Health-Related Information and the Internet

It has now become commonplace for patients to present healthcare professionals with information regarding pharmaceutical and medical information downloaded from the Internet. Some even place considerable pressure on healthcare professionals to bow to their requests based on the information obtained.

We therefore need to be equipped with the necessary skills in order to guide our patients with regards to the retrieval and appropriate use of such information.

The Internet has today become an integral part of our lives and at times we wonder what life was like without it. It is an infinite source of information, which is extremely valuable, provided that it originates from reliable sources. The very same information, which is presented to us, is also presented to our patients. Due to our training we can, in most cases, distinguish between a reliable and non-reliable source, and can also interpret the data presented to us. These are two very important advantages which we have over our patients, and which at times they may not fully appreciate.

While we should always encourage our patients to seek information regarding health-related issues, as this would help them to better participate in the management of their condition, possibly leading to better outcomes, we need to be more proactive in ensuring that they are getting the right information. Clearly we have no control over what is accessible through the Internet; we can however pinpoint certain common indicators which should trigger an alert. Products described or marketed with the following phrases should be viewed with caution:

- 'natural' usually implying absolute safety and efficacy i.e. may be used by anyone, without experiencing any side-effects to definitely obtain a desired result;
- declarations from 'cured' individuals and 'famous' medical experts;
- any one product that can cure or treat a list of symptoms or diseases e.g. from cancer to wrinkles;
- advertisements for products which are 'fashionable' with the 'offer' being available for a limited amount of time;
- claims that a product is 'scientifically proven' or 'without risk'.

Patients should also be informed of the risks of buying products over the Internet. Serious problems could arise due to safety and efficacy. The risk of initiating self-treatment or changing therapy without prior consultation with healthcare professionals is also a serious threat.

The World Health Organisation (WHO) has recognised this problem and has issued a guide entitled Medical Products and the Internet. This provides assistance in identifying reliable and independent sources of information on medical products. This guide may be accessed at http://www.who.int/medicines/library/qsm/who-edm-qsm-99-4/medicines-on-internet-guide.html

It is ironic that, in this day and age, we insist on selecting and tailoring therapy according to the individuals' needs providing them with the best possible treatment, yet they are enticed to participate in a system which offers the least individualised approach. On selecting the latter system they are forgoing the opportunity for professional care and advice from their doctors, pharmacists and other healthcare professionals. It is therefore up to us to guide patients to utilise the Internet to support and complement professional care. ✶

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Part 2

Management of Type II Diabetes Mellitus

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There is currently no cure for diabetes mellitus (DM). Irrespective of whether type I or type II diabetes is treated, the overall goals of management and therapy are targeted towards patient well being and may be summarised as follows: [1,3]

- Avoiding symptoms of hypoglycaemia and hyperglycaemia
- Maintaining patients as close to euglycaemia as possible
- Slowing down of the progression of chronic complications associated with diabetes
- Normalisation of nutrition and achievement of ideal body weight
- Maintaining normal growth and development in children
- Maintaining a healthy, cheerful life free of the fear of DM

Maintaining euglycaemia in a Type II diabetic

As discussed in Part 1 of the review, the UK Prospective Diabetes Study (UKPDS) has unequivocally shown that tight glycaemic control has resulted in less complications in type II diabetes.[4] Based on these results, the American Diabetes Association (ADA) has issued goals of therapy for type II diabetes. The ADA advocates that "the results of the UKPDS mandate that treatment of Type II diabetes includes aggressive efforts to lower blood glucose levels to as close to normal as possible.[5]"

In routine clinical practice a glycosylated haemoglobin (HbA1c) less than 8% should be acceptable (normal range 3 - 8%).[3]

Diabetes care and prevention of complications

It has been recognised that chronic complications of diabetes are a major cause of kidney disease, vision loss and amputations in countries where prevalence of the disease exceeds 5%.[6] As a result, prevention of the onset has become one of the major goals of treatment. Consequently, European countries (including Malta) have collaborated to issue the "St. Vincent Declaration" where recommendations for the prevention of costly complications have been put forward.[7] These include a one third reduction in blindness due to diabetes, a one third reduction in people entering end stage diabetic renal failure and reduction in rate of limb amputations by one half.

Management of Type II diabetes

a) Diet and exercise

Reduction in total body fat by 5% may be associated with a significant improvement in glycaemic control.[2] In addition, it improves efficacy of oral or insulin treatment and helps in reducing dyslipidaemia and cardiovascular risks. A successful diet programme should be tailored around a patient's needs and the advice of a nutritionist or dietician should be sought. The pharmacist is in an ideal position to offer advice concerning:

- Special diabetic products: including chocolates and biscuits - overall, these should be avoided as they are of limited benefit. Very often, such products contain other sugars as an alternative to glucose such as sucrose, sorbitol and mannitol, that offer no advantage to diabetics. Besides, sorbitol in particular is absorbed slowly from the intestine and may produce osmotic diarrhoea.[8,10]
- Sweeteners: non-nutritive sweeteners such as aspartame should be recommended.[10]
- Sugar content of liquid medicines (both OTC and prescription). Sweetening agents to be avoided include fructose, syrup, honey and glycerol.[11]

b) Oral Hypoglycaemic Agents

The introduction of oral hypoglycaemic agents (OHA's) is considered only after lifestyle modifications have failed to reach treatment goals after at least three months. Drug therapy should not be

instituted beforehand since this will expose the patient to adverse effects inappropriately.[12] There are five classes of OHA's available that will be discussed briefly:

i. Sulphonylureas: These act primarily on the pancreas to increase the amount of insulin secreted in response to a given blood glucose level.[2] Consequently, a degree of residual pancreatic function is required. There is no evidence that there is a difference in efficacy between drugs in this class. The major differences are in the half-life (which relates to the hypoglycaemic effect) and the site of metabolism (i.e. whether renal or hepatic).[12,13] Table I is a summary of the characteristics of the sulphonylureas available.

A number of factors may influence the selection of a sulphonylurea:

- Patient's age: an elderly patient is at increased risk of hypoglycaemia. Consequently, longer acting agents (chlorpropamide in particular) should be avoided. Hypoglycaemia is a major concern with sulphonylureas and if it persists for a number of hours, the patient should be referred for medical advice and further treatment.[2]
- Patient's body weight: since sulphonylureas are associated with an increased body weight, they should be avoided in overweight patients.[12,13]
- Patient's general condition: an inadequate food intake and concurrent illness may increase the risk of hypoglycaemia.[2]
- Concurrent medication: possible drug interactions and their clinical significance should be assessed. Worth mentioning are salicylates as these have an intrinsic hypoglycaemic activity.[13]
- Renal and hepatic function: All sulphonylureas should be avoided in severe renal impairment except tolbutamide, gliquidone and gliclazide, which are hepatically metabolised. They may be used if there is no alternative therapy at lower doses due to the increased risk of hypoglycaemia.[14] However, many clinicians would prefer to avoid all sulphonylureas when the plasma creatinine concentration exceeds 200-250µmol/l. The British National Formulary recommends that all sulphonylureas should possibly be avoided in severe hepatic impairment due to the increased risk of hypoglycaemia and jaundice. Lower doses are recommended if there is no alternative.[14]

ii. Biguanides: Metformin is the only biguanide available in the UK and has only been recently introduced in the USA. Phenformin was previously available but was withdrawn in the 1970's due to the association with fatal lactic acidosis.[13] The pharmacological actions of metformin are numerous and complex and proposed mechanisms include decreased intestinal absorption of glucose, increased glucose uptake form the blood into the tissues, decreased glucose production in the liver and decreased insulin requirements.[16] The activity of the drug is therefore dependent on residual pancreatic activity. Metformin is the drug of choice in obese type II DM since it enhances weight loss.[2,16] The efficacy of metformin is considered to be comparable to that of sulphonylureas.[13] The main advantage of metformin is that it does not produce hypoglycaemia even when taken in overdosage.[13,16] It does not undergo hepatic metabolism and is eliminated renally.[16]

Lactic acidosis is of major concern with biguanide treatment since it is a rare but fatal complication with a 30-50% fatality rate. The incidence of lactic acidosis occurring with metformin treatment is much less than that with phenformin mainly because about 9% of Caucasians exhibit a genetically conferred hepatic defect of phenformin hydroxylation. This does not apply to metformin since it is not hepatically metabolised. However, this is largely preventable by a strict observance of the contraindications, all of which are conditions that predispose to development or potentiation of lactic acidosis. These include:

- acute illness (e.g. dehydration, shock, heart failure) which results in increased tissue lactate production[16]
- renal impairment resulting in accumulation of biguanide - in practice metformin is usually stopped when serum creatinine is in the range of 150-160µmol/l[2,16]
- hepatic impairment where there is a reduced lactate excretion[16]
- use of X-ray contrast media which may predispose to acute renal

Table I: Pharmacokinetic Data of sulphonylureas[2,3,13,15]

Name	Proprietary name	Max daily dose (mg)	Half life (hours)	Dosing Frequency (in 24 hours)
Chlorporpamide	Diabinese	500	35+	1
Glibenclamide (Glyburide)	Daonil Semidaonil Euglucon	15	4 - 13	1
Gliclazide	Diamicron	360	6 - 15	2
Glimepiride	Amaryl	6	5 - 8	1
Glipizide	Glibenese	20	3	1 - 2
Gliquidone	Glurenorm	60	12 - 24	2 - 3
Tolbutamide	Rastinon	2000	7	2 - 4

Table II: Recommended Combination Therapy in Type 2 Diabetes Mellitus[1]

	Monotherapy	Sulphonylureas	Metformin	Glitazones	Acarbose	Repaglinid	Insulin
Sulphonylureas	b	■	b	b	b	r	b
Metformin	b	b	■	b	b	b	b
Glitazones*	r	b	b	■	r	r	b
Acarbose	b	b	b	r	■	r	b
Repaglinide	b	r	b	r	r	■	r
Insulin	b	b	b	b	b	r	■

b=combination recommended or licensed; r= combination not recommended.

*In the USA, licensed for use as monotherapy but may only be used in combination as per European license.

failure. It is therefore recommended that metformin is stopped during the 48 hours prior to and for 72 hours after the procedure, and insulin used instead.[2,14]

Gastrointestinal upsets are a common side effect of metformin therapy but tolerance to this side effect normally develops. It is therefore recommended to start treatment at a low dose and increase gradually until a maximum dose of 3g daily is reached.[2,14]

iii. Thiazolidenediones: These drugs include troglitazone, rosiglitazone, pioglitazone and ciglitazone. Their development is a major breakthrough since they are able to reduce insulin resistance (ie there is an increased hypoglycaemic effect with a lower level of insulin) believed to be the initial defect in the development of type II DM.[17] The drugs act by binding to the gamma isoform of peroxisome proliferator-activated receptor (PPAR) expressed predominantly in adipose tissue. PPARs are transcription factors that play an important role in the regulation of genes involved in insulin response. This results in a reduced insulin resistance resulting in lower levels of insulin in circulation producing the same glucose lowering effect.[2,17,18,19]

Troglitazone was the first thiazolidenedione to be launched - in 1997 in the USA and a year later in Europe. It was withdrawn sometime after, due to reports of fatal liver failure. At least 90 cases were reported in the USA with 70 resulting in death or transplantation. Significant elevations in liver enzymes occurred in 2.2% of patients.[20,21] Pioglitazone and rosiglitazone were launched in 2000. Although there is no data comparing efficacy these newer agents appear to be much safer possibly because they interact with a slightly different nuclear receptor than troglitazone.[2,21] The FDA recommends intermittent monitoring of liver function but does not specify at what intervals. It is recommended to repeat liver function tests every three months. If the alanine aminotransferase (ALT) is 1.5 times above the normal value, this should be repeated within one week. The drug should be stopped if ALT levels are three times above normal values.[22]

The National Institute of Clinical Excellence (NICE) has issued guidelines on both the use of rosiglitazone and pioglitazone. NICE recommends that the glitazones be used in combination with metformin or sulphonylureas when the combination of metformin/ sulphonylurea fails to lower glucose levels within the range required. This combination therapy may be introduced before insulin is added on. In obese patients, combining glitazone to metformin is preferred over the combination with sulphonylurea.[23]

iv. Alpha glucosidase inhibitors: Acarbose is the only available drug in this group. Migitol is also available in the USA but still not available in Europe.[22] Acarbose acts on the brush border of the small intestine where it competitively binds to α–glucosidase enzymes and inhibits absorption of starch and sucrose. It has less effect on lactose than on other carbohydrates. This delayed absorption results in a decrease in post prandial glucose levels. Since there is no effect on insulin secretion, using the agent alone will not result in hypoglycaemia. Overall it is a very safe drug to use with a mild adverse effect profile.[22,24]

v. Repaglinide: This is a novel benzoic acid derivative and is the only drug available in its group. It is an insulin secretagogue, which stimulates the secretion of insulin but only in the presence of glucose. Consequently, when taken at meal times, it lowers the post prandial glucose concentration. It is given on a 'one meal, one tablet; no meal, no tablet basis.' [2,14]

c) Stepwise treatment: With the gradual and steady deterioration of ß cell function over time, the patient usually requires additional therapy. After failure of monotherapy, combining OHA's is the first choice. When control is not achieved in this way, combining an OHA to insulin may be considered provided the patient still has some residual pancreatic function. Insulin is normally started as a night time dose to suppress the hepatic output with subsequent increase when glycaemic control is not achieved.[2,22] Table II shows the currently recommended/licensed combinations of treatment.

d) Insulin: required when the secretion of endogenous insulin is not sufficient. The indications for insulin treatment are as follows:

- non ketotic hyperosmolar coma
- pregnancy
- failure of oral treatment
- acute myocardial infarction
- during and after major surgery
- acute illness
- fasting blood glucose > 17mmol/l [2]

A detailed discussion of insulin therapy will be presented in the third and final part of this series. ✶

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The Malta Red Cross

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President Malta Red Cross

The beginning of the Malta Red Cross occurred in response to a refugee crisis that hit the Maltese shores in 1991, when two ships entered our seas with Albanian refugees. The Malta Red Cross was established on the 24th October 1991. By Act of Parliament it was recognised as an autonomous voluntary Relief Society auxiliary to the Public Authorities and allowed to carry out its activities in the Maltese islands in accordance with the rules and principles of the International Red Cross movement.

The Malta Red Cross obtained international recognition when on 21st October 1993 it became officially recognised by the International Committee of the Red Cross (ICRC) thus joining an international network of some 175 National Societies comprising over 250 million members and volunteers. The headquarters of the Society are located in St. Ursola Street, Valletta. A branch was officially opened in Gozo on 16 February 2002.

The International Red Cross Movement

The Red Cross grew out of the activity of a Swiss banker named Henri Dunant. On 24th June 1859 a fierce battle raged in the northern Italian town of Solferino between the Franco-Sardinian forces and the Austrians which left 40,000 men dead or wounded. That same evening Dunant, passing through the area on business, was horrified by the sight of thousands of soldiers from both armies left to suffer for want of adequate medical services. He appealed to the local people to help him tend the wounded, insisting that soldiers on both sides should be cared for. On his return to Switzerland, Dunant published his experiences in a book entitled "A Memory of Solferino", which caused an immediate reaction in many European countries. In Geneva, in 1863, a committee of five (including Dunant) which later became the International Red Cross Committee convened an international conference to consider how Dunant's ideas might be implemented. A total of 16 nations responded and agreed to adopt Dunant's proposals that volunteer aid societies be formed in each country to assist army medical services and that voluntary personnel wear a distinctive sign, a white armband with a red cross. Indeed the Red Cross and Red Crescent emblem can only be used by National Societies with official authority.

What is the legal status of the International Red Cross?

The International Red Cross is a neutral, impartial and independent humanitarian organisation. Its nature and membership are non-governmental. Its mandate to protect and assist the victims of armed conflicts has been conferred on it by States through four Geneva Conventions of 1949 and their Additional Protocols of 1977. Through these agreements, which are subject to international law, the International Red Cross enjoys certain privileges such as immunity from legal process, which protects it from administrative and judicial proceedings, and inviolability of its premises, archives and other documents. Such privileges and immunities guarantee the neutrality and independence of the organisation.

The activities of the Red Cross movement are essentially humanitarian and their main purpose is to help those that suffer without discrimination. In time of peace, millions of volunteers all over the world involve themselves in health programmes and social welfare. In time of war, the Red Cross strives to protect and assist the civilian and military victims of armed conflicts and internal disturbances on a strictly neutral and impartial basis.

Mission and Purpose of the Malta Red Cross

The Malta Red Cross (MRC) builds its identity on the fundamental humanitarian principles of the Red Cross movement. The mission of the Malta Red Cross Society is to prevent and alleviate human suffering, improving the situation of the most vulnerable people with absolute impartiality and without discrimination as to race, nationality, gender, class religious beliefs or political opinions both in peace time and in time of war or internal strife.

At a local level the Malta Red Cross organises regular First Aid courses and training programmes in Malta and Gozo according to recognised international standards both in factories and in schools. Highly trained Land and Water Rescue teams are available. There is an Ambulance service and First Aid posts are set up in areas where there is most

need e.g. large public gatherings and sports events and other sensitive areas. The MRC is very active in the refugee or illegal immigrants scenario both in the initial management as well as the ongoing process of humanitarian support, tracing lost relatives and friends and relocation of these people. It has an ongoing programme of dissemination of International Humanitarian Law and participates in international relief appeals. Hopefully in the future our national society may be in a position to send trained delegates to help in regional and national disaster areas. The local Red Cross society works as much as possible in conjunction with national relief organisations as well as other non governmental organisations in a spirit of mutual cooperation and respect.

Crucial role for Red Cross Volunteers

The above mentioned activities would not be possible without the sterling work of hundreds of local volunteers who sacrifice a good part of their time to support the society without remuneration. The spirit of volunteering is the cornerstone and backbone of the Red Cross humanitarian service world-wide.

Although our membership is growing every year there is always a need for more volunteers to join the various sections of the Malta Red Cross. Non-active members are also very welcome.

For further information contact can be made with the Malta Red Cross by phone: 2122 2645 or e-mail: redcross@waldonet.net.mt
Enrolment forms for membership or participation in specific activities will be sent on request.

The Breast Care Support Group

Helen Muscat Registered Nurse
President, Breast Care Support Group

The Breast Care Support Group (BCSG) is a voluntary organisation, set up in the late eighties by a small group of women who had been through the trauma of having breast cancer, and felt that there was not enough support or advice available for women like themselves. Originally the word mastectomy was incorporated into the group title, but as surgery for breast cancer changed, so did the name of the group.

Whilst addressing the needs of women with breast cancer, the group is also involved with supporting women who have had other forms of breast disease. The needs for women who have experienced the psychological trauma of discovering a breast lump and any subsequent intervention warrants some form of support structure. Whether the lump is benign or malignant, many women who face this distressing situation need help to recover. Although only one in ten breast lumps will be malignant the other nine still need to be dealt with. The BCSG knows the importance of seeing these cases as ten individual women, as opposed to nine benign breast lumps and one malignant lump. Surgery is not always medically indicated, but the woman herself may decide to go ahead and have the lump removed. This happens because she cannot cope with the doubt she has in her mind as to whether or not she has been correctly diagnosed, or possibly because she may be afraid that if the lump is left it may become malignant. Women are aware that mistakes can be made in diagnosis, and if they live with a breast lump *in situ,* it can cause them to become depressed and anxious. Women need to be better informed about breast disease, and then allowed to decide for themselves whether or not to undergo surgery. The name of the group reflects the involvement with women who have had some intervention related to breast care, not specifically breast cancer. Members of the group are contacted by telephone on a regular basis, to support or to give advice on where to obtain the help or services that they may need.

The BCSG has members in both Malta and Gozo, with monthly meetings being held on both islands. The purpose of these meetings is to give

women the opportunity to meet others who have been through similar experiences. They are given the chance to talk about any problems that they may be experiencing with the nurse advisor to the group, who is trained in Breast Awareness However this is not all that happens at the meetings! There is a program of educational and recreational activities for these meetings, and some social events are planned each year so that members can include friends and family.

Meetings are held in Malta at the Malta Hospice Movement, which helped the group to originate, and thankfully offers ongoing support to the group. Meetings take place on the first Thursday of every month, morning or afternoon (9:30am to 11:30am and 5:30pm to 7:00pm). In Gozo, the meetings are held at The Cana Headquarters in Victoria, every first Wednesday of the month from 9.00am to 11.00am. An annual fee of Lm3 is charged to BCSG members. Quarterly newsletters are sent out to members.

Apart from this support structure, members of the group reach out to women in other ways. A member of the BCSG visits both public and private hospitals, linking with the nursing staff and consultants. Requests are made for the group to either visit or phone women in need of moral support. This can take place prior to or after surgery and/or other treatment. The role of these volunteers is to offer their moral support and encouragement. These volunteers have guidelines regarding visiting patients; they will not give advice related to treatment, choice of surgeons or discuss their own personal experiences.

A member of the group also offers a free fitting service for prosthesis. The group provides a 'comfy' which is a soft shape that can fit into the bra after surgery, prior to the woman being able to wear the regular prosthesis. This can be a real boost for women leaving hospital, and trying to cope with their altered body image.

The BCSG is aware that both the public and private sectors do not always ensure that women receive a team approach to care. The service at St. Luke's Hospital has improved a great deal. Areas for improvement, however, include the need for all women to be evaluated by a physiotherapist. Psychological support should be provided when necessary. This applies to women and their partners who may have sexual problems related to the diagnosis and treatment of breast disease. These and other issues will be worked upon in a positive way in the future.

Members of the BCSG give their committee feedback related to their treatment and care, pointing out problems and giving suggestions for improvements. The committee then makes the necessary proposals to the organisations concerned, both within the private and the public sectors.

Education has been a major consideration for this small but effective group. During the last five years educational courses for nurses have been held, and a total of over one hundred nurses have followed a basic breast awareness course, updating their knowledge and giving members of the BCSG the opportunity to form better links with the nursing profession. Breast Awareness Week, allows Health Care Professionals to work along side members of the Breast Care Support Group to promote awareness amongst the general public. This awareness week is held in the last week of October culminating with The Hilda Schembri Memorial Lecture, in memory of one of the founders of the group. Another Breast Awareness Course will be organised later this year, and professionals interested in participating can contact Marianne Micallef on Tel: 2157 2515.

Following meetings with both The Hon. Dr. L. Deguara, Minister for Health and Dr. J. Cachia, Director of Health Institutions, the Breast Care Support Group will be working with a link person from the Department of Health for this year's Breast Awareness campaign. There have been direct links with the Department of Health for a number of years, but the BCSG had been requesting a link person to work directly with for the past two years, and this is a positive outcome. The Health Promotion Unit is another sector within the Department of Health with which the BCSG enjoys good collaboration. The group, distributes educational Breast Awareness booklets that are available in both Maltese and English, and communicate any feedback in relation to awareness to the Unit. The BCSG has made proposals to Government regarding improvement of the service for women with Breast Cancer. The BCSG has promoted the role of the Breast Care Nurse and the newly established Breast Clinic at St. Luke's Hospital has the services of two part-time Breast Care Nurses. The clinic has a multidisciplinary approach, offering a holistic service to a high percentage of women who present at St. Luke's with a breast lump. The BCSG would be happier if there could be greater involvement between this team and the Oncology Department, which, evidently due to shortage of staff, has no representative at the Breast Clinic team meetings.

The BCSG is in the process of restructuring the committee, and hopes to include some health care professionals, including The Malta Hospice Movement, The College of Family Practitioners and The Commission for the Advancement of Women. This should strengthen the group and help in gaining official recognition from the Department of Health.

The organisation raises funds when there is a specific need, and recently sponsored one of the Breast Care Nurses from St. Luke's Hospital to attend a

The BCSG has a page on the Malta Hospice Movement's Website, which is currently being updated.

For further information, please contact Helen Muscat tel: 2137 5537, or e-mail: helenmuscat@hotmail.com

Towards a Framework for the Continual Improvement of Healthcare

The Integration of Improvement Knowledge with Professional Knowledge

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Keywords: quality, change, improvement, healthcare organisations, improvement knowledge

Quality improvement has become an integral part of healthcare systems. Substantial improvements can only be expected through the creation of new systems. Transforming a healthcare organisation so that it is capable of continual improvement requires a specific framework. This framework includes the linking of professional knowledge (subject, discipline and values) and improvement knowledge (system, variation, psychology and theory of knowledge) to daily work. Improvement knowledge enables linking of the knowledge and interrelationships of the elements of a system, consideration of the type of variation, teamwork and motivation of participants and the use of prediction and measurement to link theory and action.

Improvement and change of healthcare organisations and systems

Since the late 1980s and early 90s there has been an increased interest in quality and quality improvement in healthcare. The concepts of quality have become commonplace in health services and organisations to different degrees and are built into the structure of various provider units. For example the United Kingdom has made quality improvement an integral part of the healthcare system. The website of the Department of Health in the UK http://www.doh.gov.uk/ gives examples of initiatives taken in this country.

Berwick's leading article on improvement of systems[1] outlined a number of principles on improvement and change derived from what the author authoritatively called 'the central law of improvement'. He stressed on the 'indissoluble bond between improvement and change' and explained that 'not all change is improvement, but all improvement is change'. Every system is perfectly designed to achieve the results it achieves and reframes performance from a matter of effort to a matter of design. Better or worse performance cannot be obtained from a system of work (any set of activities with a common aim) merely on demand. The results of health care are themselves properties of the system of care in analogy to the length of an athlete's maximum long jump being inherent in the nature of his body. Although mere effort can achieve some improvement, this improvement is not fundamental and does not often represent a new level of capability. While different players in the health care system want to bring about change, the results everyone wants to change (performance) are properties inherent in the system and new results can only be expected through the creation of new systems. The author emphasised on change of a system, not change within a system. Stressing the current

system (relying on more of the same) hits without much effect on the historical walls of performance while introducing a truly new system leaps over these walls. Improvement begins in the will but can be achieved through a method for systematic change.[1]

Transforming a healthcare organisation so that it is capable of continual improvement

Transforming a healthcare organisation so that it is capable of continual improvement requires a framework for the continual improvement of healthcare (Table I). Central to the continual improvement of healthcare is the application of professional and improvement knowledge to daily work. Throughout most of history, medical advances have resulted from the application of professional knowledge of subject and discipline (pharmacy, medicine, nursing) in the context of a set of underlying values. These values stem from the underlying moral values of patients, families and providers, as well as from the social values implicit in social and scientific policy.

Table I A framework for the continual improvement of healthcare organisations[2]

- development of improvement knowledge to be used together with professional knowledge
- creation of leadership policy that fosters a shared sense of purpose and promotes organisational learning
- mastery of tools and methods that accelerate improvement of work
- application of systematic strategies for building and using knowledge to the process of daily work

Now healthcare is being asked to do better, in a way that will increase the impact of healthcare for even more segments of society. Today a second body of knowledge, improvement knowledge, is available for use in the improvement of healthcare in a new way - through continual improvement of health care. Joining professional knowledge with improvement knowledge makes possible the continual improvement of healthcare, characterised by more improvements of a different kind and a faster pace than before.[2]

Improvement knowledge consists of four elements:[2]

- knowledge of systems
- knowledge of variation
- knowledge of psychology
- theory of knowledge

Knowledge of a system

Guiding an organisation effectively toward continual improvement depends on the organisation's leaders developing, basing their leadership on, and communicating to everyone knowledge of the organisation as a system of production, that is, a group of interdependent people, items, processes, and products and services that have a common purpose or aim.[3] Table II lists some of the considerations about a system.

Table II Considerations about a system[2] the means of 'production' of a system

what is created, made or produced (services/products), how services/ products are produced (processes), for whom they are produced (beneficiaries or customers) and with dependence upon whom (suppliers)
The aim of the system
developing and deepening customer knowledge and understanding the needs of the organisation
How to improve the system
developing knowledge of what must be done to improve towards a shared vision and formulating specific plans (design or redesign) based on these improvement priorities

Making wise decisions about what and how to improve requires linking knowledge of the various elements in a system and it is critical to understand the interrelationship of the essential elements. Changes that will improve the overall system are those that increase the system's capacity to deliver services and products that meet the needs and expectations of the customer it seeks to serve.[2]

Batalden and Stoltz (1993)[2] noted a number of problems which healthcare workers encounter in relation to their systems:

- difficulty with defining what they do
- failure to think often enough and deeply enough about the need that their clients, patients and patients' families have for their work
- making assumptions about what customers need and failing to study and to check these assumptions thus missing the opportunity for improvement or making inappropriate changes
- traditionally thinking about an organisation as a collection of departments with various functions rather than as the flow of linked processes forming the core process, to which additional processes provide support
- focusing improvement efforts on departmental gains at the cost of failing to improve the system
- rarely coming together to learn from the work of others and from their own experiences.

These observations may be used for reflection on how we relate to the system in which we work, whatever it may be.

Knowledge of variation

Variation is always present in processes, products and people. Baltaden and Stoltz (1993)[2] gave the analogy of variation in body temperature and explained that the point-to-point differences observed over time (the variation) are caused by a variety of factors or influences. When the value falls above or below the

expected range we look for some special circumstance or event. Understanding variation over time is the key to recognising and using differences observed for the purpose of continual improvement. Deming[4] described two types of causes of variation: 'common causes', or causes found regularly within every occurrence of the process and 'special causes', specific causes or sets of circumstances not regularly present in the system which influence variation. Distinguishing the type of variation present in a process is critical for improvement because each type of variation requires a different type of action.

While plotting data over time is commonly done in the management of patients it is usually not done in the management of other processes in health care work. Moreover data are most commonly presented in tabular form, which encourages two point comparisons rather than processes occurring over time. Variation is rarely studied as a guide to causal theory and subsequent action. People are suspicious and fearful of measures related to their work, probably because information has historically been used to judge people, not process performance.[2]

Knowledge of psychology

Early management theorists assumed that workers represent a component of the production capability of an organisation, an asset or resource to be managed. In the resource-based management system, direction setting comes from top, the role of leadership is to think and plan and the role of workers is to act and carry out the plan.[5] Deming (1993)[6] and Juran (1989)[7] both pointed out that in the vast majority of cases the variation in outputs can be attributed to the effect of multiple causes in a system of common-cause variation, not to individual workers. Improving the performance of such a system requires fundamental change in the system, not further work on the behaviour of the below-average worker. Motivating performance and improvement (with least risk of overall system suboptimisation) may be accomplished by removing barriers to the internal or intrinsic motivation of workers. Fundamental to human behaviour is curiosity, a desire to learn by taking action on the environment, and pride and joy in the accomplishment of that which one believes to be worthwhile. Batalden and Stoltz (1993)[2] believed that usable knowledge of what nurtures curiosity and learning, joy and pride of work in workers in a health care setting is often limited and incompletely integrated into daily work. The prevalence and extent of fear among health care workers is underestimated by leaders. Fear serves as a silent thief, often robbing healthcare organisations of precious energy for improvement.

Theory of knowledge

Developing a theory allows us to organise and share information but does not alone lead to learning. Taking action allows us to engage in and share experiences, but does not alone lead to learning. When we link theory and action, we have the potential for learning and building knowledge. Prediction and measurement help us to link theory and action.[2]

Baltaden and Stoltz (1993)[2] demonstrated how clinicians use the model for building knowledge and learning in the routine management of patients: a preliminary diagnosis is established (theory), a trial of therapy is instituted (action), a particular response is anticipated within a certain time frame (prediction), at the appropriate time the response is evaluated (measurement). If the predicted effect of the trial and the actual response are close, the clinician has useful confirmatory knowledge; the diagnosis is probably right and the treatment probably effective. The clinician has new knowledge for managing the patient from this point on. The clinician has linked theory and action with prediction and measurement to create new knowledge that can be used to guide the next step. The same model can be used for building knowledge and learning in the integration of quality improvement as part of daily activity.

The framework towards the continual improvement of healthcare as part of normal daily activity involves the linking of professional knowledge with improvement knowledge. Batalden's statement 'if we do not like the current level of performance we must choose between change and frustration' gives one the courage to take on the challenge. ✶

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'The people who get on in this world are the people who get up and look for the circumstances they want, and, if they can't find them, make them.'
GB Shaw

Paracetamol: Safety versus Toxicity

John Stephen Forte BPharm (Hons), MSc (Lond.)

Paracetamol is an effective analgesic-antipyretic that can be administered safely to children and adults at the appropriate therapeutic doses. The drug is readily metabolised by the liver and toxic metabolites are removed by conjugation with endogenous glutathione. Accidental or deliberate overdosage can lead to hepatic toxicity that can be fatal if not treated urgently with antidotes that replenish depleted glutathione. Pharmacists have an important role to play in patient education to help reduce the incidence of paracetamol poisoning.

Keywords: paracetamol, metabolism, toxicity, poisoning

Introduction

Paracetamol (N-acetyl-p-aminophenol) is a safe and effective agent that is widely used for its analgesic and antipyretic properties. It was first used in medicine in 1893 but only became popular in the second half of the last century.[1]

As the principal para-aminophenol derivative in use, paracetamol replaced its predecessors in the same therapeutic class, acetanilide and phenacetin, as the analgesic-antipyretic of choice for patients in whom salicylates and other nonsteroidal anti-inflammatory drugs are contraindicated.[2] Due to its weak inhibition of cyclo-oxygenase, paracetamol is not indicated as an anti-inflammatory drug.[3]

The conventional adult oral dose of paracetamol is 0.5g to 1g every 4 to 6 hours with a maximum daily dose of 4g. Rectal doses for persons over 12 years of age are 0.5g to 1g administered up to four times daily. In children, oral and rectal doses depend on age and body weight, with a maximum of four doses in a 24-hour period.[2]

Absorption of paracetamol from the gastro-intestinal tract is rapid. The peak plasma concentration is attained within 30 to 60 minutes and the elimination half-life in plasma is about 2 hours following administration of a therapeutic dose.[1] Paracetamol is distributed into most body tissues and plasma protein binding is negligible at therapeutic doses, but increases with increasing plasma concentrations.[2] The drug readily crosses the placenta although there is no published evidence of teratogenic effects.[4]

Metabolism of paracetamol

The metabolic reactions by which drugs are biotransformed in the body are divided into two phases. Phase I reactions prepare a drug for the subsequent phase II reactions. The latter are the true detoxification pathways which result in products that are generally water-soluble and easily excreted in urine or bile.[5]

The metabolic biotransformation of paracetamol predominantly proceeds through phase II pathways in the liver (Figure I). The main reaction is hepatic conjugation with glucuronic acid, which accounts for about 60% of renally excreted metabolites. Conjugation with sulphate contributes a further 35% to urinary metabolites. A small amount, about 3%, is excreted as mercapturic acid, the N-acetylcysteine conjugate.[1] Less than 5% of paracetamol is excreted unchanged in urine.[2]

The conjugates are not chemically reactive and therefore not likely to cause any organ damage. However mercapturic acid is formed via the conjugation reaction between a potentially hepatotoxic reactive intermediate and sulphydryl groups in glutathione. This reactive intermediate is probably N-acetyl-p-benzoquinoneimine (NAPQI), a cytotoxic electrophile that binds to cellular proteins.[6] Compared with

Table I: Factors influencing the metabolism and toxicity of paracetamol

Drug interactions

- Exposure to drugs that are inducers of hepatic drug-metabolising enzymes, e.g. phenobarbital, increases susceptibility to hepatotoxic effects of paracetamol.[6]
- Inhibition of glucuronidation of both paracetamol and zidovudine may occur when the drugs are administered concurrently resulting in increased toxicity of both drugs.[4]
- Resistance to the hepatotoxic effects of paracetamol is seen in the presence of drugs that are inhibitors of microsomal enzymes.[6] Cimetidine, an inhibitor of cytochrome P-450, decreases the toxicity of paracetamol by preventing formation of hepatotoxic metabolites while having no effect on conjugation reactions that yield non-toxic metabolites.[16]

Alcohol

- Acute exposure to alcohol (ethanol) decreases metabolism of paracetamol by Phase II pathways so that the drug exhibits a longer elimination half-life.[5]
- Chronic exposure to alcohol with no hepatocellular changes leads to induction of Phase I and Phase II metabolism. Induction of cytochrome P450 2E1 increases Phase I metabolic oxidation of paracetamol with enhanced toxicity due to increased formation of toxic metabolite.[5]
- When the extent of alcoholic liver disease becomes extensive there is a reduction in the metabolism of paracetamol as seen in cirrhosis.[5]

Diet

- Animal studies have shown that hepatotoxicity of paracetamol increases after a low-protein diet. This may be due to reduced levels of intracellular glutathione that offsets the reduced amount of cytochrome P450 caused by protein deficiency.[6]
- An increase in hepatotoxicity of paracetamol has also been seen in animals after overnight fasting due to depletion of glutathione levels.[6]

Genetics

- Genetic control of drug metabolism is exemplified by the appearance of racial differences in glucuronidation of paracetamol between Caucasians and Chinese.[5]
- Variability in rates of metabolic oxidation of paracetamol by cytochrome P450 in human populations has been identified. Where the rate of oxidation is highest there is increased susceptibility to hepatotoxicity of paracetamol. At the lowest rate, about 25% of the highest, there is relative resistance to hepatotoxicity.[5]
- CYP2D6, one of the pharmacogenetically important cytochrome P450 isoforms that exhibits polymorphism, may contribute significantly to the formation of the toxic metabolite at toxic doses of paracetamol especially in CYP2D6 ultra-rapid and extensive metabolisers.[8]

glucuronidation and sulphation, conjugation with glutathione is a minor pathway of paracetamol biotransformation, even though the liver contains high levels of both glutathione and glutathione transferases. The relatively low rate of glutathione conjugation reflects the slow rate of formation of NAPQI by the dehydrogenation of paracetamol, a reaction catalysed by the hepatic and renal phase I mixed-function oxidases, the cytochrome P450 isozymes namely CYP2E1, CYP1A2, CYP3A4[7] and CYP2D6.[8]

Glutathione plays an essential role in protecting hepatocytes from injury by chemically reactive metabolites. When low doses of paracetamol are administered, NAPQI preferentially combines with glutathione. As the dose is increased, the availability of glutathione in tissues is decreased until, at a certain threshold dose, accumulation of NAPQI results in a sharp increase in binding to sulphydryl groups in hepatocytes with formation of adducts, arylation of hepatic cellular macromolecules and ensuing centrilobular necrosis. Thus, at therapeutic doses of paracetamol, glutathione provides the cell with a means of preventing the reactive metabolite from attaining a critical, effective concentration.[9]

The paracetamol-glutathione conjugate that is formed in the liver is converted to mercapturic acid in the kidneys and excreted in urine. Glutathione is a tripeptide consisting of the amino acids cysteine, glutamic acid and glycine. Thus the formation of mercapturic acid involves the sequential cleavage of glutamic acid and glycine from the glutathione moiety in the conjugate to give the cysteine conjugate which is, in turn, N-acetylated to the mercapturic acid.[7]

Besides hepatic damage, paracetamol can also induce damage to the kidney medulla. Prostaglandin synthetase, which is more predominant than cytochrome P450 in the kidneys, is involved in the formation of NAPQI via an intermediate free radical, N-acetylbenzosemiquinoneimine, that can bind to renal proteins.[7] This free radical may undergo reduction with glutathione to reform paracetamol.[5] Therefore the biotransformation of the free radical is adversely affected by depletion of glutathione.

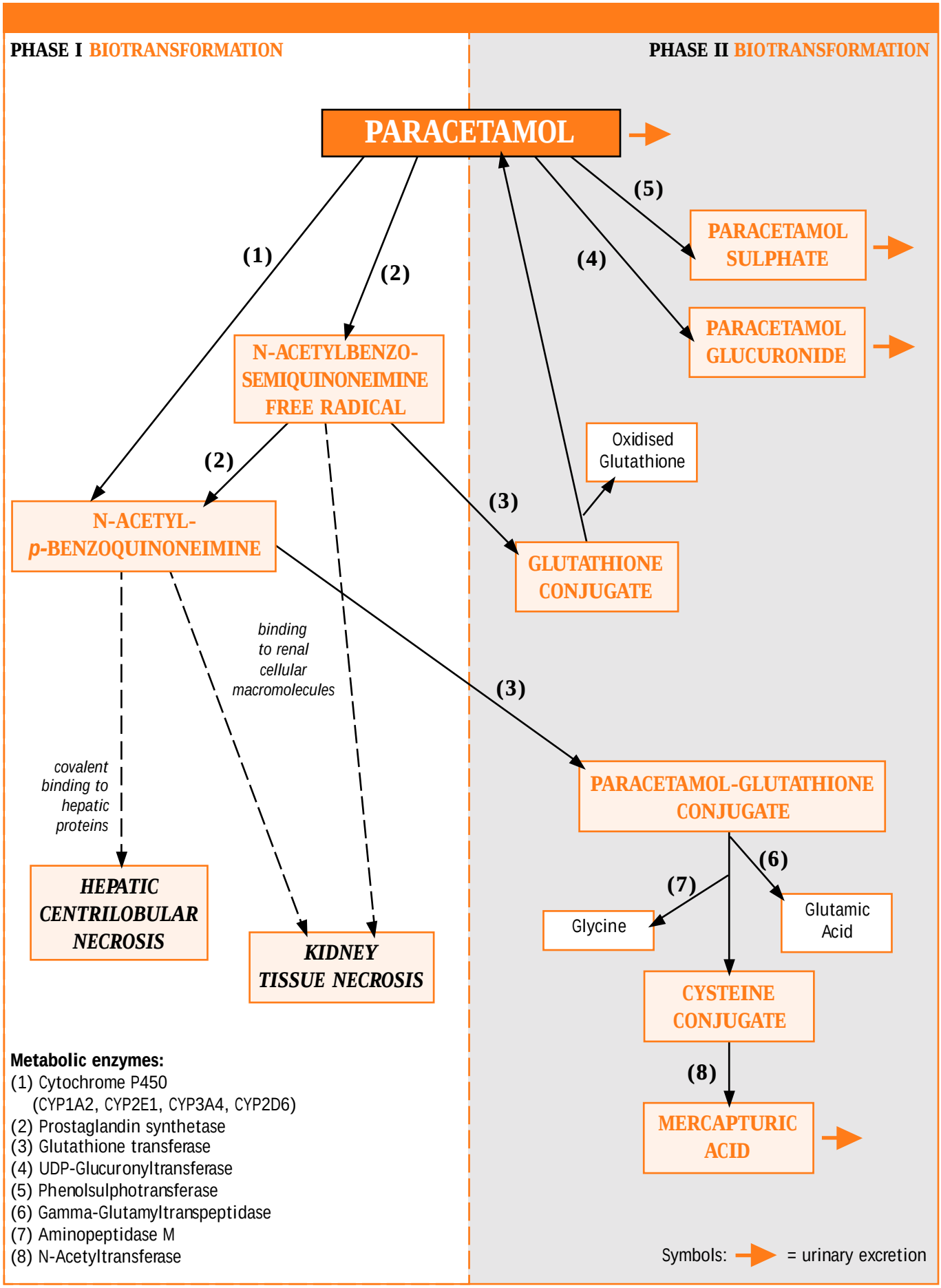
Paracetamol toxicity and treatment

When administered in the recommended therapeutic doses, paracetamol is usually well tolerated. Hypersensitivity reactions including skin and other allergic reactions may occur occasionally. Haematological reactions have also been reported. Prolonged use of the drug may cause nephropathy and animal studies have indicated the possibility of tumour-inducing effects.[4]

The major toxic effects of paracetamol are by far associated with acute overdosage, which is primarily manifested as a dose-dependent hepatocellular necrosis unless treated promptly. Renal tubular necrosis occurs less commonly and may be seen in the absence of liver damage.[4] Myocardial abnormalities and pancreatitis are also non-hepatic symptoms of overdosage.[2]

The early symptoms of overdosage are not alarming and in the first 12 hours could include nausea, vomiting, lethargy and sweating.[2,10] While damage to the liver starts to take place within hours of ingestion, clinical manifestations such as abdominal pain and tenderness followed by jaundice may only be apparent after 24 to 48 hours and may be delayed by 4 to 6 days after ingestion.[2,4] Abnormal liver function tests with increases in

Figure 1: Pathways of paracetamol metabolism and toxicity



(Adapted from References 5,6,7)

seen as early as 8 hours from ingestion although they may result later within the first 24 hours.[10] Liver damage reaches a maximum in 72 to 96 hours after ingestion and may progress to hepatic failure with ensuing complications.[2] Acute renal tubular damage may occur concurrently with liver damage.[1,2]

The metabolism and consequently the toxicity of paracetamol are influenced by a number of factors (Table I). The adult minimum toxic dose of about 12g may be lowered to 6 g in high-risk patients because of increased susceptibility.[4] Thus there may be a relatively narrow margin between the recommended adult daily dose of 4 g and the minimum toxic dose. Paracetamol doses of 20 to 25 g are potentially fatal.[1]

The relatively mild symptoms that are seen in the first hours after ingestion and the delay in clinical manifestations of hepatic damage may deter patients from seeking prompt treatment at a hospital even in the absence of symptoms. Gastric lavage is usually performed if ingestion was within 2 to 4 hours of admission[1,2] and full supportive measures are instituted.

Although peak plasma paracetamol concentration is best measured at least 4 hours after ingestion and not later than 16 hours from ingestion,[2] therapy should not be delayed if significant overdosage is suspected.[1,2] Plasma paracetamol concentrations are compared against a standard nomogram reference line that relates plasma concentration to time after ingestion. When the plasma concentration of the patient is above the normal reference line treatment must be instituted. For patients who are at increased risk of toxicity a lower high-risk treatment line is employed.[2]

Methionine and N-acetylcysteine are the two antidotes that are used to treat paracetamol toxicity. The former is available as an oral preparation and the latter as oral and intravenous formulations. Oral administration is the preferred treatment route in the United States.[10] However, in the United Kingdom, intravenous N-acetylcysteine is preferred because the unpleasant taste and odour of the oral form of the antidote may exacerbate the early symptoms of nausea and vomiting.[2,10]

N-Acetylcysteine is a well-tolerated source of intracellular cysteine, the rate-limiting amino acid in glutathione synthesis.[11] There are four mechanisms by which the antidote may act:[6]

- promotion of the synthesis of glutathione which is necessary for the detoxication of the reactive metabolite, NAPQI, by conjugation;
- stimulation of the synthesis of glutathione used in the protection of protein thiols;
- relief of the saturation of sulphate conjugation which occurs during paracetamol overdose; and
- direct involvement in the reduction of NAPQI.

N-Acetylcysteine may be effective when administered 15 hours or more after an overdose[6] and may even be of benefit 24 hours after paracetamol ingestion.[11,12] Since by this time most of the metabolite NAPQI would have reacted with cellular proteins, the antidote may, at a late stage, afford protection against subsequent cellular changes.[6]

Methionine is not as effective when administration is delayed. This may possibly be due to inhibition of glutathione synthesis by thiol-containing enzymes involved in the synthetic pathway.[6]

Table II: Pharmacy Practice Points: Preparations containing Paracetamol

- Paracetamol-containing products are generally classified as over-the-counter preparations to be dispensed at the discretion of the pharmacist unless compounded with active ingredients that have prescription status. **Avoid dispensing large quantities unless justified.**
- Paracetamol is considered to be a safe and effective drug only if taken for its intended use and at the recommended therapeutic doses for children and adults. **Advise patients never to exceed the stated doses unless under the supervision of a physician.**
- There are several multi-ingredient preparations, such as cold and flu products and compound analgesics, that contain paracetamol. **Advise patients not to take more than one product containing paracetamol at any time to avoid the risk of exceeding the recommended daily dose.**
- Paracetamol is also known by the name acetaminophen. This terminology is primarily used in products originating from the United States and Canada. **Always inform patients that acetaminophen is the same as paracetamol when dispensing such products.**
- The liver and the kidneys are the major organs in the body that are susceptible to the toxic effects of paracetamol. **Products containing paracetamol should be used with caution in patients with impaired hepatic or renal function, dependent on alcohol, or taking medicines that are potentially hepatotoxic.**
- Clinical manifestations of paracetamol toxicity are seen several hours after an accidental or intentional overdose but treatment is more successful if the antidote is administered as soon as possible after ingestion. **Always refer a patient with suspected or confirmed paracetamol overdose to hospital for emergency examination and treatment even in the absence of symptoms.**

Pharmacy practice points

The relative ease with which paracetamol can be obtained as a non-prescription medicine is believed to be a major factor that accounts for the relatively high incidence of accidental and deliberate overdosage in the United Kingdom and the United States.[10]

Several measures have been taken to reduce incidents of paracetamol poisoning. In the United States, standards for product labelling were revised to clarify dosing instructions and introduce a more specific warning

statement.[13] The regulatory authorities in the United Kingdom subjected some oral paracetamol dosage forms to prescription control with exemptions based on restricted pack sizes, number of packs that could be supplied, and requirements for warning statements.[14]

Restricting the sale of paracetamol preparations solely from pharmacies, as is the case in Malta, or restricting the amount that can be supplied should not be expected to offer sufficient protection against incidents of overdosage. Adults, including parents administering paracetamol to their children, are known to have difficulty measuring and administering a correct dose of a medicine. Of more concern is the fact that many adults fail to associate brand names with the active ingredient in the product, leading to excessive cumulative doses when multiple sources of paracetamol are administered.[15]

Notwithstanding the fact that intentional paracetamol poisoning cannot be prevented without direct intervention, the pharmacist has an important role to play in reducing the incidence of accidental poisoning.

Table II lists several practice points that could contribute to improved patient education on the use of paracetamol.

Conclusion

At therapeutic doses, paracetamol exhibits a good safety profile that makes it a popular drug found in most households. However the ease with which it may be obtained should not be interpreted as a guarantee of absolute safety. Some patients are at an increased risk of poisoning at lower doses than are normal for the rest of the population. In any case, the consequences of overdosage are severe and can lead to death. Thus early and prompt treatment of poisoning is imperative even in the absence of symptoms. Pharmacists advising patients on caution in the use of paracetamol can reassure them that, in using the drug correctly, they can benefit from its therapeutic efficacy in the treatment of mild and moderate symptoms. ✶

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The President and Council of The Malta College of Pharmacy Practice would like to congratulate the final year pharmacy students for successfully passing their exams after five years of very hard work. We wish them well in their chosen Career and welcome them all to form part of the College.

Flow-Through Dissolution Testing

A comparison with stirred beaker methods

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Keywords: dissolution testing, flow-through apparatus

Dissolution testing of solid dosage forms is well-established as a standard technique to assess drug release from tablets and capsules. It is currently the most useful in vitro method for assuring batch-to-batch uniformity, and is a valuable quality control procedure for comparing release profiles of different batches of finished products.[1]

The earliest dissolution apparata included Pernarowski's basket dissolution assembly[2] and Poole's paddle design.[3] Until recently, official dissolution testing methods were based entirely on modifications of these static models. However, these methods suffer from a number of disadvantages[4] and the need for a new official dissolution test was recognised, resulting in the introduction of the flow-through dissolution apparatus in the United States Pharmacopeia[5] and the British Pharmaceopoeia.[6]

Basic Design of Dissolution Apparata

The traditional dissolution apparata are based on a stirred-tank static system model, where the drug is dissolved in a relatively large, fixed volume of dissolution medium contained in a cylindrical vessel with a hemispherical bottom. The vessel is partially immersed in a suitable water bath to maintain the temperature of the medium at 37°C. A forced convection type of agitation is accomplished by means of a stirring, rotating or oscillating device, generally a motor-driven paddle or wire-mesh basket. Discrete samples are periodically withdrawn from the dissolution medium and analysed.

In flow-through methods, the assembly consists of a reservoir and pump for the dissolution medium, a thermostatically-controlled flow-through cell and a water bath that maintains the dissolution medium at 37°C (Figure I). The pump is separated from the dissolution unit in order to shield the latter against vibrations originating from the pump. The cell is made of transparent and inert material, and is mounted vertically with a screen and filter system that prevents escape of undissolved particles from the top of the cell. The bottom cone is usually filled with small 1-mm glass beads with one 5-mm bead positioned at the apex to protect the fluid entry tube. The dosage form under investigation is placed on the beads or on a wire carrier inside the cell and a continuous flow of the dissolution medium from the reservoir is forced upwards through the cell by the pump. The dissolution fluid is usually collected in a separate reservoir as it leaves the dissolution cell; fractions are removed at specified intervals and analysed.

Comparison of the flow-through method with static volume dissolution testing.

The advantages and disadvantages of the flow-through method are listed in Table I. Three particularly important issues warrant further discussion.

1. Flow characteristics of the dissolution medium

One of the factors responsible for the inherent lack of homogeneity in the beaker methods results from the agitation methods. Agitating the liquid by stirring with a wire mesh basket or a propeller creates a certain degree of turbulent solvent flow, which causes a variable shear rate of solvent transfer over the surface of the particles, resulting in excessive variations in the individual rates of dissolution. The movement of solute over any particle will depend on the position of the particle in the vessel and the character of the stirring process at each position

within the container. The latter varies markedly with the geometry of the vessel, the volume of the liquid, and the speed and form of motion created by the agitator.[4] The apparatus thus introduces an inherent variability into the dissolution process, which is extrinsic to the product under study. This can result in a lack of reproducibility, and consequently, these systems have to be greatly standardised, reducing investigative flexibility.

The objective of the flow-through design was to expose the dosage form to a homogeneous, non-turbulent, laminar flow, devoid of the problems associated with a stirring mechanism. However, achieving this goal can also be problematic, since both the nature of the pump[7,8] and, to a greater extent, the flow rate[9,10] can affect the pattern of flow inside the cell. Thus in earlier designs, at high flow rates, a column of solvent moved rapidly upwards and randomly dispersed after striking the upper screen and filter holder, with widespread turbulence. The drug particles resided in eddies within this type of flow, resulting in decreased dissolution rates. On the other hand, at relatively low flow rates, while the solvent entering the chamber had laminar characteristics, after striking the upper screen some of the solvent returned to the bottom of the cell, with laminar or turbulent characteristics, creating an undesirable two-directional flow. The best results were thus obtained with intermediate flow rates; within a certain range of flow rates, the dissolution rate was found to vary logarithmically with the flow rate.[9] The range of useful flow rates was increased when a bed of glass beads was added to the cell to act as dampers.[10]

Table I: Advantages and disadvantages of the flow-through dissolution apparatus

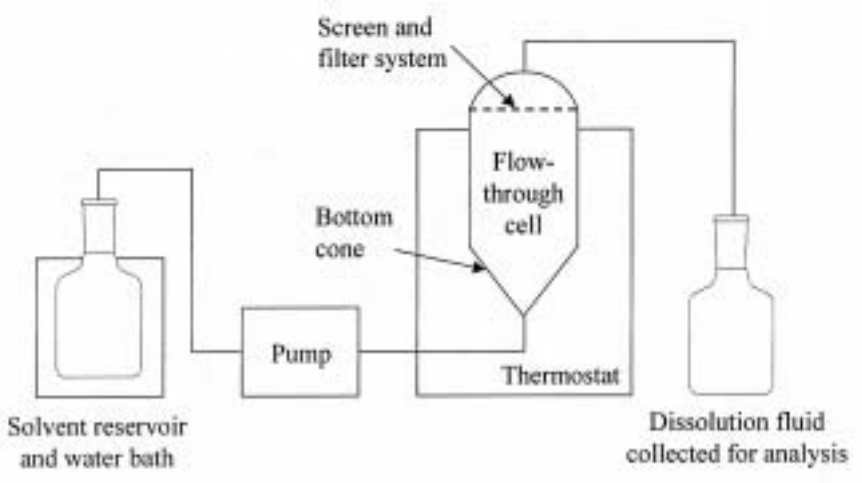
Advantages:

- Laminar flow characteristics over a wide range of solvent flow rates
- Infinite sink ideal for low solubility drugs
- Differential rather than cumulative time profile of dissolved drug concentration
- Dwell time of dosage form in medium is minimal, reducing risk of drug degradation
- pH modification of dissolution medium is easy
- Samples for analysis easily obtained without altering dissolved drug concentration

Disadvantages:

- Large volumes of media required to maintain flow rate
- Risk of clogging of filters
- Validation of flow rate during testing is difficult

Figure I: Schematic representation of a flow-through dissolution apparatus.



2. Liquid Volume

In the beaker methods, the liquid volume must be fixed beforehand; two major considerations require that the liquid volume be a large one.

a) Dissolution rate is directly proportional to the concentration gradient between the saturation solubility concentration at the solid/liquid interface, and the solute concentration in the bulk of the system. Since the former concentration remains constant, it is important that the bulk solute concentration be kept as low as possible in order to maintain a relatively constant concentration gradient. This is achieved by dissolving the dosage form in a large volume of medium.[4]

b) In all beaker methods the drug concentration in the liquid increases from zero up to either the saturation limit or the concentration which corresponds to the completely dissolved drug amount. This concentration increase is different from the in vivo process in which the dissolved material is removed continuously from the dissolution medium by absorption. In order to improve the chances of achieving good in vitro-in vivo correlations in this area, dissolution processes must be studied by methods in which the liquid acts as a perfect sink, that is, the concentration never exceeds 10-20% of the saturation. The need for a perfect sink necessitates using a relatively large volume of solvent.[4]

While the rate of agitation should be kept low in order to establish meaningful in vitro-in vivo correlations and to detect subtle differences between formulations, low agitation of a high volume system results in poor homogeneity, and the sample withdrawn for analysis might not be representative of the whole system. A relatively high rate of agitation is thus required, accentuating the lack of homogeneity in flow patterns mentioned previously. Thus, there is an inherent disagreement existing in these systems between the requirements for homogeneity, large volumes, and low

the major advantage of the open flow-through apparatus is that perfect sink conditions can be maintained without the use of large vessels, while maintaining relatively low degrees of agitation.

3. Data Generation

The beaker methods are based on the concept of a fixed volume and thus produce data expressed as an integral function, since the dissolved molecules are accumulating in the solution. On the other hand, since the flow-through technique continuously exposes the dosage form to fresh solvent, data generation occurs non-cumulatively in a differential form.[4] Consequently, the beaker methods produce average dissolution rates at best, making it difficult to detect subtle but possibly important differences in formulations, which are more readily detected in the data generated by the flow-through apparatus.

Comparative studies for the assessment of the flow-through apparatus

The first comparative evaluations of the flow-through apparatus relative to other apparata were performed in the 1970's.[11,12] More recently, a collaborative study involving four Swedish laboratories compared the dissolution of the USP salicylic acid calibrator tablet in the USP paddle apparatus and in a flow-through system.[13]

The results indicated a better reproducibility over a wide range of flow rates for the flow-through method than the paddle method. However, a similar study performed by the same group in 1989 using the USP prednisolone calibrator tablets yielded conflicting results.[14] Nevertheless the latter study showed the flow-through apparatus to be sensitive to formulation behaviour, and also capable of discriminating between different containers in the same batch - a factor of extreme importance for tablets of drugs which are sensitive to storage conditions, such as prednisolone. It was thus concluded that, in spite of the variability between the dissolution methods, the flow-through apparatus could be considered as capable as the beaker methods in generating reliable data, an assessment confirmed by the Scandinavian laboratories in a subsequent study using the sparingly soluble drug phenacetin.[15]

Conclusion

The official apparata all have their inherent advantages and disadvantages and are thus ideal for dissolution testing of different systems. While the conventional stirred beaker apparata are most suited for dissolution testing of immediate-release dosage forms of drugs with good solubility characteristics, the flow-through apparatus, whilst suitable for most solid dosage forms, yields maximum benefit in evaluating the dissolution of poorly-soluble drugs, primarily due to the fact that the system provides an infinite sink similar to that encountered under physiological conditions. ✶

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