MEETING REPORT

Report of the UK DURG Regional Meeting on New Horizons in Pharmacovigilance*

SUMMARY
The UK Drug Utilization Research Group’s (DURG) Regional Meeting ‘New Horizons: Pharmacovigilance’ was hosted by the Drug Safety Research Unit (DSRU) at Southampton on 08 May 2000. Opening the meeting, Dr Keith Beard, UK DURG chairman, welcomed delegates and speakers and thanked the DSRU team for hosting the meeting. With reference to the theme of the meeting — new horizons in pharmacovigilance — Dr Beard said that drug utilization is a very broad subject area. Introducing the first speaker Dr Saad Shakir, Director of the DSRU, Dr Beard said ‘no horizon is going to be newer or more exciting than that of pharmacogenomics’. Copyright © 2000 John Wiley & Sons, Ltd.

PHARMACOGENETICS: POTENTIAL IMPACT ON PHARMACOVIGILANCE

Dr Shakir referred to a recent definition of pharmacogenetics as ‘the study of the effects of inherited differences in the metabolism and disposition of drugs, and genetic polymorphism in the targets of drug therapy (such as receptors) on the efficacy and toxicity of medications’. He went on to describe polymorphism as ‘the occurrence in a population of two or more genetically determined forms in such frequencies so that the rarest of them could not be maintained by mutation alone’. The scope of pharmacogenetics is broad, and includes:

- the precise definition of diseases by mechanisms, providing distinct disease subtypes with differential response to treatment
- variations in drug targets (receptors) and their associated pathways that determine responses to drugs
- molecular variants in host metabolic enzymes which determine drug concentrations and toxicities.

Dr Shakir gave several specific examples of genetic variation which can affect the responses to and toxicities of certain drugs. One study had investigated the effect of $\beta_2$-adrenoceptor genotype on the response to salbutamol (albuterol) and had shown that the two genotypes respond differently to salbutamol challenge — FEV$_1$ was higher and the response was more rapid in ARg16 homozygotes than in carriers of the Gly16 variant. Some other examples related to genetic differences which had effects on drug metabolism, e.g. isoniazid peripheral neuropathy is more likely in ethnic groups that have slow acetylator status (as it is caused by the parent compound), whereas hepatocellular necrosis is more common in rapid acetylators (as it is caused by a hepatotoxic metabolite of isoniazid).

The identification of extensive and poor metabolizers could be done by phenotyping, where the patient is given a marker drug and the urinary ratio of the parent drug to metabolite is measured (extensive metabolizers would have a low ratio, whereas the ratio in poor metabolizers would be high), or by genotyping, using molecular biological techniques. Dr Shakir listed several issues in pharmacoepidemiology that relate to a patient’s metabolizer status and the fact that type A reactions depend on drug concentration: poor metabolizers who have higher than usual plasma or tissue drug concentrations are at an increased risk of adverse reactions, particularly for drugs with a narrow therapeutic window, and extensive metabolizers may be at a higher risk of type A reactions caused by metabolites. Also, inhibition of a cytochrome P450 (CYP) isoenzyme will increase the risk of type A reactions to concurrently used drugs metabolized by the same enzyme. For example, ketoconazole inhibits CYP3A4 and increases the toxicity of terfenadine.

According to Dr Shakir, pharmacogenetics raises several practical issues for pharmacoepidemiology — there is a need for better under-
standing of the pharmacology and pharmacogenetics of drugs under study, case definitions need to be as precise as possible, follow-up questions need to consider ethnicity and effects of other drugs, and statistical issues arise as only small numbers of patients may be involved. The DSRU is undertaking several collaborative projects to study the biological basis of adverse drug reactions (ADRs). These include studies investigating skin reactions with antiepileptic agents, visual field defects with vigabatrin, and QT interval prolongation with non-cardiovascular drugs. Summing up, Dr Shahir said ‘what is happening now is a revolution of trying to understand the genotype on the basis of experimental, clinical and epidemiological evidence’.

DRUGS IN PREGNANCY

The next speaker Dr Patricia McElhatton, Head of the National Teratology Information Service and lecturer in reproductive toxicology, Regional Drugs and Therapeutics Centre, Newcastle, gave an overview of the National Teratology Information Service (NTIS) and risk assessment of drug exposure during pregnancy.

The UK NTIS is part of the National Poisons Information Service and is funded by the Department of Health. Its role is to provide a national, confidential 24-hour service on all aspects of the toxicity of drugs and chemicals in pregnancy. The NTIS also works closely with the UK Health and Safety Executive to monitor the potential teratological hazards associated with chemical exposures in the environment, at work and in the home. The NTIS is a founder member of the European Network of Teratology Information Services (ENTIS), established in 1990, which provides a forum for members to collaborate and share data with the objective of preventing birth defects.

Dr McElhatton said that drug exposure during pregnancy was usually inadvertent, although there are women who need to take medicines during pregnancy. She referred to a recent UK survey that had found that around 35% of women had taken medicines at least once during pregnancy, and that 6% had taken medicines (excluding iron and vitamin supplements) during the first 3 months of pregnancy. Dr McElhatton said that around 1 in 40 babies have a birth defect and that, in most cases, the cause is unknown. Possible causes included hereditary defects, effects of maternal disease or malnutrition, physical injury or chemical injury. A key objective is to detect increases in malformation rates, although this is difficult. For example, to detect a doubling in the incidence of cleft palate (which occurs in ≤1 in 1000 births), 23,000 pregnancies would need to be studied. ‘This leaves us with a big problem as to what is the denominator’, McElhatton remarked.

In 1999, the NTIS received almost 7500 enquiries, mainly from health-care professionals, on the use of drugs in pregnancy. In assessing the risk of drug or chemical exposure during pregnancy, the risk to the fetus must be balanced against the risks associated with failing to treat the mother. Factors that need to be considered include the stage of pregnancy (major malformations occur during organogenesis, but other forms of fetotoxicity, e.g. deafness, growth retardation, can also occur at other stages), the nature of the drug or chemical to which the woman has been exposed (often animal data have to be considered in risk assessment), the clinical condition of the patient, and the patient’s previous obstetric history and family history of malformations. McElhatton explained that it was possible to make up a ‘dysmorphogenic calendar’ which can be used to determine what malformation is most likely to occur if a toxic insult is given during a particular period of pregnancy. According to McElhatton, there is a very wide gap in knowledge of potential toxins to male reproduction. Most effects related to infertility, although it was not clear if male exposure alone could cause malformations.

Concluding, McElhatton said that the causes of birth defects were very complex, multifactorial, but largely unknown. From our current knowledge, it would seem that most drugs present little risk, but low-grade teratogenicity cannot be ruled out. A few drugs carry significant risk and should be avoided. The principles of prescribing in pregnancy were to evaluate the need, use a drug that has been on the market for longer periods, use the lowest dose for the shortest period, and to avoid polypharmacy.

In response to questions from members of the audience, McElhatton explained that data are being collected on successful pregnancies where there had been drug exposure; these data are fed into FETIS, a database developed by ENTIS, which can be used to generate hypotheses for testing in epidemiological studies. Also, the NTIS was receiving increasing numbers of enquiries with regard to the use of herbal products during pregnancy. She said that the safety of such products was a myth; it was known that some could cause muscle

relaxation (which may lead to premature delivery), but that absolutely nothing was known about their effects in terms of congenital malformations.

STATISTICS IN DRUG SAFETY INVESTIGATIONS

Professor Stephen Evans, principal consultant statistician, Quintiles, and visiting professor at the London School of Hygiene and Tropical Medicine, discussed aspects of the use of statistics to study drug safety.

Professor Evans said that safety was rarely a primary outcome in randomized clinical trials (RCTs) and that while there were always concerns about whether a drug is efficacious, the same level of effort was not put into investigating drug safety. What was (inevitably) not known about a drug at the time of licensing was its effects in subgroups (the elderly, children, those with renal and hepatic impairment), and rare adverse effects, including those associated with drug interactions; substantial data on use for more than one year, for drugs intended for long-term use, were also sometimes lacking.

There were several areas where statistics had contributed to drug safety investigations. These included study design, analysis of data from prescription event monitoring (PEM) studies, decisions regarding causation, e.g. Bayesian algorithms, and proportional reporting ratios (PRRs).

With regard to spontaneous reporting, Professor Evans warned that ‘the yellow card has the danger of being the golden calf of pharmacovigilance’. The aim, he continued, was not necessarily to increase the number of reports, but to increase the intensity of signals of safety problems. Furthermore, yellow card reports should not be used to estimate incidence. The Poisson method could be used to investigate whether the incidence of adverse events (as opposed to adverse reactions) is higher in people treated with a particular drug than in a comparable population. This method involves obtaining the expected number of events in a given population from existing sources of data, and then comparing the observed number of events with the expected number using the Poisson distribution. The strengths of this approach include its statistical robustness, it can be used to verify the existence of a signal and it can be used to estimate the magnitude of the effect. However, the Poisson method also has weaknesses, such as its dependence on the accuracy of both the numerator and denominator for the two incidence rates used. According to Professor Evans, the method was of most use for serious diseases of rapid onset, and where large numbers of relatively healthy people are given a medicine. Vaccination was one example where it can be helpful. PRRs could be used to compare the proportion of reports for a specific ADR in a drug with the proportion for that ADR in all other drugs. PRRs could be used to screen for signals and also for continuing monitoring. PRR was simple to use, but requires extensive data on drugs and ADR reports. Summing up, Professor Evans warned that there was a potential for misinterpretation of signals and that careful evaluation was required.

OTC MEDICINES PHARMACOVIGILANCE

Dr Christine Bond, Department of General Practice and Primary Care, University of Aberdeen, described a collaborative project between the department at Aberdeen and the DSRU. The project was investigating the safety of over-the-counter (OTC) ibuprofen using a network of community pharmacies.

Dr Bond presented details of the Grampian pilot study involving 62 pharmacies which had recruited 555 customers who had purchased OTC ibuprofen, mainly for back pain (25%), joint pain (19%) and headache (18%). One-week follow-up data indicated that 4.5% of recruits were no longer taking ibuprofen because the medicine had ‘upset them’. Also, 38% of recruits had used other medicines while taking ibuprofen; 7% had taken ibuprofen with medicines used for gastrointestinal complaints, and 4% had used ibuprofen with medicines used for asthma. Six-month follow-up data (response = 70%) indicated that ‘ever users’ of ibuprofen were more likely than ‘never users’ to have experienced gastrointestinal symptoms, skin conditions and to have consulted a doctor in the previous 6 months. Also, instances of contraindicated and excessive use of ibuprofen were identified during the course of the study. According to Dr Bond, the study had demonstrated the feasibility of and need for pharmacovigilance studies of OTC medicines.

Ms Deborah Layton, research pharmacist, DSRU, presented data from the parallel pilot study carried out using a community pharmacy network in Hampshire. The same follow-up questionnaires
were used as in the Aberdeen arm of the study. Overall, the study aimed to recruit a cohort of 10,000 users of ibuprofen products purchased OTC, to determine users’ characteristics, and to monitor drug usage over a one-year period. Forth-nine percent of Hampshire pharmacies were recruited to take part in the study; each pharmacy recruited a median of 2 recruits (range 0 to 35). In total, 6.4% \((n = 466)\) of the 7320 consent forms given out were returned. Seven days post purchase, 49% of recruits had discontinued the use of ibuprofen; of these, 3.1% stated that the medicine had ‘upset them’. Forty-one percent stated that they were taking concomitant medication, and 52% stated that they had not consulted a health-case professional regarding their purchase.

Ms Layton highlighted the similarities between the results at the two centres. She concluded by saying that findings of both studies indicated several areas of concern, namely, the use of OTC ibuprofen by patients with asthma and those with a history of stomach or peptic ulcer, the concomitant use of prescription non-steroidal anti-inflammatory drugs (NSAIDs), the potential for drug interactions with concomitant medication, and the use of ibuprofen at higher than recommended doses and for prolonged periods. Ms Layton said that although non-prescription drugs were generally safe, there was a need to quantify and understand the risks. She recommended that health-case professionals should routinely ask about OTC medicine use.

**PEM: AN UPDATE**

Dr Lynda Wilton, senior research fellow, DSRU, gave an overview of prescription event monitoring (PEM) and described some of the variations in its methodology. For example, there have been changes to the green form, which now included questions on doses used at the start of treatment and at each event, and also, importantly, whether the drug had been stopped and the date of the last prescription. In addition, for specific studies, additional questions of past medical history and/or concomitant medication may be added. Pilot studies have been carried out for re-sending green forms to non-responders and for identifying ‘new’ GPs. The ‘second send’ of green forms had increased the response rate from around 60% to between 70% and 80%. PEM methodology now includes specific follow-up questionnaires, and where appropriate, contact with hospital specialists.

With regard to analysing PEM data, Dr Wilton said ‘it is important not to be fixed in your methods of analysis, but to look at the data … and the pattern of reporting’. She went on to give several specific examples of findings from PEM studies where hypotheses had been strengthened, such as gynaecomastia with finasteride, rash with lamotrigine, and visual field defects with vigabatrin, or refuted, such as diabetes with nicorandil and depression with calcium channel blockers.

An important area was monitoring pregnancy outcomes for women who had been exposed to drugs during pregnancy. There was very limited knowledge at the time of marketing of the effects of new drugs on human pregnancy, Dr Wilton emphasized. The DSRU now held data on 1228 women who had taken drugs during pregnancy. For these women, there were 24 reports of congenital anomalies, but no pattern was noted. Another important and underresearched area was the use of drugs in children. Forty-seven (64%) drugs monitored by PEM were prescribed to children (aged 2 to 11 years), and children represented 1.3% of all patients on whom PEM data were held. However, only 7 of the 47 drugs used in children were licensed for all or part of this age range when marketed. Summing up, Dr Wilton highlighted that PEM monitors the safety of recently marketed medicines under conditions of everyday clinical use. The methodology is hypothesis generating, but it can also be used to strengthen or refute hypotheses. In addition, it can be used to investigate literature or regulatory concerns.

Dr Sian Taylor, clinical research fellow, DSRU, complemented Dr Wilton’s overview of PEM by describing three studies that represented modifications to the PEM process. Two of these studies were monitoring new drug delivery systems. A prospective observational study, was monitoring the switch from CFC-containing to CFC-free Ventolin Evohaler in the UK. In this study, regular users of Ventolin were selected by the GP. The GP provides baseline data (e.g. asthma severity, smoking status) and outcome data for the period before, during and after the transition to Ventolin Evohaler. GPs receive payment for participation. Similarly, an observational crossover study was monitoring the switch from CFC-containing to CFC-free Flixotide Evohaler in the UK. This study was comparing pre-exposure event rates with post-exposure event rates. Again, GPs receive payment for participation. The third study was assessing the safety and GPs’ compliance with SPC recommendations for the use of
Eucardic (carvedilol) in chronic heart failure — a new indication for an established drug. This is a longitudinal study in which GPs select patients, and provide baseline and outcome data. Dr Taylor concluded by saying that these modifications to PEM methodology allowed a more detailed analysis to be carried out.

Following on, Dr Nayan Acharya, Glaxo-Wellcome research fellow, DSRU, and Department of Dermatology, Southampton University Hospitals, described the development and validation of a test that could be used to investigate cutaneous ADRs utilizing the PEM cohort. The assay involves the incubation of the drug with peripheral blood mononuclear cells (PBMCs) for 48 h which initiates the immune response, and then adding fresh PBMCs, which results in a proliferative response of lymphocytes to the drug metabolite. The aim of the test is to explore the metabolic pathways that convert drugs to immunogenic metabolites, and to examine the immune responses to those metabolites. The test, if shown to be reproducible and robust, may have several applications — it could be used to confirm the causality of a suspect drug, to elicit the immune responses involved, and to identify a culprit drug where there was polypharmacy. Looking ahead, Dr Acharya suggested that the test could be an important tool in pharmacogenetics for predicting at-risk populations.

EXPANDING THE HORIZONS

The late afternoon session at the meeting comprised three short presentations of submitted abstracts.

Ms Jo Barnes, teaching and research fellow, Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London, described a postal questionnaire survey of over 1300 community pharmacists in six regions in England (at the time of the survey, these pharmacists were not involved in the Committee on Safety of Medicines’ pilot scheme for pharmacist ADR reporting). The survey had explored pharmacists’ experiences with herbal and complementary remedies, in particular, whether pharmacists receive or identify reports of suspected ADRs associated with such products. A 67% response rate was achieved after two follow-up mailings. Overall, 90 pharmacists (11%) provided 107 reports of suspected ADRs associated with herbal and complementary remedies for the year preceding the survey.

Ms Angela Emerson and Mr Mark Tomlin, Pharmacy Department, Southampton General Hospital, discussed a prospective non-interventional observational study that had been carried out to explore the role of the hospital pharmacist in ADR reporting. A research pharmacist collected exposure and adverse event data for 303 hospital inpatients exposed to selected drugs; adverse event data were also recorded independently by a pharmacovigilance physician. Exposure data were obtained mainly from pharmacy computer records and from clinical pharmacist ward rounds. The study findings indicate a good degree of correlation between the pharmacist’s and physician’s judgments. Overall 25 suspected ADRs were recorded. Ms Emerson and Mr Tomlin concluded that the approach was a feasible method for monitoring adverse events in hospital.

The last paper was given by Dr Margaret Hudson, Medicines Control Agency, who described a surveillance study of adverse reactions associated with the use of medications in HIV-infected pregnant women. All reports in the pregnancy system organ class (SOC) involving antiretroviral medicines were identified. There were 107 reports of congenital abnormalities in association with maternal exposure to antiretroviral drugs. Of these, most abnormalities were classed as ‘miscellaneous’; other groups included cardiovascular, alimentary tract, urinary tract and limb deformities.

DIPEx: A MULTIMEDIA APPROACH

Sue Ziebland, senior research fellow, ICRF General Practice Research Group, Oxford, gave a detailed description of DIPEx (Database of Individual Patients’ Experiences of Illness), a multimedia website and CD-ROM that aims to improve understanding of people’s experiences of illness. DIPEx provides systematic analysis of people’s narrative descriptions of their experiences of illness and treatments, and is linked with regularly updated evidence-based information about treatments and other resources, such as the Cochrane Library, the National Electronic Library for Health, support groups and other websites (which are subject to critical appraisal).

DIPEx is being developed for conditions where there is a lot of research, support and information for patients (e.g. breast cancer) as well as for conditions where there is little research or information on patients’ experiences (e.g. bowel-cancer screening) and other conditions involving, for example, many investigations and informal carers. Quali-
tative research methodology is used for gathering narratives of patients’ experiences. A literature and field review is first carried out to inform sampling and interviews. The sampling method used is intended to ensure that the fullest possible range of experiences is represented, irrespective of their frequency of occurrence. For example, among carers of people with Alzheimer’s disease, both spouses and children are interviewed. Interviews are collected until all categories, including both anticipated and emerging themes, are saturated. For each topic, DIPEx provides three main areas:

- a short filmed presentation of themes from a collection of approximately 40 narrative interviews
- a description of the condition, its prevalence and prevention, as well as information on treatments and their evidence base; frequently asked questions and answers; explanatory models, graphics and films
- links to other websites, references to books and films, details on support groups, feedback from users.

The DIPEx team is keen to seek collaboration with other research groups, and thought is being given to the possibility of using DIPEx to gather information on suspected ADRs. It is intended that DIPEx will be available in GPs’ surgeries, public libraries, support groups and cancer information centres, as well as in the home for those with access to the internet. An important feature of DIPEx is that it addresses the overlapping needs of professionals and the general public — the same database will be available for patients, carers, professionals, students, policy makers and researchers.

CHILDREN’S EAR PROBLEMS

Dr Ian Williamson, GP and academic, Department of Primary Care, Aldermoor Health Centre, University of Southampton, discussed therapeutic approaches to children’s ear problems in the community. Glue ear was the most common reason for surgery in children — by age 10, around 80% of children are affected.

Summarizing systematic reviews in the area, Dr Williamson said that antibiotics had a number-needed-to-treat (NNT) of around 7. There were, however, no long-term benefits — effects were lost after about 6 weeks. Autoinflation (a technique which involved blowing up a balloon through one nostril) had been subject to systematic review of 6 RCTs, although none of these had been carried out in a primary care setting.

Concluding, Dr Williamson said there was a need for non-antibiotic treatment approaches and management, and a need for RCTs in the primary care setting. His priorities for RCTs would be leukotriene receptor antagonists, autoinflation and nasal corticosteroids.

Closing the meeting, Dr Shakir thanked the DURG and the speakers and attendees. He said the aims of the meeting had been to address important new horizons and new areas in pharmacovigilance, such as herbal products, HIV drugs, new methodologies and hospital-based studies, and that these aims had been met.

REFERENCES


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