Adverse Drug Reactions and the role of the Pharmacist – Hepatotoxicity

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Introduction

In the last five years, the Irish Medicines Board (IMB) has issued advice, warnings or taken other regulatory action with respect of co-amoxiclav (amoxicillin-clavulanate),[1] black cohosh root,[2] methotrexate,[3] a preparation containing a hydroalcoholic extracts of green tea,[4] terbinafine[5] and nimesulide[6] because of actual or potential toxicity to the liver. Drug-induced hepatotoxicity is an international problem and it is the leading cause of drug withdrawal by drug regulatory authorities, despite affecting only one in 10,000 to one in 100,000 exposed persons.[7–9] In an unpredictable proportion of these patients the condition will develop into fulminant or acute liver failure and four out of five of these patients will not survive unless they receive a liver transplant.[9]

By contrast, drug-induced liver injury (DILI), marked by raised plasma liver function test levels (LFTs), occurs quite frequently in patients receiving many different classes of drugs, but many of these cases are asymptomatic, do not lead to hepatotoxicity and may resolve without any intervention.[7–9] Commonly used drugs such as paracetamol, antibiotics, antivirals, NSAIDs, antidepressants, antiepileptics, herbal preparations and statins are among those identified as more frequent causes of DILI, and rarely of hepatotoxicity, in a number of studies from around the world.[7–9] With so many widely used drugs capable of producing DILI and also with the potential to produce hepatotoxicity, leading to significant morbidity and adding to the demand for liver transplantation, this is an important factor in determining drug use. Little attention has been paid to addressing the problem in primary care and it is usually when a drug's authorisation is suspended or withdrawn that this unpreparedness becomes apparent to everyone.

In acute situations, such as the suspension of nimesulide (Aulin®) earlier this year, community pharmacists find themselves having to answer patients' concerns about the likelihood that they could have/could still suffer from the adverse drug reaction in question, and to provide advice about an alternative drug. Pharmacists themselves may have concerns that they do not know enough about the patient's condition, and since they cannot readily access relevant aspects of the patient's history, they may feel powerless to help. Similarly, they may not feel competent to deal with the specialist clinical issues that drug-induced hepatotoxicity cases raise, and they may not appreciate the procedural technicalities of drug regulation and pharmacovigilance that determine the timing and nature of any regulatory action. Much media coverage and comment is predicated upon the unreal dichotomies of 'safe' and 'unsafe' and of 'competent' and 'incompetent', which colours any discussion with a patient from the outset. These newsworthy events also raise more general questions in people's minds, such as why the drug regulatory process and the pharmacovigilance system did not prevent this episode. As a consequence, pharmacists and other healthcare professionals may feel that their communications skills are inadequate to these tasks.[11] Yet, these are not isolated instances and they will recur, so a logical approach, drawn from agreed and, as far as possible evidence-based, guidance for healthcare professionals when managing a potentially serious ADR, is needed. To prevent such toxicity, all healthcare professionals also need to understand the process of pharmacovigilance and reporting ADRs.

This paper links three inter-related themes: *knowledge*, *identification* and *action*. A number of commonly used drugs capable of causing hepatotoxicity are taken as examples, to illustrate how the existing knowledge and present systems of regulation can be applied in day-to-day practice, and to highlight the limitations of what is known and therefore of the recommendations that can be offered. The discussion of these issues is aimed at the community pharmacist whose patients receive most of their services within primary care.

Knowledge of the drug

The first requirement is knowledge of the drug and its history in use. This is not as banal or condescending as it may appear. Informal and also public comments by some pharmacists at the time of nimesulide's suspension indicate that the level of knowledge about nimesulide was not as detailed as it should have been. Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) that was approved for use in Ireland in 1995 for the relief of the symptoms of osteoarthritis, painful joint disorders, post-operative dental pain and inflammation, and dysmenorrhoea.[10] Its Product Authorisation was suspended because of its association with liver damage.[6] The IMB had issued advice about nimesulide, particularly concerning possible hepatotoxicity, and altered the terms of its product authorisation on four occasions from 1999–2004, prior to its suspension.[10–13] The manufacturer had also issued a letter about the drug at the time of the last IMB communication in 2004. Once a drug is approved for use in patients, new information about its pharmacology continues to be discovered and this is true even for 'old' drugs (≥5 years old). Therefore, the pharmacist's monitoring role applies as much to a drug's pharmacology as it does to their patient's condition(s) and indeed, to concentrate on one and neglect the other leads to inadequate knowledge and areas of poor professional competence. That is why 'therapeutic update' is provided for in the service contract with the HSE[14] and why the ICCPE was formed to deliver it and why the pharmacy regulatory body, the Pharmaceutical Society of Ireland, is charged with promoting continuing education in support of Continuing Professional Development[15] in order to sustain fitness to practice.

Identification of symptoms and the recognition of hepatotoxicity

For an organ that is so central to our survival, the liver remains complex and poorly understood. This is also true of drug hepatotoxicity and DILI. Hepatotoxicity is usually detected from the signs and symptoms exhibited by a patient and their temporal relationship to drug-taking.[7–9, 16–17] Detection, rather than diagnosis, is needed and pharmacists need not feel that the linking of the drug to the symptoms must be certain, but rather about the suspicion that it may be. The patient care decision that is required is whether to discontinue the drug and refer, to continue the drug and refer, or to wait and see; it is neither a final judgement on the drug nor on the prescriber. By contrast the IMB must decide whether the reports that it receives about a drug constitute grounds for intervention. To do this the IMB requires a report of a suspected ADR, not a report of an ADR confirmed by clinical investigations. The drug may or may not be associated with the adverse event, but that will be determined by IMB staff, taking all of the reports about a drug into consideration. In the case of rare events therefore, every report is vital to enable the IMB to discern the overall pattern of ADRs and this is particularly true for hepatotoxicity, since it is rare but when severe can often be fatal.

Drug-induced hepatotoxicity is not associated with a single, unique, easily identifiable and consistent set of signs and symptoms.[7–9, 16–18] There are several types of cells in the liver, each of which can be injured in a number of ways, and the patient's genetic make-up in the susceptibility of their cells and of their metabolic pathways (including drugs) all contribute to this variability.[7, 16] Given this background, it is not surprising that some drugs have been associated with more than one type of hepatotoxicity while others are only associated with one type, e.g. oestrogens and anabolic agents consistently produce cholestasis. Three basic patterns of symptoms can be recognised[16–18] and are shown in Table 1 on the following page.

A group of symptoms as described (patterns 1–3), rather than individual symptoms, can be considered suspicious, thus pruritis alone is not as indicative as jaundice with pruritis. 'Mixed' reactions can occur in which jaundice may develop along with the symptoms of hepatocellular injury, and these cases are often

Table 1 – Symptoms and types of hepatotoxicity

SYMPTOMS	TYPE OF HEPATOTOXICITY
Pattern 1: fever, malaise, anorexia, nausea, possibly with pain or discomfort in the right upper quadrant of the abdomen, and in some cases dark urine	Hepatocellular necrosis/hepatitis – indicative of the destruction of liver cells
Pattern 2: jaundice with pruritis	Cholestatic jaundice – indicative of the liver's inability to produce and secrete bile
Pattern 3: fever associated with a skin rash	Hypersensitivity or an immune reaction, which may also present as hepatitis

particularly serious.[19] The signs and symptoms of allergy, in cases of allergic-induced hepatotoxicity with drugs such as sulphonamides and phenytoin, may present so quickly and be so marked that the possibility of liver injury may be initially overlooked. In practice therefore, pharmacists should consider the possibility of liver damage with any drug for which hepatotoxicity is a well reported/publicised ADR and if the patient reports any of these symptoms allied to a likely onset-time.

In the case of a new drug, particularly those belonging to new classes for which the nature and types of possible ADRs have not yet been discovered and reported, all reactions to these drugs should be reported. Similarly, if the symptom(s) is/are so debilitating that the patient cannot come to the pharmacy themselves, but telephones, or sends someone to speak for them, reporting and referral are both called for. Patients with dark urine, pale stools, jaundice and abdominal pain should be sent to the GP and the practice informed that the patient is on their way because the patient's condition can deteriorate rapidly.

Pharmacists may feel that symptoms alone are insufficient evidence upon which to base a report. Whilst it is possible to check some of the patient's signs – appearance and demeanour, blood pressure, temperature and respiratory rate and so on – these are not distinguishing indices. There is no simple and precise test(s) to identify hepatotoxicity. Additional signs and investigations will be needed, and these will be done in hospital.[7–9,16,19] Plasma enzyme levels, also somewhat misleadingly called liver function tests may be measured (they do not measure function and some prefer the term liver chemistry tests). These include ALT (alanine aminotransferase) AST (aspartate aminotransferase), gamma GT (gamma glutamyl transferase), ALP (alkaline phosphatase) and bilirubin (usually reported as conjugated and unconjugated [excreted in bile] forms). ALT is not specific to the liver and may be raised in many types of injury. The INR/prothrombin time (PT) may be measured, and in hospital a liver biopsy might be taken and an ultrasound scan performed. Although these tests may be helpful, alone they are insufficient evidence to identify an adverse drug reaction and also, because the results will only be available at a later date, they cannot be used to guide the initial clinical response but to differentiate apparently similar syndromes.[16–19] LFTs are often raised during drug treatment, but in many cases do not progress to liver damage.[8–9,19] Similarly bilirubin levels may rise and yet the patient remains symptom free. These patterns reflect the liver's capacity to suffer damage yet maintain function, and in some cases to adapt to the presence of a toxin. In the case of statins and other lipid-lowering drugs, the rise in LFTs occurs because of their action in the liver but they hardly ever cause hepatotoxicity.9 In most cases the signs of hepatotoxicity subside when the drug is withdrawn, even when some hepatocellular damage has occurred. And with some drugs, such as isoniazid, LFTs may revert to within the normal range even when the drug is continued.[8,20]

Nimesulide is thought by some to be more likely to produce a fulminant (progressive) type of hepatic failure, and when this occurs it is often fatal and the only treatment for severe cases is transplantation.[16–18] Unfortunately, there is no way to predict rapidly and precisely which patient's symptoms will progress to a potentially fatal outcome. Given these facts, although it goes against the grain for many pharmacists, suspicion is a better guide to patient care than hard evidence in such cases.[18]

Communications skills play their part throughout this process. The first conversation with a new patient, particularly when the patient is receiving a drug for the first time, is crucial because it establishes in their mind what the pharmacist's role and responsibilities are and how this relates to them and to their medicines.[21] Similarly, long-term treatment requires regular review and this should be explained to patients. Written material should be used in support of the verbal information that is provided. Patient Information Leaflets (PILs) and cautionary and warning labels are part of this. One consequence of not incorporating PILs into your counselling is that patients come to regard pharmacists as providers of products, and the pharmaceutical company as the providers of medicines information.[22] Patient communication is more effective when verbal and written methods are combined, and the pharmacist 'personalises' the information for the patient.

Although drug-induced hepatotoxicity is uncommon, the accessibility of community pharmacies, and the recognition by the public that information about medicines can be obtained from and checked by pharmacists, means it is likely that patients suffering these symptoms may consult in the pharmacy first of all. Hence the need for pharmacists to consider how best to respond to such a scenario. An automatic referral without discussion or explanation could be interpreted by a patient as the pharmacist avoiding the problem because they lack expertise or self-confidence.

Patient Medication Record and Medication History

Reviewing the Patient Medication Record (PMR) and taking a relevant medication history are crucial activities in identifying an ADR.

An accurate PMR (i.e. one that is complete for the patient and for which no accidental duplicates have been created by locum or inexperienced staff) is a pre-requisite. The dose, frequency of use, and start/stop dates of all prescription medicines should be reviewed. If more than one potentially hepatotoxic drug is being taken by the patient, this may increase the risk of toxicity and each of the drugs should be noted. Rifampicin plus isoniazid[20] and amoxicillin with clavulanate[24] are examples in which there is evidence of increased hepatoxicity with combinations, while there is some, but less substantial, evidence that two or more NSAIDs[23] increases the risk of toxicity. Hepatotoxicity with nimesulide and most other drugs commonly occurs in response to therapeutic doses, or cumulative therapeutic doses, rather than an overdose. There are some exceptions: paracetamol is mainly hepatotoxic in overdose, methotrexate and amiodarone through cumulative doses.[7] Pharmacists should check the PMR to confirm that the patient received and took the drug, and for the duration of consumption, rather than look for excessive doses, and communicate this as appropriate.

Hepatotoxicity, and its signs and symptoms, may occur any time between one week and three months after starting drug treatment (hepatitis and cholestatic jaundice patterns). Allergy-mediated hepatotoxicity usually occurs more quickly and is apparent within three to four weeks.[7–9, 16–19] Toxicity due to cumulative doses can occur several months after starting therapy. The drug need not be taken at the time that symptoms occur because the toxicity could be delayed, as sometime occurs with co-amoxiclav,[24] hence the importance of reviewing not just the immediate past but the previous six months or so of the PMR. The onset of symptoms relative to the taking of the suspect drug are of crucial importance, not only for the pharmacist's decision-making but for relaying to everyone else who is or becomes involved in the case.

However, if the PMR indicates that the patient is new to the practice, it cannot be assumed that the patient is new to the drug. In this case it is a good idea to take a brief medication history, and record it in the 'clinical notes' or equivalent section in the dispensing record for future reference.

In all cases, any drugs that were discontinued, even for reasons apparently unrelated to the present symptoms, must be recorded together with those reasons. Going through a print-out of the PMR with the patient will improve both the accuracy and speed of the process.

Taking of medication histories is one of the principal contributions that the pharmacist makes to the health service since they can usually identify more drugs and drug-related problems than others.[25] Non-prescription medicines, herbal preparations and some vitamins (e.g. vitamin A), can be hepatotoxic or could exacerbate hepatotoxicity. Therefore, the dose, frequency of use, and start/stop dates of all of these preparations are relevant, so information about all of these must be sought as well.[9, 17, 26, 29] Recently, the EMEA has warned about Black Cohosh root preparations,[2] and others, such as kava kava, germander, chaparral

leaf, skullcap, valerian, and mentha containing Pennyroyal oil, are recognised hepatotoxins.[9, 17, 26 ,32]

Hepatotoxicity with alcoholic extracts of green tea have previously been reported by the EMEA, and these extracts have recently been marketed in other products in Europe and North America and are once again associated with toxicity.[27]

Complications and Contributing factors

Symptoms of ADRs are often non-specific since they are caused by injury and/or loss of function of one or more of the body's main organs or systems. This means that it can be difficult to distinguish between the symptoms of an ADR and the progression of the patient's condition, or of a deterioration in organ function that appears unrelated to the suspect drug. However, there are recognised complicating factors: in the case of hepatotoxicity, a history of viral hepatitis – particularly Hepatitis C, excessive consumption of alcohol, and blood transfusion.[16–18] If blood flow to the liver is reduced, as may be the case in congestive heart failure, this can also increase the liver's susceptibility. If any of these complications are reported by the patient, they should be communicated, along with the details of the patient's drug history, to the patient's GP and recorded in the patient's PMR.

A separate issue is whether liver disease affects drug metabolism. In many circumstances the liver continues to function, particularly as a metabolising organ, even when damaged, so drug metabolism may not be altered or impaired until the damage is severe.[29–30] Rifampicin, which induces some of the metabolising enzymes in the liver, may enhance the toxicity of drugs by increasing the formation of toxic metabolites.[20, 26] Less specifically, but potentially as dangerous, reduced metabolic capacity (cirrhosis) or excretory capacity (renal failure or obstructive jaundice) will alter the pharmacokinetic handling of a drug and could cause accumulation of the drug or a metabolite, which may cause toxicity.[7–8, 16–19]

Drug misusers may be more at risk, partly because of the cocktail of drugs that they may have taken, some of which (e.g. cocaine and ecstasy) can be hepatotoxic, and also because a substantial proportion of them carry one form or other of viral hepatitis.

Pharmacists should be aware that women and older persons are more at risk of ADRs in general and possibly hepatotoxicity, and older women are disproportionately represented among the reported cases of fatal hepatic injury.[18–19] Whether this is because they consume more medicines or because of their physiological status remains unclear. Hepatotoxicity with co-amoxiclav is an exception, where elderly men appear to be more at risk.[24]

The BNF provides some advice in Appendix 2, but it is a summary of general advice. The SPCs set out some of the cautionary circumstances for the use of the drug but these are also general statements: they are based upon limited information, and have been agreed after discussion between the drug regulatory agency and the market authorisation holder. Whether these are sufficiently clear and practical to enable healthcare professionals to act upon them has been questioned in a UK study.[29] The IMB's Drug Safety Newsletter may also contain advice, issued as ADR reports are filed in Ireland and in other countries. In the case of older drugs with a known history of liver disease, there may be more specific advice in the SPC or in guidelines from specialist groups.[20, 28, 31–32]

There are several reasons why information about risk factors and guidance about effective interventions are hard to find: firstly, many cases probably go undetected, because of the similarity of the symptoms to a deterioration in the patient's condition(s); secondly, in acute cases there may be neither the time nor the opportunity to collect evidence about causation or it may be clinically inadvisable to do so; and thirdly, those patients who recover may not be followed up because of lack of resources or may be lost to follow-up once they return home. In the near future a new book about drugs and the liver will be published that may provide a useful single source of knowledge and advice about this complex area of healthcare.

Action

Suspected Drug

Discontinuing or reducing the dose of a suspected drug are actions that many pharmacists are reluctant to take. Since patients who are seriously affected by an ADR are unlikely to appear in person in a pharmacy, few pharmacists have first-hand experience of this situation.

Discontinuation would be required if:

- a serious ADR is suspected – severe symptoms and the need for hospitalisation are regarded as serious (see below for complete definition of the term)
- an ADR has the potential to produce serious organ damage and is an established reaction with this drug
- the patient has complicating factors (viral hepatitis, etc.) and lives alone, or has little family/social support at home, or is a carer of another patient
- the drug is used to relieve symptoms and an alternative drug that would not be expected to exacerbate the ADR is available
- discontinuing the drug would not cause an acute deterioration in the patient's condition

The balancing of the risks and benefits of drug therapy can be done by asking three questions:

- Why has the suspect drug been prescribed? (Whether the drug is being used to provide symptomatic relief, like an NSAID, or to control a condition, or to eliminate an infection, such as anti-tuberculosis drugs)
- How important is the drug for the stability of the patient's condition at the moment? (e.g. statins in hyperlipidaemia after a liver transplant)
- What is the risk to the patient if the suspect drug is continued or discontinued? (e.g. antiepileptics for controlling epilepsy and antidepressants for patients with depression)

If more than one of the patient's prescription and non-prescription medicines is potentially hepatotoxic, then each of them should be stopped until the patient's condition has been stabilised, and an assessment of the risks and benefits of each medicinal product can be made.[30]

Reducing the dose of the suspected drug cannot be recommended in serious ADR cases, and especially not in cases of hepatotoxicity, unless discontinuation would put the patient at greater risk from the condition that the drug is being used to treat, and in these cases, an alternative treatment will be sought.

'Re-challenge' is the term used to describe restarting the patient on the drug after an episode of toxicity. It is rarely used because of concerns about safety, and ethically it is unreasonable to expose a patient to such a risk in order to improve the reliability of the diagnosis.[7–9]

The criteria for guiding the choice of alternative drug are not well defined, and if it is necessary to continue drug treatment, regular monitoring may be used to try to detect developing toxicity. However, this is not always clinically useful or cost-effective. Epilepsy and the treatment of tuberculosis are conditions in which essential drugs need to be continued and alternatives considered. Drugs that are not metabolised in the liver but are excreted unchanged in the urine are possible candidates. Examples of antiepileptics would be gabapentin, levetiracetam and vigabatrin, and these drugs have not been associated with hepatotoxicity.[28] Drugs with similar chemical structures are usually unsuitable, e.g. sulphonamides. However, statins can be restarted, and amoxicillin has been used safely following cases of co-amoxiclav-induced hepatic reactions.[24] Guidelines exist for choosing alternative drugs and drug combinations to treat tuberculosis.[20] The use of antidepressants in patients suffering depression is a particularly difficult situation.[32]

Immediate discontinuation of a suspect drug in the case of apparent hepatotoxicity, as well as in other serious ADRs, is the single most important clinical intervention.[16–19, 30] It could save the patient's life.

Patient Care

Using a drug to treat the side effects caused by another drug is rarely good practice. The possible association of a drug with the symptoms should caution pharmacists to consider carefully whether treatment of the symptoms is appropriate, and if so, with what. If a patient suffering from hepatocellular toxicity (fever, malaise, anorexia, nausea, possibly with pain or discomfort in the right upper quadrant of the abdomen) is treated symptomatically and there is no consideration of hepatotoxicity, there is a danger that they will be treated with a drug that may exacerbate the condition. For example, in the case of nimesulide patients, another NSAID, such as ibuprofen, might be recommended for symptoms of fever and malaise, which by itself can cause liver damage and if taken simultaneously with another NSAID may increase the risk of liver damage. Since it is unethical to deny the patient treatment, these are difficult judgements to make and while some may decide that paracetamol is the only suitable drug in this circumstance, others may differ. Whatever is decided, monitoring is essential.

If patients are admitted to hospital they will receive supportive care and there are no drugs specifically indicated for treating or ameliorating hepatotoxicity. Corticosteroids have been used

in certain cases of allergic-induced injury but the evidence base for this is limited.[16–17] Apart from N-acetylcysteine for paracetamol overdose, antidotes are not available for most drugs. Ursodeoxycholic acid and a selective antihistamine such as cetirizine or loratadine are some of the approaches that have been used for the symptom of pruritis.[16–17]

In the longer term, patients who recover without needing a transplant may still suffer significant chronic liver disease[34] and a concomitant decrease in their quality of life.

Pharmacovigilance

Pharmacists, particularly community pharmacists, are reluctant to report ADRs.[35] Apart from time, the main constraints are uncertainty of attribution and concern about interfering with the prescriber's role in the care of the patient.[35] Neither of these latter two reasons should stop pharmacists from reporting.

Events do not imply causation and can be reported. The pharmacovigilance system will analyse all of the reports about a drug that come from healthcare professionals and pharmaceutical companies, follow up those where clarification is needed and evaluate the accumulated evidence. The fewer reports they receive, the less clear the picture will be.

Clinical trials are designed to establish the efficacy of a drug and the patients are selected for this purpose. This, together with the limited numbers of patients included and the limited period of the trial, means that uncommon ADRs are not usually detected and the rate at which ADRs occur in clinical trials may be less than in general practice. This is why submitting suspected ADRs for newly marketed drugs is essential.

A change in the frequency of a well known ADR may be the result of the drug being used in patients who are more seriously ill, whose condition is not one of the authorised indications, or because of a previously unrecognised interaction. It is therefore important to know why the drug is being used.

A rare ADR is more likely to occur when the drug is very frequently used (nimesulide was one of the most frequently prescribed of all the NSAIDs) and the IMB can request data on the prescribing frequency of drugs from the Primary Care Reimbursement Service when necessary.

ADR reports are collated and assessed by the pharmacovigilance section of the IMB and if the same case is reported by different healthcare professionals they will be able to link the reports so that double-counting will not occur.

The IMB requests reports from pharmacists as well as other healthcare professionals. Each healthcare professional who contributes to the care of a patient is responsible for exercising their 'duty of care'. This should be done in an appropriate way, independently of the views of others.

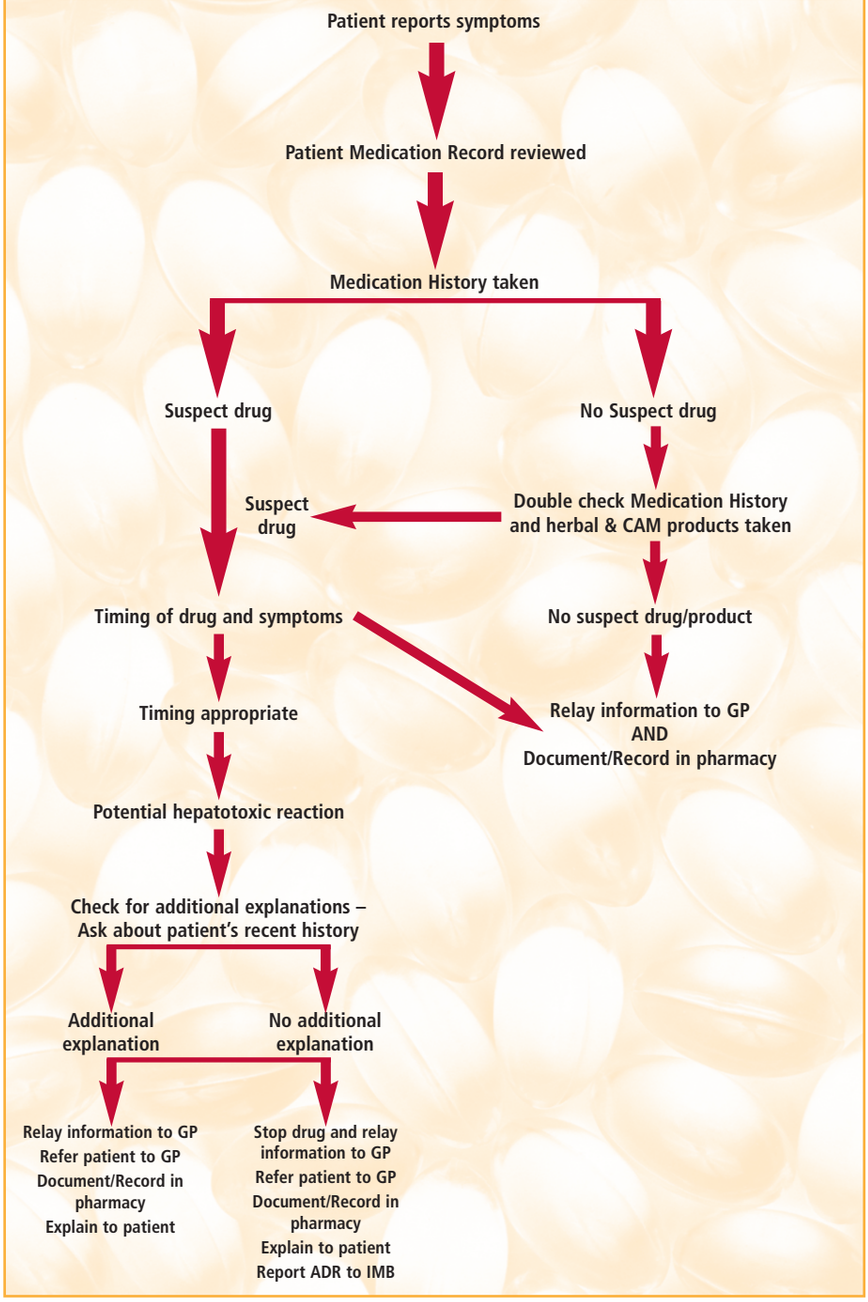
Although patient care is the first and most pressing responsibility when an ADR is suspected, reporting the ADR is an essential contribution to the care of other patients.

Reporting an ADR

The IMB is the body responsible for Pharmacovigilance: http://www.imb.ie/EN/Safety--Quality/Reporting-Suspected-Product-Problems~.aspx

According to the IMB's 2004 Annual Report, community pharmacists returned 70 reports and hospital pharmacists 32 reports, some of which were product defects, out of the 933 returned by healthcare professionals. As of November 2007, the IMB has extended the reporting of ADRs to consumers.

Figure 1 – ADRs and the role of the pharmacist – hepatotoxicity



What to report

- All suspected reactions to new products
- Serious suspected reactions to established products – defined as "an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or incapacity, or in a congenital anomaly/birth defect"
- Any suspected increase in the frequency of minor reactions
- All suspected reactions to vaccines
- All suspected teratogenic effects

How to report

- Complete a yellow card, e.g. in the Irish Medicines Formulary
- Fill in a form online – log on to www.imb.ie and follow the link to 'On-line Reporting' under the Safety & Quality section of the website, where further instructions on how to complete an individual case report are available.
- Download a form from the 'Publications' section of the website, complete and send to FREEPOST, Pharmacovigilance Section, Human Medicines Department, Irish Medicines Board,

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Any questions or clarifications may be communicated by telephone: 01 676 4971 or fax 01 676 7836.

Follow up

Because so many drugs have been rarely associated with hepatotoxicity, it is likely that, once the patient has been assessed, a drug or drugs that are not thought to have contributed to the patient's condition will be restarted, either as before or another drug from the same pharmacological class. Recording what happened to the patient and in particular why one drug may have been prescribed in favour of another, retains and passes on the experience for others who work in the practice and for use in future cases.

Whilst dealing with patients' concerns is done on an individual basis, the 'Questions and Answers' document that the IMB produces for serious episodes can be downloaded and shown or given to patients.[36] It includes contact details for the IMB's pharmacovigilance unit, because, although many people use the internet to retrieve information, most will not have heard of or found the IMB's website. The provision of this material sets the patient's concerns in the context of the national response and may provide them with some reassurance. A copy should be kept and ultimately filed. Pharmacists may want to display the copy during the first few days to alert other patients who, despite the media coverage, are not aware of the withdrawal of the drug and the reasons for withdrawal.

Dispensaries are often festooned with sticky notes carrying messages about patients' medicines. Surely there is a better way to inform staff about current issues: a dispensary logbook with each day's events/reminders; a 'flag' on a patient's PMR? Follow up is also about ensuring that patients are aware of the symptoms that they need to report and who they should contact.

If an incident has occurred, it represents an opportunity to discuss with the GP or GP practice what lessons can be learnt to provide a speedy, co-ordinated and consistent approach. Pharmacists will want to know what advice the GP and/or the hospital has given the patient about drugs to avoid, particularly among non-prescription and herbal medicines. Improvements in patient care often come from evaluating the response to critical incidents.

Summary

Referring, on the basis of recognising potential danger symptoms, assessing medication use, providing a written record of the patient's medicines and communicating concerns, is a central part of the pharmacist's role. Investigation and treatment by the GP or hospital will be facilitated if the pharmacist asks the questions based upon their knowledge of the patient. Stopping the use of a drug is often the best way to avoid serious injury to a patient. Pharmacists have a responsibility to report the ADRs that they encounter. The information upon which the ADR report is based may be incomplete or seem insubstantial to the pharmacist, but its provenance will be assessed by the pharmacovigilance unit of the IMB. The more ADRs that are reported, the more likely preventative action can be taken. The nimesulide case illustrates that drugs that have been in use for some time may be causing a greater number of serious ADRs than is apparent because reporting levels are low and advice about the prescribing and monitoring of a drug is not being followed.[11, 13] The latest drug to be withdrawn because of hepatotoxicity is also an NSAID. Lumiracoxib, one of the newer coxibs, was withdrawn by the Australian authorities in August 2007 because of eight cases, including two deaths and two patients requiring transplants.[37] The accompanying flow chart summarises the approach to dealing with suspected hepatotoxicity (Figure 1). Early referral of patients is recommended by the American Association for the Study of Liver Disease.[30] Gastroenterologists and hepatologists regard drug-induced hepatotoxicity as challenging in many respects,[8,17,19] so community pharmacists can be reassured that by exercising their professional judgement based upon their knowledge of the drug and a careful assessment of the circumstances, they will be making a valuable contribution to patient safety. This is true irrespective of whether the suspicion of drug-induced hepatotoxicity was confirmed or not. In the latter situation a potentially serious adverse consequence was avoided and the patient's condition will have been clarified by the investigations that were performed.

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