, aspirin, naproxen, tolmetyn and fenoprofen are COX-1 selective in vitro.[9,10] Zomepirac, niflumic acid, sodiun salicylate, diflusinal, piroxicam, tomoxiprol, meclofenamate, sulindac and diclofenac have a less than five-fold selectivity to COX-2.[9,10] Nimesulide, celecoxib, meloxicam and etodolac have a five to fifty fold selectivity towards COX-2, whilst still producing full inhibition of COX-1. Rofecoxib has a greater than 50-fold selectivity towards COX-2.[9,10]

Both COX-1 and COX-2 are predominantly located on the lumenal side of the endoplasmic reticulum membrane and the nuclear membrane and each consists of a long, largely hydrophobic, channel with a bend at the end, the channel being wider in COX-2.[11] Arachidonic acid enters and has two oxygens inserted and a free radical extracted, resulting in the 5-carbon ring characteristic of the prostaglandins. The crucial structural difference between COX-1 and COX-2 is at position 523; here COX-1 has a bulky isoleucine whilst COX-2 has the much smaller valine; which leaves a gap which gives access to a side-pocket.[8,11] This side-pocket is believed to be the binding site for COX-2 inhibitors which in general have a rigid side-extension which can reach across the channel and interact with the side-pocket.[8,11] This aspect is the basis of COX-2 inhibitor's selectivity for COX-2; they are in fact too bulky to fit into the COX-1 channel.[8,11]

since October 2001), was voluntarily withdrawn world-wide on 30th September, 2004.[27,28] By the time it was withdrawn, rofecoxib had been taken by an estimated 80 million people and sales had reached US$2.5 billion in 2003.[29]

The rofecoxib withdrawal triggered a debate regarding safety issues; in particular the cardiovascular toxicity of other COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib. In December, 2004 the Adenoma Prevention with Celecoxib (APC) Study was stopped for the same reasons as the APPROVe study: patients on celecoxib (200mg twice daily or 400mg daily) had dose-dependently a 2.5 and 3.4 fold increased risk for cardiovasacular events when compared to placebo.[30] 8 April, 2005 saw the suspension of sales and marketing of valdecoxib in Europe and the US.[31,32] This action followed increasing concerns about the risk of serious skin reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis, in addition to established class-evidence of cardiovascular risk, with the selective COX-2 inhibitors as well as evidence from two randomised, placebo-controlled trials in patients who had undergone a coronary-artery bypass grafting which showed that valdecoxib and its prodrug parecoxib increased the risk of servious cardiovascular events almost 3 fold.[33-36]

Several drug regulatory agencies worldwide have undertaken a full review of all selective COX-2-inhibitors. The Australian Therapeutics Goods Administration (TGA), European Medicines Agency (EMeA – of which both Medicines

and Healthcare products Regulatory Agency [MHRA] – UK and Medicines Authority [MA] – Malta are parties to) and the New Zealand Devices Safety Authority (MEDSAFE) have all issued preliminary accelerated reviews of the selective COX-2-inhibitors, and pending a full review, have all announced interim regulatory restrictions on the use of these medicines. Analysis by these agencies suggests a class-effect with an increased risk of cardio-vascular events for all COX-2 inhibitors which risk may increase with dose and duration of exposure.[37-42] As per MHRA guidance this risk was considered unlikely to exceed one extra serious thrombotic event per 100 patient years, over the rate for no treatment.[39]

Various reports concur with EMeA's decision that cardiovascular toxicity represents a group effect of selective COX-2-inhibitors.[43,44] The very similar cardiovascular toxicity can be explained by their common mechanism of action. Both rofecoxib and celecoxib for example suppress the formation of PGI_2, which is mostly produced by COX-2 in endothelium and which inhibits platelet aggregation causing vasodilation and prevents proliferation of vascular smooth-muscle cells. These effects contrast sharply with those of thromboxane (TxA_2), the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction and vascular proliferation.[14] Selective COX-2-inhibitors tend to cause a metabolic shift towards TxA_2 and consequently predispose patients to thrombotic stroke and myocardial infarction.[14]

Unexpectedly the Food and Drug Administration (FDA) – USA came to a different conclusion. FDA declared that despite the limitations of the available data, overall, there is evidence, that selective COX-2-inhibitors are associated with an increased risk of serious adverse cardiovascular (CV) events (e.g., MI, stroke, and death). However FDA unlike EMeA doubted that it is the presence of, or the degree of, COX-2 selectivity that accounts for these observations. In various controlled clinical trials, COX-2 selective drugs have been indistinguishable from non-selective NSAIDs (such as ibuprofen, diclofenac and naproxen) in studies of substantial size and duration.[45] Further, FDA declares that although on theoretical grounds the addition of low-dose aspirin (a COX-1 inhibitor) to a COX-2 selective drug should resolve any increased cardiovascular risk caused by COX-2 selectivity, this effect has not in fact been observed in several studies in which such comparisons are possible. FDA declares that taken together, these observations raise serious questions about the so called "COX-2 hypothesis," which suggests that COX-2 selectivity contributes to increased CV risk and that it remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug's potential for an increased risk of adverse CV events compared to drugs that are less COX-2 selective. FDA declares that an increased risk for serious (CV) adverse events, represents a class effect of all NSAIDs (excluding aspirin) and not just selective COX-2 inhibitors.[45,46]

Practice Points

- Selective COX-2 inhibitors should not be prescribed to patients with cerebrovascular disease, established ischaemic heart disease, or those with moderate heart failure (NHYA class II-IV).
- For all patients, the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a COX-2 inhibitor, particularly for those with risk factors for heart disease and those taking low dose aspirin, for whom gastrointestinal benefit has not been conclusively demonstrated.
- The lowest effective dose of selective COX-2 inhibitor should be used for the shortest necessary period. Periodic re-evaluation is recommended, especially for osteoarthritis patients who may only require intermittent treatment.
- Gastroprotective agents (such as H_2-receptor antagonists [e.g. ranitidine] or proton-pump inhibitors [e.g. omeprazole]) should be considered for patients switched to non-selective NSAIDs (i.e. traditional NSAIDs).
- Selective COX-2 inhibitors should not be used routinely in the management of patients with rheumatoid arthritis or osteoarthritis.
- Selective COX-2 inhibitors should be used in preference to standard NSAIDs only when specifically indicated (i.e. for patients with a history of gastroduodenal ulcer or perforation or gastrointestinal bleeding or in patients who are at a particularly high risk of developing gastroduodenal ulcer, perforation, or bleeding such as patients aged over 65 years, patients who are taking other medicines which increase the risk of gastrointestinal effects, patients who are debilitated or those receiving long-term treatment with maximal doses of standard NSAIDs) *and always* after an assessment of cardiovascular risk.
- MHRA Guidelines also indicate that etoricoxib may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses. Etoricoxib treatment should therefore not be initiated in patients whose hypertension is not under control. Careful monitoring of blood pressure is advised for patients taking etoricoxib.

Conclusion

The selective COX-2-inhibitors situation should spur us to be more conscious as regards the importance of medicines information and pharmacovigilance. The continuous monitoring of the safe use of medicinal products - one of the main activities in pharmacovigilance - is critical to the protection of public health. European

legislation is in place to ensure that all stakeholders including National Competent Authorities (eg. MA-Malta), marketing authorisation holders, applicants and sponsors of clinical trials in the European Economic Area (EEA) collect, collate and exchange adverse drug reactions. This is essential to ensure that rapid and appropriate responses are made to potential safety issues related to medicinal products.

The various regulatory restriction of the COX-2 inhibitors go to show the extreme importance of post-market surveillance which include Phase 4 studies, epidemiological studies as well as spontaneous reporting by prescribers and other healthcare professionals. Underreporting of suspected ADRs by health professionals is a major obstacle in drug safety monitoring. Locally this can be done through the Medicines Authority, Malta. [48,49]

It is already known that warnings and letters to health care professionals have little or no effect, so it would seem that much more emphasis should be placed on better communication strategies.[50] Medicines Information Centers are essential in providing useful, accurate and unbiased information that can be accessed at an appropriate place and time by everyone with an interest in effective use of medicines be it health-care professionals or the patient.

Addendum

Following the submission of this review two observational studies have been published addressing the issue of cardiovascular safety of COX-2 inhibitors and NSAIDs. A case-control study found a similar risk of myocardial infarction for celecoxib, rofecoxib, ibuprofen and naproxen and a somewhat higher risk with diclofenac; with the authors warranting a reconsideration of the cardiovascualr safety of all NSAIDs.[51] A retrospective cohort study in patients with congestive heart failure found lower mortality in patients treated with celecoxib than with rofecoxib and traditional NSAIDs.[52] These results should be interpreted with caution. For example the two studies contradict each other as regards the similar risk of myocardial infarction for naproxen and rofecoxib. Both studies were also criticised as regards quality of the data.[53]

The Medicines Authority Malta, has reassured patients and health-care professionals regarding the safety of ibuprofen but has advised prescribers and patients alike that the lowest effective dose of NSAIDs should be used for the shortest period of time necessary for treatment.[54]

References

1 Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998; 105:31S–38S.

2 Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 1993; 105:1078–1088.

3 Henry D, Lim LL-Y, Garcìa Rodriguez LA, Perez Gutthann S, Carson J, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries J. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: result of a collaborative meta-analysis. BMJ 1996; 312:1563–1566

4 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991; 115:787–796.

5 Garcìa Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998; 158:33–39.

6 Rang H, Dale M, Ritter J, Moore P. Pharmacology (5th Edition). 2003 Churchill Livingstone, London

7 Chandrasekharan N, Dai H, Lamar Turepu Ross K, Evanson N, Tomsik J, Elton T, Simmons D. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. Proc Nat Acad Scien 2002; 99: 13926-13931

8 Chandrasekharan N, Simmons D. The cycloxygenases. Genome Biology 2004; 5:241

9 Warner T, Giuliano F, Vojnovic I, Bukasa A, Mitchell J, Vane J. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. Proc Natl Acad Sci 1999; 96: 7563-7568

10 Vane J. Aspirin and other anti-inflammatory drugs. Thorax 2000; 55: S3-S9

11 Hawkey CJ. Cox-2 Inhibitors. Lancet 1999; 353:307-314

12 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343:1520-8, 2 p following 1528

13 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000; 284:1247-55

14 Klotz U. Reassessment of the benefit/risk-ratio of selective COX-2-inhibitors. Swiss Med Wkly 2005; 135: 166-168

15 Cerezo J, Hristov R, Sansuan A, Rodriguez J. Outcome trials of COX-2 selective inhibitors: global safety evaluation does not promise benefits. Eur J Clin Pharmacol 2003; 59: 169-175

16 Juni P, Rutjes A, Dieppe P. Are selective COX2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? BMJ 2002; 324:639-640

17 Topol E, Falk G. A coxib a day won't keep the doctor away. Lancet 2004; 364:639-640

18 Juni P, Dieppe P, Egger M. Risk of myocardial infarction associated with selective COX-2 inhibitors: questions remain. Arch Intern Med 2002; 162:2639-40; author reply 2640-2

19 Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, Gertz BJ. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 2001; 104:2280-8.

20 Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. Arch Intern Med 2002; 162:1111-5. Erratum in: Arch Intern Med 2002;162(16)

21 Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002; 162: 1099–1104.

22 Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med 2002; 162:1105-1100

23 WHO International Drug Monitoring Programme. Report of the 23rd Annual Meeting of Representatives of the National Centres participating in the WHO International Drug Monitoring Programme, Tunis, Tunisia, 11-14 November 2000, p21-22

24 Edwards R. Regulation of Vioxx: success or failure? Uppsala Reports 2005; 29:11-13

25 Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe B, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; 364:2021-9

26 Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352:1092-102

27 Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe B, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; Dec 4;364(9450):2021-9

28 Merck. Merck announces voluntary worldwide withdrawal of VIOXX®. 30th September, 2004. Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (Last accessed Sept 30, 2004).

29 Topol EJ. Failing the public health: rofecoxib, Merck, and the FDA. N Engl J Med 2004; 351: 1707–09.

30 Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352:1071-80

31 FDA Alert for Health Professionals – Valdecoxib (available as Bextra). 7th April, 2005. Available at http://www.fda.gov/cder/drug/InfoSheets/HCP/valdecoxibHCP.pdf (Last accessed on 28th May, 2005)

32 European Medicines Agency Statement on the Suspension of the use of Bextra. 7th April, 2005 Available at http://medicinesauthority.gov.mt/pub/emea_statement_bextra070405.pdf (Last accessed on 28th May, 2005)

33 Ray W, Griffin M, Stein C. Cardiovascular toxicity of valdecoxib. N Engl J Med 2004; 351:2767

34 Medicines Authority Malta. Suspension of Bextra® (valdecoxib) as an interim measure. Circular P10/2005. 8th April, 2005. Available at: http://medicinesauthority.gov.mt/pub/ma_circular_p10-2005.pdf (Last accessed 28th May, 2005).

35 Duff G. Voluntary suspension of Valdecoxib (Bextra) - Letter to Healthcare professionals. 7th April, 2005. Available at: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/bextraddl.pdf (Last accessed 27th April, 2005)

36 Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005; 352(11):1081-91.

37 Medicines Authority Malta. CELECOXIB (Celebrex® / Onsenal®); ETORICOXIB (Arcoxia®); VALDECOXIB (Bextra®/Valdyn®) and Parecoxib (Prexige®); and cardiovascular safety. 17th February, 2005. Available at http://www.health.gov.mt/mru/pub/MA_cox2Inhibitors.pdf (Last accessed 27th April, 2005)

38 Duff G. MHRA issues updated on advice of the safety of selective Cox-2 inhibitors. 17th February, 2005. Available at http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ddlcox2170205.pdf. (Last accessed 27th April, 2005)

39 Mc Ewan J. Therapeutic Goods Administration – Australia expanded information on Cox-2 inhibitors for doctors and pharmacists (amended). 14th February, 2005Available on http://www.tga.gov.au/media/2005/050214_cox2.pdf (Last accessed on 27th May, 2005)

40 European Medicines Agency. European Medicines Agency announces regulatory action on COX-2 inhibitors – Public Statement. 17th February, 2005. Available at http://www.emea.eu.int/pdfs/human/press/pr/6275705en.pdf. Last accessed on 27th May, 2005.

41 MEDSAFE – New Zealand Medicines and Medical Devices Safety Authority. Minutes of meeting between the MARC Chair and MEDSAFE pharmacovigilance team re COX-2 Inhibitor Cardiovascular safety. 11th February, 2005. Available on http://www.medsafe.govt.nz/search.htm. (Last accessed on 27th May, 2005)

42 World Health Organisation. Cycloxygenase (COX)-2 inhibitors – Updated information. WHO Pharmaceuticals Newsletter 2005, 2: 6-7

43 Drazen J. COX-2 inhibitors – a lesson in unexpected problems. N Engl J Med 2005; 352: 1131-1132

44 Psaty B, Furberg C. COX-2 inhibitors- lesson in drug safety. N Engl J Med 2005; 352: 1133-1135

45 Jenkins J, Seligman P. FDA Decision Memo - Analysis and Recommendations for Agency Action - COX-2 Selective and Non-selective NSAIDs (Issued 4/6/2005, posted 4/15/2005) Available at http://www.fda.gov/cder/drug/infopage/COX2/default.htm (Last accessed 26th May, 2005)

46 Mc Ewan J. Therapeutic Goods Administration – Australia expanded information on Cox-2 inhibitors for doctors and pharmacists (amended). Available on http://www.tga.gov.au/media/2005/050214_cox2.pdf 14th February, 2005 (Last accessed on 27th May, 2005)

47 Mehta D. (Ed.) British National Formulary 49th Edition, March 2005. Available at: http://www.bnf.org (Last accessed 27th April, 2005)

48 Medicines Authority Malta. Adverse Drug Reaction Reporting Card. Available at: http://medicinesauthority.gov.mt/pub/adr_reporting_card_new_logo_15.12.04_jjb_edits.doc (Last accessed 28th May, 2005).

49 Medicines Authority Malta. Adverse Drug Reaction Reporting and Pharmacovigilance – Guidance Notes for Healthcare Professionals. Available at: http://medicinesauthority.gov.mt/pub/adr_and_%20pharmacovigilance_%20guidance_%20notes_%20for_%20hcps.pdf (Last accessed 28th May, 2005)

50 Uhi K, Honig P. Risk management of marketed drugs: FDA and the interface with the practice of medicine. Pharmacoepidemiology & Drug Safety 2001; 10: 205-208

51 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitord or conventional non-steroidal anti-inflammatory drugs: population based case-control analysis. BMJ 2005; 330: 1336-1342

52 Hudson M, Hugues R, Pilote L. Differences in outcomes oif patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. BMJ 2005; 330: 1370-1375

53 Juni P, Reichenbach S, Egger M. COX 2 inhibitors, traditional NSAIDs, and the heart. BMJ 2005; 330: 1342-1343

54 Medicines Authority Malta. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and their recent association with an increased risk of mycordial infarction (heart attack). Circular P14/2005 (10th June, 2005). Available at http://www.medicinesauthority.gov.mt/pub/ma_circular-p14-2005.pdf (Last accessed on 30th June, 2005)

Drug-induced peptic ulcer disease

Valerie Vella B Pharm(Hons), PgDip Clin Pharm (Aberdeen)

Clinical Pharmacist, St Luke's Hospital, Guardamangia, Malta
Email: valerie.vella@gov.mt

Key words: Peptic ulcer, medicines, prostaglandins, gastrointestinal protection, gastrointestinal toxicity

For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality.[1] Peptic ulcer disease is a heterogeneous group of disorders involving the gastrointestinal tract and results from an imbalance between the aggressive forces of gastric acid and pepsin and the defensive mechanisms of the gastric mucosa.[1,2,3]

Introduction

Following the discovery of the association of peptic ulcer disease with *Helicobacter pylori* infection there has been a decline in the prevalence of uncomplicated peptic ulcer disease. In contrast, a striking rise in admissions for ulcer haemorrhage and perforation among elderly people is now being observed. This rise has been attributed to the increased use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin.[1] Drug-induced peptic ulcers are not exclusive to anti-inflammatory drugs, other medicines such as bisphosphonates, potassium supplements, corticosteriods, anticoagulants and chemotherapy play a role.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Commonly prescribed for a variety of musculoskeletal complaints such as rheumatoid arthritis and short-term management of pain in osteoarthritis,[4,5] NSAIDs are associated with both upper and lower gastrointestinal tract complications. Prevalence rates vary significantly[6] as estimates do not make a distinction between causal and non-causal associations or because estimates are observed in high-risk populations only.[7] The prevalence of endoscopically confirmed gastrointestinal ulcers in NSAID users is quoted to be between 15% and 30%. Between 12% to 30% of NSAID-induced ulcers are gastric ulcers, whereas 2% to 19% are duodenal ulcers. NSAID-induced ulcers are symptomatic only in 1% of patients after three to six months and in 2 to 4% of patients after one year. Inappropriately they do not correlate well with pain because the analgesic action of NSAIDs may mask the ulcer pain.[2]

Understanding the method by which NSAIDs cause gastric damage has helped in the development of prophylactic agents that reduce their toxicity.[1] The mechanism by which NSAIDs are thought to damage the gastrointestinal tract is four-fold.

a) Topical injury

Originally it was thought that NSAIDs damaged the gastric epithelium by intracellular accumulation of these drugs in an ionised state.[1] However the fact that enteric-coated formulations, pro-drugs, rectal and parenteral administration of NSAIDs still resulted in gastrointestinal damage despite the apparent absence of direct mucosal contact implies a minor role for topical injury[1,2].

b) Inhibition of prostaglandin synthesis

In 1971 Vane discovered that NSAIDs act by the inhibition of cyclooxygenase the enzyme that converts arachidonic acid to prostaglandins. As prostaglandins play a major role in the maintenance of gastroduodenal defence mechanisms; their depletion due to NSAIDs and aspirin impairs cytoprotection resulting in mucosal injury, erosions and ulceration.[1, 8]

c) Nitric Oxide

Recent attention has focused on the role of nitric oxide (NO) in maintenance of gastric-mucosal blood flow.[1] Like prostaglandins nitric oxide has been shown to increase mucosal blood flow, stimulate mucus secretion and inhibit neutrophil

adherence.[1] In animals NO-releasing NSAIDs produce less gastric damage than their parent drugs and they even promote ulcer-healing.[1,9]

d) Neutrophil-mediated injury

Neutrophil adherence to the endothelium of gastric microcirculation damages the mucosa by liberating oxygen-free radicals, releasing proteases and obstructing capillary blood flow. NSAIDs are thought to stimulate neutrophil adherence by up-regulation of adhesion molecules.[1]

The overall result is that NSAIDs cause damage as they impair the ability of the gastrointestinal mucosa to respond to injury.[9] Not all NSAIDs have the same potential to cause peptic ulcer disease, in fact ibuprofen in low doses (up to 1200mg daily) is said to have the same Odds Ratio[2] as paracetamol in causing upper gastrointestinal bleeding.[7] Diclofenac also has a low odds ratio although higher than that for ibuprofen. Indomethacin, naproxen and piroxicam have an intermediate odds ratio† whereas azapropazone and ketoprofen, has a very high odds ratio, and should thus be avoided in high-risk patients[7, 8,10,11,12,13]

Cyclo-oxygenase (COX 2) selective inhibitors

There are at least two isoforms of cyclo-oxygenase: COX 1 and COX 2. The former is found in high concentrations in platelets, vascular endothelial cells, the stomach and in kidney collecting tubules and is responsible for the prostaglandins which are essential for maintenance of normal endocrine function, renal function, gastric mucosal integrity and haemostasis.[4] COX 2 is significantly increased by inflammatory and mitogenic stimuli. By selectively blocking COX 2, COX 2 selective inhibitors have a theoretical advantage over the traditional NSAIDS with respect to reduction in GI side-effects.[4,14] Published clinical trials assessing the gastroerosive potential of coxibs demonstrate conflicting data. [9, 15, 16,17]

Cyclo-oxygenase inhibiting nitric oxide donators

COX-inhibiting nitric oxide donators, CINODs, are a new class of analgesic drugs designed to provide analgesic efficacy through COX-inhibition and gastrointestinal safety through the protective effects of controlled nitric oxide donation[9,18]. AZD3582 was the first CINOD to enter clinical development.[19] Although initial reports were promising, a recent study has indicated that the much expected superior gastrointestinal tolerability of AZD3582 is no better than that provided by naproxen.[20]

Aspirin

Aside from its use as an anti-inflammatory, aspirin in low dose is frequently indicated for the secondary prevention of thrombotic cerebrovascular or cardiovascular disease.[4,5,21] Incidence of peptic ulcers has been reported to be as high as 35%.[7] Advising patients to take enteric coated tablets or to take the preparation after food may minimise gastrointestinal symptoms as dyspepsia, but as for NSAIDs ulceration is mainly attributable to its systemic effect on prostaglandin synthesis.[5] Co-prescription of aspirin with standard NSAIDs augments the risk of such complications and risk reduction of upper gastrointestinal events associated with COX 2 selective inhibitors may not be evident when they are combined with aspirin.[4]

Clopidogrel

Clopidogrel is an antiplatelet drug indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease.[21,22] It is also given in combination with aspirin in patients suffering from non-ST segment elevation acute coronary syndrome.[22] The risk of gastric and duodenal ulcers with clopidogrel is between 0.1 – 1.0%.[22] Unfortunately clopidogrel is not a solution to patients who are unable to take aspirin because of gastrointestinal complications. A number of small studies have in fact revealed that in patients with a history of bleeding and peptic ulcer the combination of aspirin and a proton pump inhibitor is safer than clopidogrel in terms of bleeding side effects.[23]

Bisphosphonates

Bisphosphonates such as alendronate, etidronate and risedronate, are now used extensively in the treatment of patients with osteoporosis and Paget's disease and prophylaxis of osteoporosis.[24,25] All bisphosphonates cause gastrointestinal side-effects[14,26] however post-marketing surveillance indicated that alendronate and risedronate are associated with severe oesophageal reactions and gastric and duodenal ulceration.[14,25,27,28,29] It is unclear whether variation in ulcerogenic potential reflects differences in dosing, formulation or chemical structure.[29]

Studies with alendronate indicate that the oesophageal damage is consistent with a topical irritant effect.[28] Failure of alendronate tablets to pass through the oesophagus may result in prolonged local mucosal exposure to the drug, leading to erosive or ulcerative mucosal damage with inflammation and thickening of the oesophageal wall.[30] For most part such reactions can be avoided by appropriate administration of the alendronate tablets. These include swallowing the tablet whole with plenty of water (not less than 200ml) on an empty stomach at least thirty minutes before food while sitting or standing. Patients should also be reminded to stand or sit upright for at least one hour after taking the tablet.[31] On the other hand gastroduodenal injury appears to be an acute phenomenon not associated with significant complications, except in high-

† Odds ratio (OR) is defined as the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. If OR is greater than one, then the effects of the treatment are more than those of the control treatment.

risk situations such as the presence of motility disorders or concurrent use of NSAIDs or anticoagulants.[25] In a small study carried out on 26 healthy volunteers the risk of gastric ulcers in patients taking alendronate and naproxen increased to 38% compared to 8% in those receiving alendronate alone.[32]

Potassium supplements

Potassium chloride in some of its solid forms may be retained in a fixed location within the oesophagus resulting in oesophageal haemorrhage. It is thought that oesophageal injury is caused by the wax-matrix of slow release tablets. These tablets should be avoided in patients with significant cardiomegaly particularly those who have undergone cardiac surgery as these conditions seem to favour tablet retention in the oesophagus. They should also be prescribed with caution in patients with a history of peptic ulcers.[30]

Patients should always be advised to swallow potassium chloride tablets whole with fluid during meals while sitting or standing.[21]

Corticosteroids

Although controversial over the years, current evidence suggests that corticosteriods alone do not impart detectable risk for peptic ulceration.[33] Nevertheless the product characteristics of commonly used corticosteriods still indicate that they should be used with caution in patients with a history of peptic ulceration.[34,35] Additionally they state that corticosteriods may be responsible for peptic ulcers with possible perforation and haemorrhage.[34,35]

Corticosteroids may exacerbate NSAID-induced ulceration.[33,34,35] Combination use in a case control study of 1415 patients increased the risk for peptic ulcer disease compared to corticosteroid alone by four times.[33] Some studies have in fact theorised that corticosteriods act only as an NSAID specific risk magnifier.[7]

Practice Points

- Patients should always receive correct administration instructions. This is especially important when dispensing medicines known to cause topical gastrointestinal damage.
- Gastroprotective agents as proton pump inhibitors and misoprostol should be co-prescribed with NSAIDs to protect against gastrointestinal side-effects.
- Patients complaining of dyspepsia or frequently consuming antacids should be questioned about gastrointestinal symptoms and referred if deemed necessary.
- Patients with active peptic ulcers should be advised to avoid smoking, excessive alcohol intake and over-the-counter preparations containing aspirin and NSAIDs.
- Bleeding peptic ulcers have a mortality rate of about 6%, therefore patients should thus be made familiar with the symptoms of peptic ulcers such as lack of appetite an early sense of fullness with eating, nausea, vomiting, bloating, blood in the stools or black, tarry stools.

Anticoagulants

Acute gastrointestinal haemorrhage is a severe complication of peptic ulcers in patients receiving long-term oral anticoagulant therapy.[36] Correspondingly the risk of peptic ulcer in patients receiving intravenous or subcutaneous unfractionated heparin can be as high as 10%.[37,38] Although the risk of peptic ulcer with low molecular weight heparins has not yet been quantified, their use in patients with either a history or an active peptic ulcer is contraindicated,[39,40] the same holds for the use of unfractionated heparin.

Concomitant administration of anticoagulation with NSAIDs magnifies the risk and is preferably avoided.[33,36]

Chemotherapy

A number of cytotoxics used in the management of cancer may induce acute mucosal injury to the stomach and duodenum.[40] In two separate studies carried out on a total of 410 patients receiving either a combination of cyclophosphamide, methotrexate and 5-fluorouracil, or 5-fluorouracil alone revealed that if gastroprotection with omeprazole was not provided the risk of chemotherapy-induced gastroduodenal mucosal injury was significantly higher.[41,42]

Another study indicates that duodenal, gastric or pyloric ulcerations and erosions associated with hepatic artery infusion of 5-fluorouracil have responded to discontinuation of chemotherapy.[33]

Illicit drugs

Crack was introduced as an illicit street drug in 1986 and since then in America the number of patients treated for gastroduodenal perforations due to crack has increased significantly.[43] In a retrospective study of all patients undergoing surgical management for peptic ulcer disease in a teaching hospital in California it was revealed that patients with recent use of crack cocaine and/or alcohol are more likely to present with duodenal perforations.[44] Occurrence rate is believed to be of 16%.[43]

Conclusion

In theory any drug, which is administered via the oral route, can cause gastrointestinal injury. Highly caustic coatings and direct medication injury can lead to acute inflammation, which can for the most part be avoided by appropriate administration instructions.[30] Drugs causing gastrointestinal toxicity as a consequence of a systemic effect should be co-prescribed with suitable prophylactic agents such as proton pump inhibitors and misoprostol. The importance of gastroprotection is vital in preventing patient morbidity and mortality especially in patients with a number of risk factors which include patients over the age of sixty, smokers, patients with a history of peptic ulcer disease, and patients on high doses of NSAIDs, or concomitant use of anticoagulants, aspirin, bisphosphonates or corticosteriods.[3,6,8]

References

1 Chan FKL, Leung WK. Peptic-Ulcer disease. Lancet 2002; 360:933-941.

2 Kradjan WA. Gastrointestinal Disorders. In: Koda-Kimble MA, Young LY, editors. Applied Therapeutics – The Clinical Use of Drugs. 7th ed. Maryland: Lippincott Williams & Wilkins; 2000.

3 Laurence DR, Bennett PN, Brown MJ. Stomach and oesophagus. In: Laurence DR, Bennett PN, Brown MJ, editors. Clinical Pharmacology, 8th ed. London: Churchill Livingstone; 1997.

4 NICE Clinical Guideline. Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. London: *National Institute for Clinical Excellence*, 2001.

5 Martindale – The Extra Pharmacopoeia. Reynolds JEF, editor. 13th ed. London: The Pharmaceutical Press; 1993.

6 Lanas A. Prevention and treatment of non-steroidal anti-inflammatory drug gastroenteropathy. Rev Gastroenterol Mex. 2004; 69(6):251-260.

7 Hawkey CJ, Longman MJS. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. Gut 2003; 52:600-608.

8 Palmer KR, Penman ID, Paterson-Brown S. Alimentary tract and pancreatic disease. In: Haslett C, Chilvers ER, Boon NA, Colledge NR, editors. Davidson's Principles and Practice of Medicine, 19th ed. Edinburgh: Churchill Livingstone; 2002.

9 Perini R, Fiorucci S, Wallace JL. Mechanisms of Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury and repair: a window of opportunity for cylooxygenase-inhibiting nitric oxide donors. Can J Gastroenterol 2004; 18(4):229-236.

10 Rodriguez G, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343(8900):769-772.

11 Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343(8905):1075-1078.

12 Russell RI. Defining patients at risk of non-steroidal anti-inflammatory drug gastropatchy. Ital J Gastroenterol Hepatol 1999; 31(S1):14-18.

13 Lewis SC, Langman MJ, Laporte JR, et al. Dose-response relationships between individual nonaspirin Nonsteroidal anti-inflammatory drugs and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. Br J Clin Pharmacol 2002; 54(3):320-326.

14 Kinnear M, Ghosh S. Peptic Ulcer Disease. In Walker R, Edwards C editors. Clinical Pharmacy and Therapeutics, 2nd ed. Edinburgh: Churchill Livingstone; 1999.

15 Hooper L, Brown TJ, Elliott R et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ 2004; 329:948-958.

16 Gomez Cerezo J, Lubomirov Hristov R, Carcas Sansuan AJ et al. Outcome trials of COX-2 selective inhibitors:global safety evaluation does not promise benegits. Eur J Clin Pharmacol 2003; 59(2):169-175.

17 Kwong MR. Have Cox2 inhibitors lived up to expectations? Best Pract Res Clin Gastroenterol; 2004; 18(S):13

18 Lanas A, Bajador E, Serrano P et al. Nitrovasodilators, low-dose aspirin, other Nonsteroidal anti-inflammatory drugs and the risk of upper gastrointestinal bleeding. N Engl J Med 2000; 343(12):834-839

19 Hoogstrate J, Anderson LI, Berge OG, Jonzon B, Ojteg G. COX-inhibiting nitric oxide donators (CINODs) – a new paradigm in the treatment of pain and inflammation. Inflammopharmacology 2003;11(4):423-428.

20. Lohmander LS, McKeith D, Svensson O. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. Ann Rheum Dis 2005; 64:449-456.

21 British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. Edition48 UK:Phamaceutical Press; 2004

22 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Plavix. 2005. http://www.emc.medicines.org.uk (Last accessed on 27th April 2005).

23 Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352(3):238-244

24 Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. Dig Dis Sci 2002; 47(8):1665-16678.

25 Lanza FL. Gastrointestinal adverse effects of bisphosphonates: etiology, incidence and prevention. Treat Endocrinol 2002; 1(4):210.

26 Taggart H, Bolognese MA, Lindsay R et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. Mayo Clin Proc. 2002; 77(3):262-270.

27 Marshall JK, Rainsford KD, James C, et al. A randomised controlled trial to assess alendronate-associated injury of the upper gastrointestinal tract. Aliment Pharmacol Ther. 2000; 14(11):1451-1457.

28 Graham DY, Malaty HM. Alendronate gastric ulcers. Aliment Pharmacol Ther. 1999; 13(4):515-519.

29 Marshall JK. The gastrointestinal tolerability and safety or oral bisphosphonates. Expert Opin Drug Saf 2002; 1(1):71-78.

30 Jaspersen D. Drug-Induced Oesophageal Disorders, Pathogenesis, Incidence, Prevention and Management. Drug Safety 2000; 22(3):237-249

31 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Fosamax Once Weekly 70mg Tablets. 2005. http://www.emc.medicines.org.uk (Last accessed on 27th April 2005).

32 Graham DY, Malaty HM. Alendronate and naproxen are synergistic for development of gastric ulcers. Arch Intern Med 2001; 161(1):107-110.

33 Unusual causes of and diseases associated with peptic ulcer disease. http://www.uptodate.com/physicians/gasthepa_toclist.asp#Gastrointestinal_disease (Last accessed on 23rd April 2005).

34 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Decadron. 2004. http://www.emc.medicines.org.uk (Last accessed on 25th May 2005).

35 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Deltacortril. 2004. http://www.emc.medicines.org.uk (Last accessed on 25th May 2005).

36 Thomopoulos KC, Mimidis KP, Theocharis GJ et al. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: endoscopic findings, clinical management and outcome. World J Gastroenterol 2005; 11(9):165-1368.

37 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Heparin Sodium Solution for Infusion. 2002. http://www.emc.medicines.org.uk (Last accessed on 25th May 2005).

38 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Calciparine. 2004. http://www.emc.medicines.org.uk (Last accessed on 25th May 2005).

39 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Enoxaparin. 2004. http://www.emc.medicines.org.uk (Last accessed on 20th May 2005).

40 Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Dalteparin. 2004. http://www.emc.medicines.org.uk (Last accessed on 20th May 2005).

41 Sartori S, Trevisani L, Nielson I, et al. Misoprostol and omeprazole in the prevention of chemotherapy-induced acute gastroduodenal mucosal injury. A randomised, placebo-controlled pilot study. Cancer 1996; 78(7): 1477-1482.

42 Sartori S, Trevisani L, Nielson I, et al. Randomized trial of omeprazole or ranitidine versus placebo in the prevention of chemotherapy-induced gastroduodenal injury. J Clin Oncol. 2000; 18(3): 463-467.

43 Lee HS, LaMaute HR, Pizzi WF, eta al. Acute gastroduodenal perforations associated with use of crack. Ann Surg 1990; 211(1):15-17.

44 Sharma R, Organ CH Jr, Hirvela ER et al. Clinical Observation of the temporal association between crack cocaine and duodenal ulcer perforation. Am J Surg 1997; 174(6):629-632.

45 Kimmey MB. Cardioprotective effects and gastrointestinal risks of aspirin: maintaining the delicate balance. Am J Med 2004; 117(S5A):72S-78S.

46 Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, McGowan J. Prevention of NSAID-induced gastroduodenal ulcers (Cochrane Review). In: *The Cochrane Library*, Issue 2, Chichester, UK: John Wiley& Sons, Ltd, 2004.

Malaria and the traveller

[1]Antonella Tonna BPharm(Hons), MRPharmS, MSc
[2]Ivan Tonna MD, MRCP (UK), MSc

[1]Clinical Pharmacist, Oxford Radcliffe Hospitals, Oxford
[2]Specialist Registrar, Infectious Diseases, Oxford Radcliffe Hospitals, Oxford

Email: ivantonna@hotmail.com

Key words: Malaria, *Plasmodium falciparum*, traveller, chemoprophylaxis, insect bite avoidance

Malaria has reached epidemic proportions. About 40% of the world's population live in malarious areas. It is estimated that 400 million people are infected by malaria each year and of these, 1-3 million die, mostly children under five years of age.[1] In the year 2000, malaria was estimated to be the cause for the loss of nearly 45 million Disability Adjusted Life Years (DALYs) and this accounts for 13% of all DALYs associated with infectious diseases.[2] Malaria has gained importance in Western Europe, including Malta, mainly due to the increasing tourism to malaria endemic countries. There have been 21 reported cases of malaria in Malta between the years 2000-2003.[3]

Life cycle of malaria parasite

There are two phases in the malaria life cycle (Figure 1); one occurring in the intermediate host (humans, birds, reptiles) and the other occurring in the definitive host (mosquitoes). This review will concentrate mainly on the intermediate host.

When an infected anophele mosquito bites a human being, sporozoites are inoculated into the subcutaneous tissue, or rarely, into the bloodstream. These are then taken up by hepatocytes through a receptor-mediated mechanism.[4] Here, the sporozoites develop into schizonts and depending on the infecting plasmodium species, will either divide into a large number of merozoites or enter into a dormant phase, hypnozoites, the latter occurring with infection by *Plasmodium ovale* and *vivax*. Once merozoites are released into the circulation, they invade erythrocytes and become ring-shaped trophozoites.[5] Trophozoites enlarge by feeding on haemoglobin and the by-product of digestion is released within the red blood cell as insoluble haemozoin. When the trophozoite has become mature, it forms a schizont and starts to divide so that by the end of the cycle, there would be between 8-24 merozoites ready to emerge and infect new red cells. This cycle is known as erythrocytic schizogony. Eventually some of the merozoites will differentiate into immature gametocytes. These are important for continuation of the life cycle within the definitive host. Once immature gametocytes are taken up by the mosquito during a blood meal, they differentiate into macrogametes and microgametes within the stomach. After a process of exflagellation, the microgamete releases 6-8 flagella, one of which goes on to fertilise the macrogamete. Within 24 hours the resulting zygote develops into an ookinete and this penetrates the midgut wall to become an oocyst lying between the midgut epithelium and basal lamina.[6] Following a series of asexual divisions, a number of sporozoites are formed. These are then released from the oocyst and migrate towards the salivary glands ready to be transferred during the mosquito's next blood meal.

Classification and mode of action of antimalarials

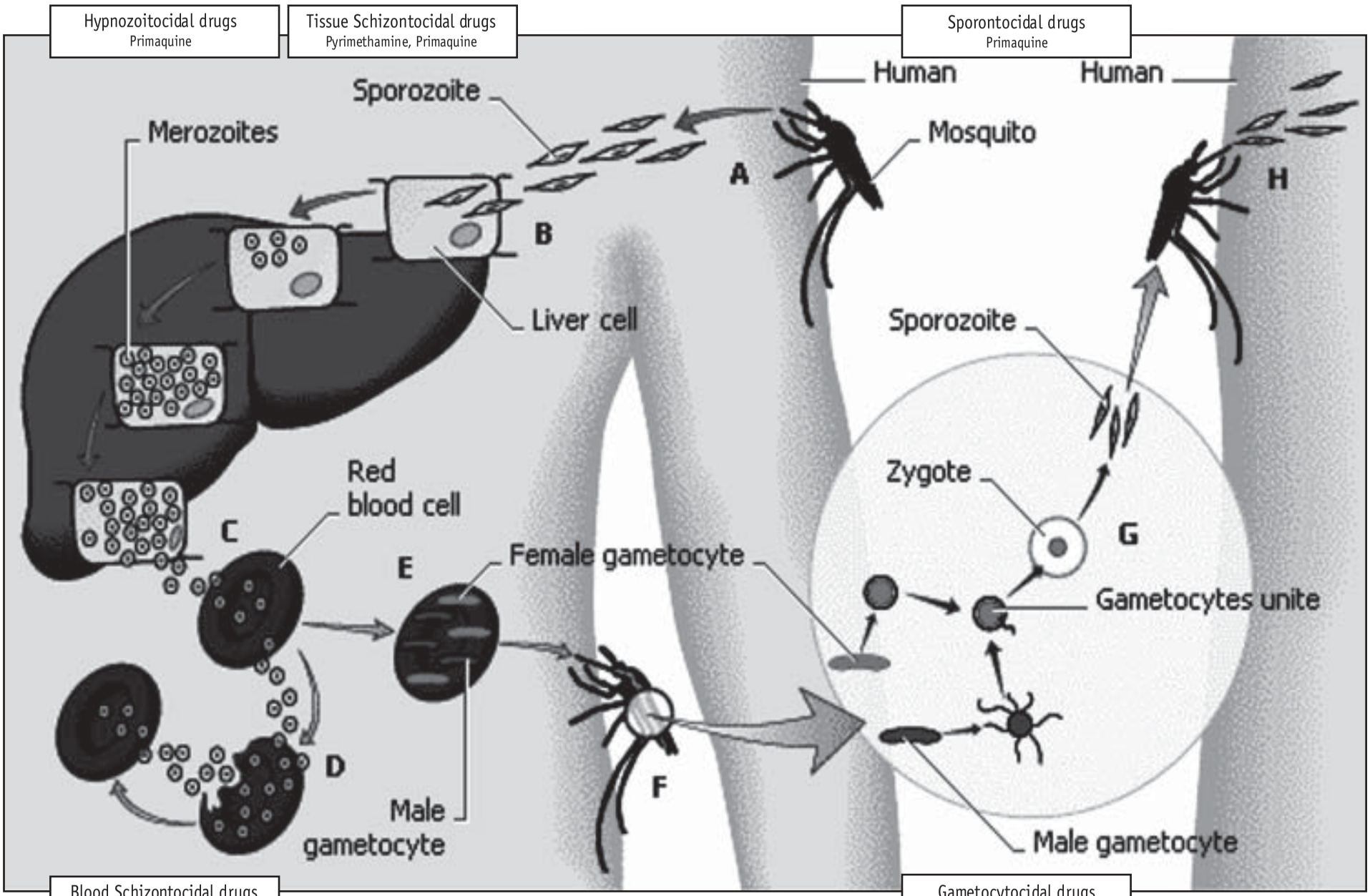
Antimalarials may be classified depending upon the stage of the malaria cycle they act upon. This in turn will determine their use. (Figure 1, Table 1)

A. Tissue schizontocides – defined as compounds acting on pre-erythrocytic forms in the liver. This may in turn be divided into:

Tissue schizontocides used for causal prophylaxis. These agents prevent development of the parasite within the liver. Thus, merozoites are not released into the bloodstream and both the asexual and sexual stages of the lifecycle are prevented. Example include pyrimethamine.[7,8]

Tissue schizontocides used to prevent relapse. These kill the dormant hypnozoites in the liver that are responsible for relapses seen with *P. vivax* and *P. ovale* infections. Example includes primaquine.[7,8,9]

Figure 1: Action of antimalarial drugs at different stages in the life cycle of Malaria parasite in the Anopheles mosquito and human hosts



Adapted with permission from Microsoft Encarta Encyclopaedia 2004

Table 1: Mode of action and use of antimalarials

Drug Class	Classification	Mode of action	Use
Arylaminoalcohols Quinine Quinidine Mefloquine Halofantrine	Blood schizontocides	Precise mode of action is still not clear. Believed to act by inhibiting the polymerisation of haemin into haemozoin[12]	• Treatment of acute disease – quinine is the drug of choice. Due to its increased cardiotoxicity, quinidine is used only if quinine is not available[7] • Suppressive prophylaxis – mefloquine is used in areas of chloroquine-resistant malaria
4 – aminoquinolines and related compounds Chloroquine Amodiaquine Mepacrine Pyronaridine	Blood schizontocides	Precise mode of action still not clear. Believed to act by inhibiting the polymerisation of haemin into haemozoin. Also appears to affect cell growth by interfering with DNA[12,13]	• Treatment of non-falciparum malaria - should not be used in falciparum, unknown infective species or mixed infection[14] • Suppressive prophylaxis – Chloroquine • Amodiaquine, Mepacrine and Pyronaridine – use obsolete and not recommended[7]
Sulfones and sulfonamides[a] Dapsone Sulfamethoxypyrazine Sulfadoxine	Type I antifolate inhibitors	Compete for dihydropteroate synthase found only in the malaria parasite and required in the pathway to synthesize DNA[7,8]	• Causal prophylaxis • Treatment
Biguanides and diaminopyrimidines Proguanil Chlorproguanil Pyrimethamine[a]	Type II antifolate inhibitors	Inhibit dihydrofolate reductase used by the malaria parasites to make folinic acid cofactors for synthesis of DNA. Prevent the completion of schizogony leading to large abnormal looking trophozites[11]	• Causal prophylaxis • Treatment of infections resistant to other blood schizontocides[7] • Used in combination with quinine to ensure clinical cure in quinine-resistant falciparum malaria[7] • Pyrimethamine should only be used in combination[14]
8 – aminoquinolines Primaquine	Hypnozoiticidal and gametocytocidal	Converted to quinone active metabolites in liver and are particularly active against non-growing stages of the parasite[7]	• Prevention of transmission of falciparum • Antirelapse for vivax and ovale malaria
Antibiotics Doxycycline Clindamycin Fluoroquinolones	Blood schizontocides	Inhibitors of parasitic ribosomal protein synthesis. Azithromycin is under investigation for antimalarial activity [7,12]	• Treatment: used in combination with quinine in effecting cure[7,14] • Doxycycline: a suppressive prophylactic for multiresistant falciparum malaria[14]
Peroxide antimalarials Artemisinin (from the Chinese medicinal plant *Artemisia annua*)	Blood schizontocides	Act on malaria parasite engaged in digesting haemoglobin in erythrocytes where they are thought to interfere with the conversion of haem to the nontoxic haemozin[7,15]	• Acute uncomplicated falciparum including parasites resistant to chloroquine and quinine[14]
Hydroxynaphthoquinones Atovaquone	Blood schizontocides	Atovaquone acts on the electron transport chain in the malarial mitochondrion causing collapse of the mitochondrial membrane potential. Proguanil potentiates this[16,17]	• Atovaquone (250mg) with proguanil (100mg) combination (Malarone™) indicated for prophylaxis and treatment particularly where drug-resistant falciparum malaria exists[16]

a In most cases Type I antifolate drugs are combined with Type II antifolate drugs for synergistic action. Combinations include: dapsone with pyrimethamine (Maloprim™, Deltaprim™), sulfamethoxyprazine with pyrimethamine (Metakelfin™), sulfadoxine with pyrimethamine (Fansidar™)

B. Blood schizontocides – these act on the asexual erythrocytic part of the malaria life cycle. They act in one of two ways. Drugs, such as mefloquine and quinine, concentrate in the parasite lysosomes within the infected erthyrocytes, thus interfering with the parasitic digestion of haemoglobin. The breakdown product, haemin, is toxic to the parasite and is normally polymerised into non-toxic haemozoin, an action inhibited by the drugs. Sulfones and proguanil have antifolate activity, thereby inhibiting different stages of DNA production in the parasite. [7,8,10,11]

C. Gametocytocides – these include primaquine and destroy the sexual forms of the parasite in the blood, hence preventing transmission to the mosquito.[7,8,9]

D. Sporontocides – these prevent parasite transmission by preventing oocyte formation within the mosquito stomach wall. Sporozoite formation is therefore inhibited and this prevents parasite transmission to the human host. Primaquine exhibits this mode of action.[7,8]

Use of antimalarial combinations

Multidrug resistance is the biggest challenge hindering effective prophylaxis and treatment and has made it necessary to use antimalarial combinations. Combination therapy has been defined by the World Health Organization (WHO) as "*the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination*".[18] Drugs used in combination are usually blood schizontocidal drugs that have different modes of action on the parasite. Various factors contribute towards making an ideal combination. These include: safety (synergistic and additive adverse effects may be a problem when drugs are used in combination), acceptability to the patient (side effect profile, product presentation, co-formulation in a single formulation, packaging ensuring stability in hotter climates, simple dose schedules) and potential to delay or prevent resistance development.[18,19] Limitations to use of combination therapy include: cost (with combinations costing up to 10 times that of monotherapy), lack of evidence in particular patient groups, such as pregnancy and paediatrics and the choice of drug combinations depending on the resistance patterns.[18]

Malaria and the traveller

The UK Guidelines for travellers define the aim of prophylaxis as *'to prevent illness and death in people who travel to areas where malaria is transmitted.'*[20] The risk of acquiring malaria can be reduced by providing adequate and evidence-based advice to travellers and appropriate chemoprophylactic cover when needed. It is very common for travellers preparing to go abroad to present at community pharmacies for insect bite repellents and over-the-counter medications to take on their journey abroad. To ensure successful malaria prophylaxis, the pharmacist requires a sound knowledge of four key steps: **A**wareness, **B**ites, **C**ompliance and **D**iagnosis.[20]

Awareness – knowing about the risk of malaria

In choosing the most effective regimen and ensuring that appropriate advice is given, various factors affecting the risk of malaria need to be considered for each individual. These include:

- **Places to be visited**
  Malaria is only present in particular areas of the world and is endemic and easily transmissible in areas lying between 64° North and 32° South.[21] Within this region, risk of transmission may be higher in one area compared to another; for example, in parts of Tanzania, malaria is holoendemic and transmission occurs perennially while in Sudan, malaria is mesoendemic and transmission is seasonal.[22] The difference lies in the entomological inoculation rate, which is the average number of infective bites per unit time. This varies in different areas and can range from less than 1 to more than 1000 infected bites per year in different parts of Africa.[23]
- **Areas of drug resistance**
  The presence of chloroquine-resistant falciparum malaria is increasing worldwide with only small areas of the world still having chloroquine-sensitive *Plasmodium falciparum;* for example, the Caribbean regions.[20]
- **Duration of visit**
  The duration of stay in a malarious area is important. It is known that the longer one spends in a malarious region the higher the risk of acquiring malaria.[20] In fact, with short visits to certain areas of Africa, the use of chemoprophylaxis is questionable since the risks of adverse events with these medications may outweigh the risks of acquiring the disease.[12] In such cases, expert advice needs to be sought.
- **Type of traveller and degree of exposure**
  This includes pattern of activity at dusk/dawn and mode of travel. Backpackers and travellers working in rural areas are at higher risk. Likewise those visiting friends and relatives may be at a higher risk due to the often misconceived idea that since they frequently visit the malarious areas they are immune to the disease.[12,20]

Bites – learning how to prevent or avoid mosquito bites

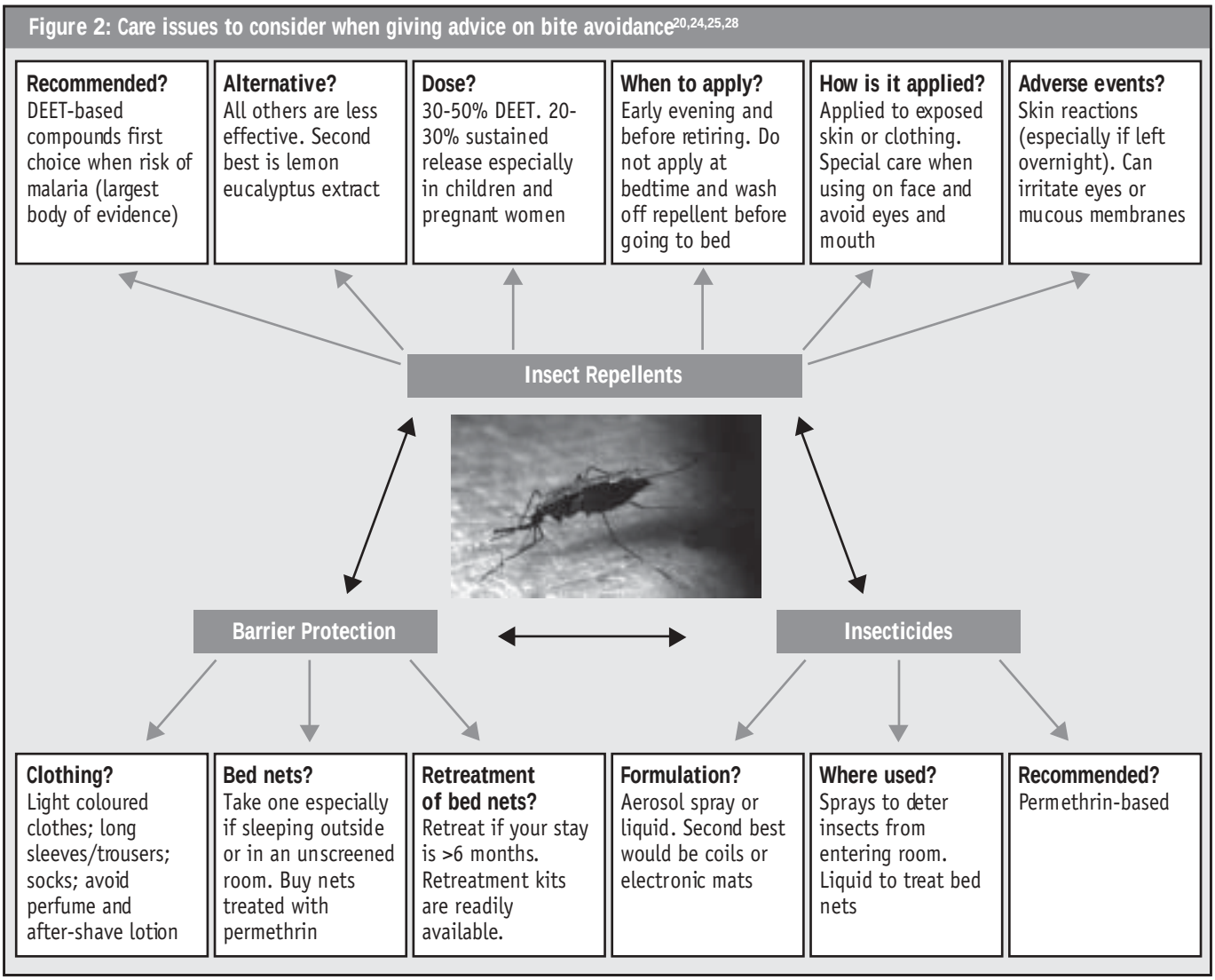
Travellers need to be advised on precautions to prevent insect bites (Figure 2). Since insect repellents are the mainstay of bite avoidance, the pharmacist should have a sound knowledge to ensure effective use. Repellents need to be applied frequently since their duration of activity is diminished by sweat on the skin, the ambient and body temperatures, windy conditions and activities such as swimming.[24,25] Travellers should therefore be advised to reapply more frequently than the time stated on the label if the effects seem to be wearing off.[24] Repellents are also not suitable for overnight protection and insecticide-impregnated mosquito nets are therefore crucial unless an air-conditioned room with sealed windows is used.[25] When a sunscreen is needed, this

should be applied first and the repellent applied over.[24] Sunscreens may lose some of their efficacy and therefore other additional precautions should be taken.[26,27] It is worth noting that research has indicated that travellers are more likely to comply with chemoprophylaxis rather than use of repellents and consequently the pharmacist needs to select a product that is acceptable to the patient to maximise concordance.[24] DEET remains the 'gold standard' and an independent trial comparing this to other repellents showed DEET to be the most effective.[24] Unfortunately, DEET-containing products are not always readily available due to controversy about adverse effects. Due to the length of time it has been on the market, the largest amount of evidence is available for DEET and analysis indicates a remarkable safety profile.[27,28] In fact, guidelines formulated by expert panels still recommend it as the first choice where there is a risk of malaria.[20] Patients should be warned that DEET may damage plastic objects and synthetic fabrics.[25] Pharmacists should also note that there is little or no evidence to support the use of electronic devices that claim to repel mosquitoes by emitting an ultrasonic noise.[20,24]

Compliance with appropriate chemoprophylaxis

It is crucial to refer to suitable updated sources (examples of suitable sources are listed at the end). One should keep in mind that different drugs are available in different countries and guidelines may therefore vary leading to confusion. It is recommended to start treatment one week before to enable any adverse effects to be detected beforehand and to ensure that the blood level of the drug is within therapeutic range prior to reaching the malaria endemic region.[12,14,20] Mefloquine is an exception and current guidance recommends starting the drug two and a half weeks before travel ensuring that 3 doses are taken before travel and any adverse effects noted.[10,12,14,20] Atovaquone/proguanil prophylaxis should be started 24 to 48 hours before departure.[14,16] All regimens should be taken regularly during the travel period and for up to four weeks (one week in the case of atovaquone/proguanil) after return in case there is any parasite emerging from the pre-erythrocytic stage.[12,14,16,20] Drugs may be taken after meals with water to minimise adverse effects. It is worth noting that the rate of malaria contraction due to non-compliance is probably as high as that due to malaria resistance, and concordance with the prescribed regimen needs to be reinforced by the pharmacist.[12] Travellers should be advised to take enough tablets to cover

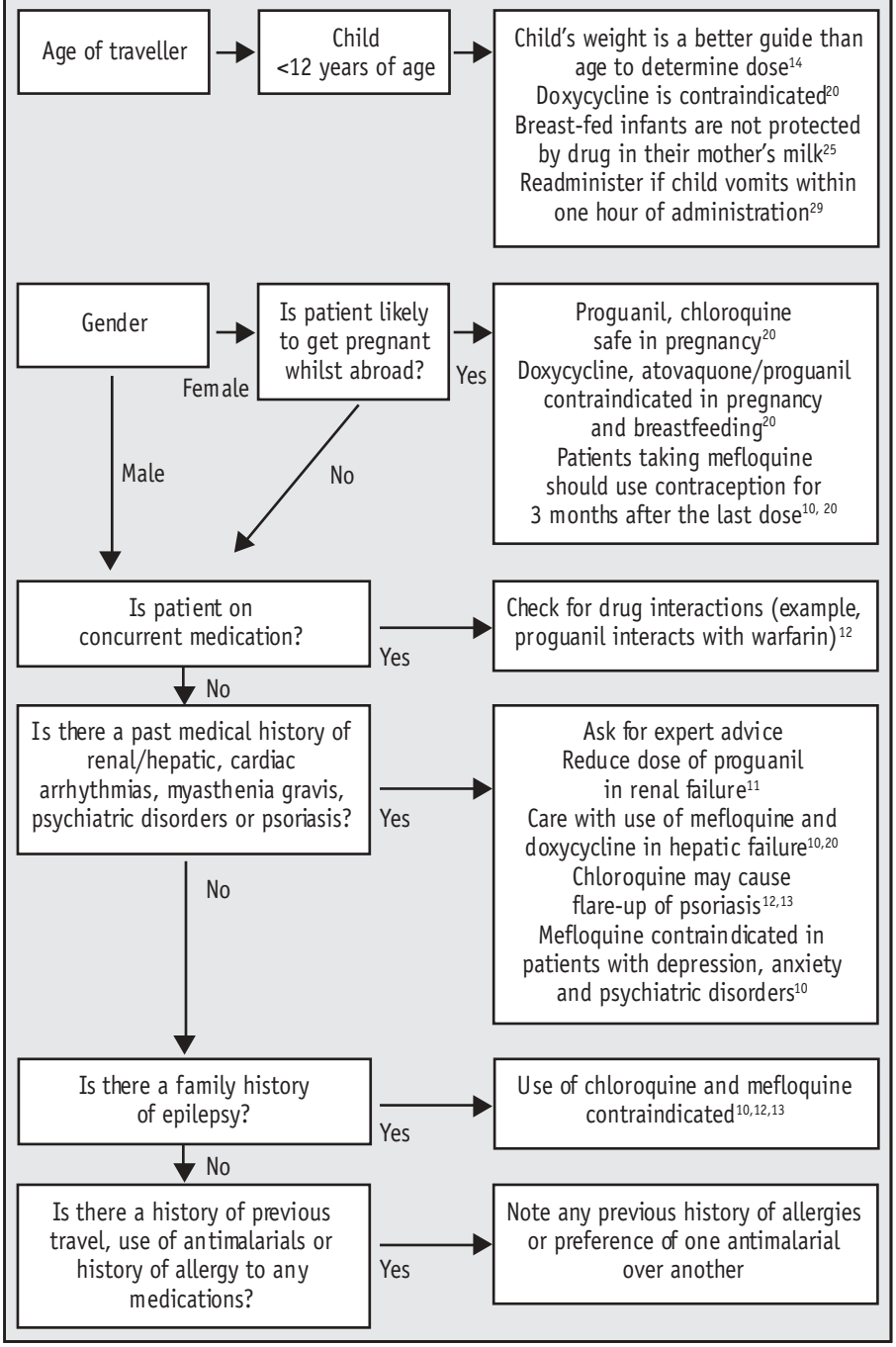
Figure 2: Care issues to consider when giving advice on bite avoidance[20,24,25,28]



the whole trip since it may be a problem to obtain these in the visiting country.[25] To ensure the most effective and least toxic chemoprophylactic for the individual patient, a number of care issues need to be considered (Figure 3) since numerous factors may complicate the choice of treatment. The incidence of adverse effects is very difficult to predict and is sometimes based on subjectivity. Though databases for reporting adverse effects are available, it is difficult to determine the exact incidence of adverse effects when drugs are used as antimalarials, since many are also used for other conditions, often at higher doses and for longer periods of time.[20] This is further compounded by the fact that increasing parasite resistance is leading to the use of newer drugs where there is less experience with respect to adverse effects.

Long-term travellers (>6 months) may pose a particular challenge since most chemoprophylactic agents are only licensed for a limited period. The following options may be considered: switching from one drug to another when the limit is reached; using proguanil with chloroquine despite the fact that resistance has been reported (may be used for periods up to 5 years[14]); not using chemoprophylaxis and seeking advice if a malaria attack occurs, or continuing beyond the licensed duration of the drug. The latter is considered the more suitable since most adverse effects occur at the start of treatment rather than later.[20]

Figure 3 : Care issues to consider when choosing appropriate antimalarial prophylaxis



Diagnosing breakthrough malaria swiftly and obtaining proper treatment

Emergency standby treatment is recommended for travellers taking prophylaxis and, who are unlikely to be within 24 hours reach of a doctor. The drug given should be different to the chemoprophylactic drug. Atovaquone/proguanil or co-artemether (artemisinin with lumefantrine) are recommended as stand-by treatment, with quinine recommended only in pregnancy.[20] Travellers should be advised to seek medical advice if they develop a febrile illness within 3 months of return.

Conclusion

Since the discovery of the malaria parasites in human blood by Charles Louis Alphonse Laveran in 1880 and the description of the complete life cycle in birds by Ronald Ross in 1898, there have been numerous breakthroughs in elucidating the pathogenesis as well as the treatment of this deadly disease.[30,31] No sooner had any hopes of malaria eradication been put forward that the first drawbacks were seen. Resistance to the most common antimalarials has necessitated looking at other alternatives, including combination treatment, in order to curb this disease.[18] Still, statistics about malaria infections worldwide are far from comforting. The "prevention is better than cure" adage definitely applies and in fact, advice and appropriate chemoprophylaxis to people travelling to malarious areas is as important as diagnosing and treating malaria cases. Table 2 lists sources of regularly updated information on the choice of appropriate antimalarials.

Practice Points

- There has been an increase in the number of malaria cases in developed countries due to an increase in tourism to endemic countries
- To ensure successful malaria prophylaxis, the pharmacist needs to ensure that the prospective traveller knows about the risk of malaria, how to avoid insect bites, comply with chemoprophylaxis and diagnose breakthrough malaria
- The choice of antimalarials to be used depend on the place to be visited, resistance patterns of malaria in the area, interactions with other medications, drug allergies and other contraindications
- Avoidance of insect bites involves the use of insect repellents, insecticides and barrier mechanisms
- Seek expert advice if the traveller is a child, pregnant woman, currently on drugs which may interact with antimalarials and co-morbidities which affect the pharmacokinetics and pharmacodynamics of the chemoprophylaxis to be used.

Table 2: Sources of regularly updated information on the choice of appropriate antimalarials

1. *British National Formulary* (guidelines based on Health Protection Agency recommendations). Available at http://www.bnf.org
2. *Travax* (site developed by NHS Scotland). Available at http://www.travax.scot.nhs.uk
3. *WHO international travel and health* (updated weekly by Weekly Epidemiological Record). Available at http://www.who.int/ith
4. *The Yellow Book* (health information for international travel). Available at http://www.cdc.org
5. *The International Society of Travel Medicine*. Available at http://www.istm.org

References

1. Marshall E. Malaria. A renewed assault on an old and deadly foe. Science 2000;290(5491):428-430
2. WHO World Health Report 2000, Geneva: WHO, 2000
3. Disease Surveillance Unit, Department of Public Health, Malta. Available at URL: http://www.health.gov.mt/dsu/reports/index.htm Accessed on 1st November 2004
4. Miller LH, Baruch DI, Marsh K, Doumbo OK. The pathogenic basis of malaria. Nature 2002;415(6872):673-79
5. Bannister LH, Hopkins JM, Fowler RE, Krishna S, Mitchell GH. A brief illustrated guide to the ultrastructure of Plasmodium falciparum asexual blood stages. Parasitology Today 2000;16(10): 427-33
6. Billingsley PF, Sinden RE. Determinants of malaria-mosquito specificity. Parasitology Today 1997;13(8):297-301
7. Warrell DA. Treatment and prevention of malaria. In Bruce-Chwatt's Essential Malariology. Edited by HM Gilles and DA Warrell. 3rd edition. London: Arnold Publishers; 1993.
8. Tracy JW, Webster LT Jr. Drugs Used in the Chemotherapy of Protozoal Infections: Malaria. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. Edited by Hardman JG, Limbird LE and Goodman Gilman A. 10th Edition. New York: Mc Graw Hill Companies, Inc.; 2001
9. Drug Information: Primaquine. Available at URL: www.mdbrowse.com/Druginf/P/Primaquine.htm Accessed on 29th September 2004
10. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Lariam. 2003. Available at url: www.medicines.org.uk. Accessed on: 24th September 2004
11. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Paludrine. 2001. Available at url: www.medicines.org.uk. Accessed on 28th September 2004
12. Goodyer L. Travel Medicine (4): Malaria. Pharm J 2000;264:405–10
13. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Nivaquine. 2003. Available at url: www.medicines.org.uk. Accessed on 24th September 2004
14. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary (Vol 48, September 2004). Available at URL: www.bnf.org
15. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Riamet 2002. Available at url: www.medicines.org.uk. Accessed on 5th October 2004
16. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Malarone 2002 Available at url: www.medicines.org.uk. Accessed on 1st October 2004
17. Nosten F. Prophylactic effect of Malarone against malaria: all good news? Lancet 2000;356:1864-65
18. Antimalarial Drug Combination Therapy. Report of a WHO Technical consultation. April 2001.
19. Kremsner PG, Krishna S. Antimalarial combinations Lancet 2004; 364:285-94.
20. Bradley DJ, Bannister B on behalf of the Health Protection Agency Advisory Committee on Malaria Prevention for UK travellers. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. Commun Dis Public Health 2003:6(3):180 – 99
21. Gilles HM. Epidemiology of malaria. In Bruce-Chwatt's Essential Malariology. Edited by HM Gilles and DA Warrell. 3rd edition. London. Arnold Publishers 1993
22. Babiker HA, Lines J, Hill WG, Walliker D. Population structure of Plasmodium falciparum in villages with different malaria endemicity in east Africa. Am J Trop Med Hyg 1997;56(2):141-7
23. Beier JC, Killeen GF, Githure JI. Short report: Entomologic inoculation rates and Plasmodium falciparum malaria prevalence in Africa. Am J Trop Med Hyg 1999;61(1):109-113
24. Goodyer L. Travel medicine (6): Bite avoidance. Pharm J 2000;265:298-304
25. International Association for Medical Assistance to Travellers. How to protect yourself against malaria. 2004 ed. Available at url: www.iamat.org
26. Montemarano AD, Gupta RK, Burge JR, Klein K. Insect repellents and the efficacy of sunscreens. Lancet 1997;349:1670-71
27. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. Ann Intern Med 1998;128:931-40
28. Goodyer L, Behrens RH. Short report: the safety and toxicity of insect repellents. Am J Trop Med Hyg 1998;59(2):323-24
29. Goodyer L. Childhood malaria – prevention and emergency self-treatment. Pharm J 2002;269:787-88
30. Dobson MJ. The malariology centenary. Parassitologia 1999;41:21-32
31. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis 2004;4:327-36

Controlled temperature storage of medicinals

Good practice measures in the community pharmacy

Claude A Farrugia BPharm(Hons) PhD(UIC) MRSC

Lecturer, University of Malta

Email: claude.farrugia@um.edu.mt

Key words: stability, shelf-life, controlled temperature, good practice

What is an expiry date? Quite simply, it is an assurance that a medicinal product will meet applicable standards of identity, strength, quality and purity at the time of use.[1] However, this assurance is not all-encompassing; it is only applicable under the storage conditions specified by the manufacturer on the labelling and packaging following extensive stability studies. Failure to provide for the storage conditions specified by pharmaceutical manufacturers invalidates this assurance and consequently, it is the responsibility of manufacturers, distributors, importers and dispensing pharmacists to ensure that adequate provisions are taken in their premises in this regard throughout the shelf life of the product.

Stress factors and medicinal products

Stability is defined as the extent to which a product retains, within specified limits, throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. There are various stress factors that can accelerate loss of stability. In view of the importance of chemical degradation as a means of instability, and that underlying chemical or physicochemical mechanisms are often responsible for physical instability, the major stress factor is temperature, since increases in temperature cause increases in the rate of degradation of medicinal products. However, it should not be assumed that it is merely elevated temperatures that are detrimental to a product's stability. Excessively reduced temperatures can also cause loss of stability, such as by decreasing the solubility of solutes in a given solvent, while oscillations in temperatures can cause a change in particle size in suspensions (the Ostwald ripening effect), thus altering the dissolution profile and possibility the bioavailability of the product.

Labelling of medicinal products

Given the importance of proper storage of medicinal products, some attention should be paid to the labelling of medicinal products and the instructions given thereon. The determination of the expiry date of a medicinal product is a result of stability studies under long term, accelerated and, sometimes, intermediate conditions. The selection of the combinations of temperature and humidity are determined by the climatic zone within which the medicinal product is intended to be stored and distributed. In the early years of a product's market life, its shelf life is sometimes calculated by extrapolation of stability study data through statistical analysis. The availability of suitable data allows a fairly accurate shelf life to be determined. The situation is less certain when, at the time of application for a market authorization, the product has not shown sufficient degradation, or indeed no degradation, that will allow statistical analysis of the kinetics of degradation to generate a shelf life with a degree of certainty. Under both these circumstances a shelf life which is twice the length of the long term stability study carried out to date is allowed, up to a maximum of one year beyond the data obtained in the long term study.[2] Ongoing stability studies are subsequently undertaken post-marketing to monitor the product and confirm the validity of the labelled shelf life.[3]

Malta, being a Mediterranean country, falls within Climatic Zone II (Table 1). Unless other stress factors, such as relative humidity (RH), light and microbiological

contamination, have a more predominant effect on shelf life, products intended for storage in Climatic Zone II are tested under accelerated conditions at 40°C ± 2°C, 75% RH ± 5% RH for a minimum of 6 months, and under long term conditions at 25°C ± 2°C, 60% RH ± 5% RH for a minimum of 12 months.[4] The manufacturer also has the option of additional testing under intermediate conditions of 30°C ± 2°C, 65% RH ± 5% RH, or of carrying out the long term study under these latter conditions rather than those previously mentioned, particularly if the product is intended for export to a country in Climatic Zone III or IV.[5] The outcome of the stability study determines the labelling requirements of the finished product (Table 2). However, products that suffer from stability issues at lower temperatures will also bear statements to this effect ("Do not refrigerate or freeze").[6]

Good practice in the storage of medicinal products

The European Commission's Guide to Good Manufacturing Practice, with regards to storage areas, states that "Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.".[7] Similar provisions are also listed in the Commission's Guidelines on Good Distribution Practice: "Medicinal products should normally be stored apart from other goods and under the conditions specified by the manufacturer in order to avoid any deterioration by light, moisture or temperature. Temperature should be monitored and recorded periodically. Records of temperature should be reviewed regularly.".[8]

In the case of medicinal products which do not require special storage conditions (i.e. refrigeration or freezing), these two concise statements are based on the need to store medicinal products under conditions of controlled temperature without compromise to their stability and shelf life. The word "controlled" implies a degree of control over the temperature of the environment, such that extremes of hot and cold temperature are not encountered. This, in turn, also implies the need for some degree of periodic temperature monitoring using one or more appropriately-located, calibrated devices.

Application of good practice to community pharmacies

Based on meteorological data for 2004,[9] Malta's mean kinetic temperature was 20.3°C, with the lowest mean minimum temperature being registered in January (9.4°C) and the highest mean maximum temperature in July (31.0°C). Such ranges in temperature, whilst not excessive, are certainly not consistent with the concept of a controlled temperature environment, and therefore the installation of an air-conditioning unit to cool or warm the pharmacy is necessary. Most, if not all, pharmacies in Malta are already equipped with such a unit. However, one's faith in the ability of the unit to control the temperature in the desired location/s should not be a blind one. It should not be assumed that, merely because the remote control reads 20°C, the unit's thermostat is also accurately set to 20°C, neither that the unit is effectively maintaining a temperature of 20°C in all areas of the pharmacy. It is therefore recommendable to engage in a few simple good practice measures in this regard.

- Purchase one or two min-max thermometers. How many you need depends on the size and layout of the pharmacy. There are mercury-in-glass, ethanol and electronic types: choose one which you can read and reset quickly, easily, and with a minimum of fiddling about with various buttons.
- Have the accuracy of the thermometers checked for you at least once a year, either by the supplier or the local standards authority. If your thermometer is not accurate to within 1-2°C, you should consider replacing it. You should also request a certificate confirming the results of the validation and indicating the next validation date.
- Carry out some elementary temperature mapping to see whether the average temperatures of different areas of the pharmacy are the same. If you have a long dispensing counter, you might find that temperatures are different at the two ends of the counter, particularly if one end is close to the entrance. The same applies if you have some medicines behind the counter, and a stock of medicinal products in a separate store room or dispensing room, especially if air exchange between the two areas is limited or ineffective. If the two areas do not maintain similar temperatures (within 1-2°C of each other), install two thermometers, one in either location. Do not keep one thermometer, shuttling it between the two locations; it will completely defeat the purpose of min-

Table 1: International Climatic Zones and Climatic Conditions[10]

Climatic Condition	Zone I Temperate	Zone II Mediterranean (sub-tropical)	Zone III Hot/dry or Hot/moderate RH	Zone IV Very hot/humid
Mean Annual Temperature	<20°C	20.5 - 24°C	>24°C	>24°C
Kinetic Mean Temperature	21°C	26°C	31°C	31°C
Mean Annual Relative Humidity	45%	60%	40%	70%

max monitoring over a period of time and the possibility of adversely affecting the thermometer's accuracy will increase.

- Install the thermometers in a convenient place to read (avoid having to climb on a stool each time). Make sure the location of the thermometer is a valid one, that is, as close to the medicinal products as possible.
- Monitor the maximum and minimum temperatures at least once weekly, and reset the thermometers. Log your readings: if you don't keep a record that you did it, then you didn't do it!
- Analyse the data by calculating the monthly mean kinetic temperature. The mean kinetic temperature is that single (derived) temperature that, if maintained over a period of time, would provide the same thermal challenge to a drug product as would be experienced due to a range of both higher and lower temperatures for that same time period. It normally has a higher value than the arithmetic mean temperature and takes into account the Arrhenius equation for temperature dependence of reaction rate constants.[4] An example of a calculation of the mean kinetic temperature is shown in Table 3. It can be seen that, provided the number of temperature excursions outside the 20-25°C range is small, the effect on the chemical stability of the compound is equivalent to a constant temperature maintained within range. Check that the mean kinetic temperature falls within the desired range, namely 20-25°C, but also that the number of raw data temperature excursions outside this range is limited to an acceptably small number (no more than once or twice monthly).

Practice Points

- Purchase one or more min-max thermometers.
- Have the thermometers checked and certified regularly.
- Carry out temperature mapping.
- Install the thermometers in a convenient, valid location.
- Monitor the minimum and maximum thermometers weekly and log the data.
- Analyse the data by calculating the mean kinetic temperature.
- Manage the air flow in the pharmacy to obtain effective temperature control.

What if your mean kinetic temperature falls just outside the 20-25°C or the number of temperature excursions outside this limit is excessive? In most cases, the situation may be brought under control by simple measures aimed at controlling air flow in the pharmacy, thus increasing the effectiveness of your air-conditioning unit/s.

- Keep the door to the street closed as much as possible; an open door causes exchange of air between the street and the pharmacy, decreasing the effectiveness of your temperature control.
- If the medicines in your dispensing area are behind some form of partition, keep the partitions closed during opening hours, particularly in the summer months; this will reduce exchange of slightly warmer air from the pharmacy with the medicines; the same applies if you have a separate dispensing or store area.
- Try and promote air exchange between cooler and warmer parts of the pharmacy, especially if your air-conditioner is "over-effective" in one region and "under-effective" in another. This can be done by the use of a strategically located fan. Monitor the temperatures to see if your efforts are successful.
- Remember that temperature control applies also at night and on Sundays and public holidays; failure to do so will generate numerous temperature excursions from the required range. Try and exchange the remote control of your air conditioner for one which will allow you to program the unit to turn on and off at awkward times if this feature is not currently available. The judicious use of the air conditioner at key moments in the day or night will give a more effective temperature control than leaving the unit on or off indiscriminately. Moreover, this will reduce electricity consumption and increase the life of your unit.
- If one part of your pharmacy appears to have a slightly higher mean temperature which you cannot lower, then stock your medicines accordingly: place those with a "Do not store above 25°C" or "Do not store above 30°C" in the region of the pharmacy with better temperature control, and those with no particular storage requirements in the area with poorer control.

Table 2: Storage Statements on the Medicinal Product Label[6]

Testing conditions where stability has been shown	Required labelling statement
25°C / 60% RH (long term) and 40°C / 75% RH (accelerated)	None
30°C / 65% RH (long term) and 40°C / 75% RH (accelerated)	None
25°C / 60% RH (long term) and 30°C / 65% RH (intermediate)	Do not store above 30°C or Store below 30°C
30°C / 65% RH (long term)	Do not store above 30°C or Store below 30°C
25°C / 60% RH (long term)	Do not store above 25°C or Store below 25°C
25°C / 60% RH (long term)	Do not store above 25°C or Store below 25°C

Advice to the patient

Finally, remember to advise the patient as regards appropriate storage of medicinal products. The entire objective of all these measures is to guarantee the quality of the medicinal product when administered to the patient, who should in turn be encouraged to store medicinal products in a cool place. Nevertheless, the occasional patient will admit to having left medicinal products in a sunny place and will ask if the product is still effective. A fairly good rule of thumb is to remember that a 10° rise in temperature approximately doubles the rate of most reactions. Ultimately, however, the best advice to give stems from the pharmacist's professional common sense, taking into account the time of year, the duration of exposure and the medicinal product under consideration.

Table 3: Calculation of the Mean Kinetic Temperature[11]

$$\text{Mean Kinetic Temperature} = \frac{9982.68}{-\ln \frac{\sum e^{-9982.68/T}}{n}} - 273.16$$

T is the recorded temperature in Kelvin (°C + 273.16), n is the number of readings, ln represents natural logarithms, and e is the natural logarithm base.

Week	Minimum (°C)	Maximum (°C)	Average (°C)	Average (Kelvin)	$e^{-9982.68/T}$
1	20	24	22.0	295.16	2.05×10^{-15}
2	23	27	25.0	298.16	2.88×10^{-15}
3	19	23	21.0	294.16	1.83×10^{-15}
4	21	24	22.5	295.66	2.17×10^{-15}

$$\sum e^{-9982.68/T} = 2.05 \times 10^{-15} + 2.88 \times 10^{-15} + 1.83 \times 10^{-15} + 2.17 \times 10^{-15} = 8.93 \times 10^{-15}$$

$$\text{Mean Kinetic Temperature} = \frac{9982.68}{-\ln \frac{8.93 \times 10^{-15}}{4}} - 273.16 = 22.7°C$$

References

1 Code of Federal Regulations, Title 21 Volume 4, Chapter I, Part 211, Subpart G, Section 211.137.

2 The European Agency for the Evaluation of Medicinal Products. ICH Q1E Evaluation of Stability Data (CPMP/ICH/420/02); 2003 Feb 20.

3 Ad Hoc GMP Inspections Services Group, Enterprise Directorate-General, European Commission. On going Stability (Addition to Chapter 6 of the EU Guide to Good Manufacturing Practice); 2003 Dec 15.

4 The European Agency for the Evaluation of Medicinal Products. ICH Q1A (R2) Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99); 2003 Feb 20.

5 The European Agency for the Evaluation of Medicinal Products. ICH Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV (CPMP/ICH/421/02); 2003 Feb 20.

6 Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products. Note for Guidance on Declaration of Storage Conditions: A: In the Product Information of Medicinal Products B: for Active Substances (CPMP/QWP/609/96/Rev 1); 2003 Apr 3.

7 European Commission. Premises and Equipment. In: The Rules Governing Medicinal Products in the European Union Volume 4: Good Manufacturing Practices; 1998.

8 European Commission. Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03).

9 National Statistics Office, Malta. News Release No. 55/2005: Special Observances - World Meteorological Day; 2005 Mar 23.

10 European Commission. Premises and Equipment. Stability Testing on Active Ingredients and Finished Products In: The Rules Governing Medicinal Products in the European Union Volume 3: Guidelines – Medicinal Products for Human Use; 1998.

11 Taylor J. Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products. Pharm J 2001 Jul 28;267:128-131.

Medicines Update

Dextropropoxyphene and Paracetamol (co-proxamol) advisory

Following a review of co-proxamol by the Committee on the Safety of Medicines UK (CSM), the efficacy of co-proxamol was poorly established and the risk of toxicity in overdose, both accidental and deliberate was found to be unacceptable. As a result, this compound preparation is being phased out by the end of this year in the UK. In Malta, the Medicines Authority has issued a circular (No P02/2005) which emphasised that co-proxamol is a Prescription Only Medicine (POM).

This circular, which can be accessed at http://www.health.gov.mt/mru/pub/co-proxamol.pdf also specifies that co-proxamol should not be used: for chronic pain; in patients aged below 18years of age and in alcohol-dependent, suicidal or addiction-prone patients. Refer to circular for additional cautions and specific warnings which should be taken into consideration when prescribing and dispensing co-proxamol.

Thioridazine withdrawal

Thioridazine (Melleril®) has been withdrawn worldwide after a risk-benefit analysis concluded that:

- QT prolongation and sudden death are more common in treatment with thioridazine versus other antipsychotics
- There is no clear advantage concerning other adverse drug reactions that would outweigh the risk of QT-prolongation
- The risk-benefit balance of thioridazine is negative.

This withdrawal also affects all thioridazine-containing medicinal products. Thus, no thioridazine-containing medicines will be available on the market.

Medicines Authority Circular P01/2005 http://www.health.gov.mt/mru/pub/ma_thioridazine.pdf

Interferon beta 1-b Advisory

Healthcare Professionals are reminded of the prescribing information concerning interferon beta-1b and hepatic toxicity. Hepatotoxicity has been a reported adverse reaction to ALL beta-interferons. There have been rare reports of serious hepatic injury including autoimmune hepatitis and severe liver damage leading to hepatic failure and transplant. AST (SGOT), ALT (SGPT) and -G T levels should be obtained prior to initiation of interferon beta-1b therapy and regularly during therapy. The occurrence of elevations in serum transaminases should lead to close monitoring and investigation with withdrawal of the drug if the levels become significantly increased or if there are associated symptoms suggesting the development of hepatitis.

Avonex® SPC
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=15349

Betaferon® SPC
http://emc.medicines.org.uk/emc/assets/c/html displayDocPrinterFriendly.asp?documentid=1809

Betaseron USA - Dear Healthcare professional letter
http://www.fda.gov/medwatch/SAFETY/2005/Betaseron_DHCP.pdf

Selective Serotonin Reuptake Inhibitor Antidepressants advisory

Last December, the Committee on Safety of Medicines UK (CSM) issued two advisories, one regarding the use of SSRIs in adults and another regarding use in children and adolescents. SSRIs are effective medicines in the treatment of depression and anxiety conditions, and the CSM has concluded that the balance of risks and benefits of all SSRIs in adults remains positive in their licensed indications. Clear advice is to be given in all SSRI product information in 3 areas: withdrawal reactions, dose changes and suicidal behaviour. This information can be accessed through: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/SSRI_Letter_061204.pdf http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/SSRIfinal.pdf

On the basis of this review of the available clinical trial data, CSM has advised that the balance of risks and benefits for the treatment of major depressive disorder (MDD) in under 18s is judged to be unfavourable for sertraline, citalopram and escitalopram and unassessable for fluvoxamine. In fact, sertraline, citalopram and escitalopram, as well as paroxetine and venlafaxine (as per previous advisories) are now contraindicated in paediatric MDD in the under 18s. Only fluoxetine has been shown in clinical trials to have a favourable balance of risks and benefits for the treatment of MDD in under 18s. The full document, which contains more information as regards stopping treatment with SSRIs and general advice, can be accessed at: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/cemssri%5F101203.pdf Medicines Authority circular No P11/2005 http://medicinesauthority.gov.mt/news&events.htm

Quinine and Thrombocytopenia

As a consequence of the risk of thrombocytopenia, quinine is no longer approved in Australia for the treatment of nocturnal cramps. This decision followed many reports which the ADRAC (Adverse Drug Reactions Advisory Committee- Australia) received about quinine causing thrombocytopenia. American FDA has long withdrawn this indication for quinine because of the lack of efficacy.

The Malta Medicines Authority has reviewed the licensing status of quinine and its use in nocturnal leg cramps and has issued a statement (link below) reminding all Healthcare professionals about the risks and about the importance of reporting any side effects.

Medicines Authority
http://www.health.gov.mt/mru/pub/ma_statement_quinine.pdf

Australian Prescriber Bulletin
http://www.tga.gov.au/adr/aadrb/aadr0410.htm#5

Problems with Alendronic acid 70mg tablets (Fosamax)

Even though this tablet does not contain a coating for sustaining the release of alendronate, this preparation is not manufactured to be split. Splitting the tablet may result in both dust and multiple irregularly shaped pieces of the partial tablets, that when taken by patients, could increase the potential of local irritation (oropharyngeal ulceration and oesophageal irritation).

As referred to the Summary of Product Characteristics (SPC):

"Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration."

Link to SPC: http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=4115

Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death

The European Heart Journal Advance Access online published the results from a population-based case-control study suggesting that the use of non-cardiac QTc-prolonging drugs is associated with an increased risk of sudden cardiac death, the risk being highest in women and in recent starters. The exposure of interest was the use of non-cardiac QTc-prolonging drugs, comprising chloroquine, chlorpromazine, cisapride, clarithromycin, domperidone, droperidol, erythromycin, halofrantine, haloperidol, levomethadyl, mesoridazine, pentamidine, pimozide, sparfloxacin and thioridazine. Many other drugs may cause this side effect.
http://www.druginfozone.org/Record%20Viewing/viewRecord.aspx?id=549111

The Medicines and Poisons Information Service, In Patients Dispensary, St Luke's Hospital, operates on a national basis to offer information and advice to health care professionals in primary and secondary care. It also offers the same service to patients. The Medicines Information Pharmacists have received specialised training to enable the provision of a professional dynamic service, which constantly meets the increasing demands of healthcare professionals and patients.

The Medicines and Poisons Information team includes:
Mark L Zammit BPharm (Hons), MSc (AgrVetPharm), PgDip Med Tox (Cardiff)
Corinne Bowman BPharm (Hons.), MSc (AgrVetPharm.)
Eileen Vella BPharm(Hons)

Tel: 2595 2057
Email: medinfo@gov.mt

The **Malta College of Pharmacy Practice** has formed an alliance with the **Medicines and Poisons Information Service** at St Luke's Hospital and the **Medicines Authority** to facilitate the provision of medicines information to both pharmacists and medical doctors. We are thus in the process of building a database of email address of those health care professionals who would like to receive updates. We would therefore like to invite all pharmacists and medical doctors who wish to receive updates to send an email with their name and email address to: info@mcppnet.org or to log on to the website www.mcppnet.org and register to receive these updates. The names and email address will only be used by the Malta College of Pharmacy Practice for the purpose stated above and will not be accessible to third parties.

Any registered individuals who wish to unregister from this database, are asked to email info@mcppnet.org with their request.

Using counselling skills to communicate more effectively

Juliet Higdon MA Social Anthropology, Cert Ed

Senior Accredited Counsellor/Psychotherapist
British Association for Counselling and Psychotherapy

Tavistock Centre, Full Time Advanced Programme
on a Psychodynamic Approach to Clinical Practice

RELATE Accredited Counsellor in Marital and Couple Counselling

Diploma in Social Administration
Home Office Letter of Recognition in Child Protection

Certificate in Life Coaching

Email: jhig@freenet.co.uk

Key words: relationship, transference, countertransference, counselling skills, empathic response, cross identification

The relationship between the pharmacist and the patient is explored. The use of counselling skills and psychodynamic theory are advocated in order to make the relationship more effective.

On the train from Newcastle to London one coach is reserved for smokers. It's usually full. Just as full is a second coach, reserved for those who cannot endure listening to the communication of other people. The mobile phone is banned. Others' communication is mostly boring or irritating.

We hear the husband say he is going to be late for dinner, the business man trying to make a sale, the student arranging a boozy night out. But do we care? For communication to have a meaning we have to be emotionally involved in it.

Pharmacists and patients are emotionally involved, if only briefly. The pharmacist wants to get a message to the patient. The patient wants something from the pharmacist. What that something is can be very different. It can be information or reassurance.

But it can also be something else; an acknowledgement of the patient's status, for example. 'My husband's a doctor so I know all about this.' 'I'm an educated man so don't talk down to me.' 'I'm a five star tourist and I don't understand your accent.'

How do pharmacists respond to patients and others in ways which are effective, while remaining professional and keeping their cool?

Forming a relationship

When we communicate with one another we begin to form a relationship. The relationship may be short lived. But it makes a difference to how we feel about ourselves. For example the bank teller who ignores us and goes on talking to his colleague about bank business makes us feel both unimportant and angry, both emotions we should prefer not to experience. Conversely the bank teller who greets us with a smile, deals with our request promptly, and admires our beautiful baby makes us feel good.

So he becomes our favourite bank teller. We always try to go to him and he always greets us warmly. We feel known; an interest is taken in us and we are flattered. He remembers which denomination notes we prefer to be paid in. This makes a personal link. He may also enquire about our mother. He has heard she has been ill. This is bordering on the intimate. We could be offended but we are more likely to feel that he has taken the trouble to ask and has shown some concern with our situation.

So if these things count in ordinary day to day affairs, how much more important are they when it affects a patient's health and could, in some cases be a matter of life or death?

Vulnerability

Loss of health makes us feel anxious and out of control .Our body has let us down. Our attachment to the image of the self as a healthy person is shattered, if it is something serious.[1]

Some patients turn the fear into anger and direct it at the pharmacist. This is a defence mechanism, known as displacement and Freud said that we use such mechanisms in order to protect our sense of self.[2] This is especially evident in the relationships we make.

Transference

The pharmacist has to form a relationship with the patient. But of course it needs to be a professional relationship. Some patients, particularly those who are over-anxious, may see the pharmacist as an authority figure and relate to him or her in ways they have related to authority figures in the past. In psychodynamic theory this is known as transference.[3] The patient may treat the pharmacist as a parent, whom he finds nurturing or critical. The pharmacist, in countertransference,[4] can begin to feel and act like the patient's mother, perhaps over-reassuring or feeling overly responsible. If there is not an awareness of this phenomenon, the professional relationship can be lost, with the pharmacist left to feel an inadequate parent.

Empathic counselling skills

Using counselling skills can ensure that the professional relationship is more effective. One of the most useful skills is known as empathic response. Probably most pharmacists do this instinctively, but it is worth checking out.

Winnicott calls this capacity 'cross identification', the ability to stand in another's shoes.[5] It is not about 'what would I do if this happened to me?' but, 'What is it like for that person in that situation?'

An empathic response is the pharmacist's own thoughts, said out loud about what she has picked up from listening

and observation. It could be something like, 'It sounds as if you've been in a lot of pain with your leg.' The patient thinks this pharmacist cares, and is more likely to listen, while you tell her how to take her medication.

And in this respect after-care is a significant issue. Asking the patient how he feels after taking the medication shows the pharmacist's concern for the patient. It is also evidence of continuity. The pharmacist's responsibility does not end with selling the medication. She/he is interested in the needs of the patient, she feels for his illness and the anxiety it causes.

For anxiety can make people feel stupid. When the pharmacist gives instructions, patients say they understand, because they are afraid of looking foolish. But often they do not. A response such as, 'You look a bit anxious. Don't worry. I'll go over it again to make sure it's clear.' is helpful. It makes the patient feel understood and not stupid.

Hospitalisation

This is particularly important when a patient is hospitalised. For the pharmacist, whose place of work it is, the hospital is an organisation which is familiar and where she/he has status. It is very different for the patient. Institutionalisation happens very quickly and the patient can feel both powerless and infantilised. It is hard to make any decisions. The pharmacist on the ward round needs to be aware of this and help the patient understand the information which would not normally be an issue. But fear, and a feeling of being out of control, can mean that the hospital patient needs much greater assistance in comprehending information on the medication, and in making any decisions connected with it. An acknowledgement of the anxiety about being dependent, with an observation that being ill makes people feel 'not their usual selves', can be useful.

Clarity

In any situation where there is an exchange between pharmacist and patient it is crucial that the pharmacist is clear. The skills of focusing on the details of what you have to get over to the patient, summarising the instructions concisely, and evaluating that the patient has really understood what you have said, are paramount. You can use questions to evaluate. The questions which do not readily have a 'yes' or 'no' answer, known as 'open questions' are most useful. 'I'm wondering if I've been clear enough in giving you these instructions. What do you think?' The patient has to really consider the answer, which means they are more likely to be honest.

Relationships with other professionals

What about communication with other professionals? Pharmacists report that they are often frustrated, particularly by doctors, when they have to challenge them, for example, on the clarity of a prescription. A minority will not take kindly to a challenge, but these are the ones who give the pharmacist hassle. Do you persist and make bad relations, or let it go and worry about your professional ethics?

This is where making assertive statements can be the answer. 'I feel concerned that... ' is always a good way to start. It's not aggressive, you are expressing your concern and all health professionals should be concerned about the patient. After registering your concern, for example that you are not clear about the doctor's intentions for the patient, expressed in the prescription, you must follow this up with a demand, carefully formulated. 'It is important that we are clear on the prescription for this patient, as I'm sure you will agree.' How can he/she not agree on something which affects the patient's wellbeing? 'I should like another prescription that is unambiguous.'

This is a professional request, which is hard not to respond to professionally.

The personal touch

In Britain supermarkets can dispense medicines, but most people still prefer to go to their favourite chemist shop. 'A relationship with a pharmacist who knows, recognises and talks to you is quite a different experience from the anonymous indifference of an exchange at a supermarket or high street chemist. Some may prefer efficient impersonality, but others value the personal service that small shops provide – from sympathetic inquiries about sadness or health to offers to drop off prescriptions at people's homes.'[6] Not only this. The pharmacist, who knows the patient, can stop him buying an over the counter product which could interfere with his existing medication and endanger his health. Pharmacists I have talked to in Britain say it is these sorts of relationship, where you are making a difference that make the job so worthwhile

As a consumer in pharmacies in Malta I have been very impressed by the care I have received. But then I am a 'good patient', always willing to listen and learn, because I value my health. Perhaps not all patients do; particularly women. They put the family first. They worry about their children's health. They worry about their husband's health. They have no time to be concerned for their own health. But pharmacists have a message they need to give to such women. The L'Oreal advert says 'because I'm worth it'. Pharmacists could have a significant role in helping women to think this. If people take responsibility for their own health, and put a value on it, it will make pharmacists' lives both easier and more rewarding.

Summary

In this short piece I have looked at:

- The notion of a relationship at the heart of the transaction between the pharmacist and the patient.
- Examining how anxiety can skew the professional relationship into a parental one, via the phenomena of transference and countertransference.
- How the defence mechanism of displacement may be employed with unreasonable anger centred on the pharmacist.
- The need for clarity
- Hierarchic relationships
- The importance of the personal touch

Communication skills can drive the professional relationship to make it more effective. Particularly helpful is the idea of an empathic response based on the concept of cross identification, or the capacity to walk in another's shoes.

Open questions which explore the situation are useful. Finally evaluating an encounter is a valuable learning experience.

References

1 Bowlby, J., Attachment and Loss. Volume 2. Separation, Anxiety and Anger. London: Penguin Books, 1975.
2 Freud, S., The Unconscious. Penguin Freud Library, Volume 11, 1915.
3 Higdon, J., From Counselling Skills to Counsellor. A Psychodynamic Approach. Basingstoke: Palgrave Macmillan, 2004.
4 Op cit
5 Op cit
6 Russell, J. (23.04.05) The Guardian newspaper. London.

MCPP Professional Development Programme

Master Class in Antibiotics and Chemotherapy

Dr Paul Cuschieri MD, Dip Bact (Manch), FMCPath, FRCPath
Senior Consultant Bacteriologist i/c *St Luke's Hospital*
Senior Lecturer in Microbiology and Antimicrobial Chemotherapy *University of Malta*

18/10/05 - A Historical Introduction to Antibiotics

- Historical Introduction – The Early Years
- The Modern Era of Chemotherapy
- The Role of the Medical Microbiologist: Interaction with Clinicians and Pharmacists, Antibiotic Policies

25/10/05 - Basic Concepts

- Definitions
- Searching for Effective Drugs
- Sources
- Concept of Selective Toxicity
- Properties of Useful Antibiotics
- Regulatory Considerations in the Clinical Development of Antibiotics
- Antibiotics – General Considerations
- MIC, MCC, AUC etc.
- Cidal vs Static Activity
- Classification of the Major Compounds
- Competitive vs Non-competitive Inhibition
- Lethal Synthesis
- Drug Monitoring
- Principles of Antibiotic Prophylaxis

01/11/05 - Principles of Antibiotic usage

- Principles of Antibiotic Usage - Laboratory Aspects of Interest to the Clinician
- Principles of Antibiotic Usage - Pharmacological Aspects
- Principles of Antibiotic Usage - Clinical Aspects

08/11/05 - Antibiotic Combination Therapy

- Indications
- Advantages
- Disadvantages

15/11/05 - Resistance to Antibiotics (Part 1)

- Resistance to Antibiotics – Basic Principles
- Mechanisms of Resistance
- Epidemiological Considerations

22/11/05 - Resistance to Antibiotics (Part 2)

- Remedial Measures
- The Way Ahead

A certificate of participation will be awarded to members who attended all the sessions of the Master Class and complete the course.

MCPP Professional Development Programme

A Psychodynamic Approach to Counselling Patients

Juliet Higdon will be delivering the above presentation on 29/11/05 as part of the MCPP autumn professional development programme

Juliet Higdon is a consultant, trainer, counsellor and life coach. She was formerly Head of Counselling Studies in Higher Education. She was trained in a psychodynamic approach at the Tavistock Clinic and is author of 'From Counselling Skills to Counsellor: A Psychodynamic Approach.' (Palgrave Macmillan. 2004).