

new horizons *in* *hospital pharmacy*

The 6th congress of the European Association of Hospital Pharmacists was held in Amsterdam from March 21 to 23. Over 1400 delegates were absorbed by the full programme of lectures, seminars and posters. Christine Clark reports

European surveys showed that 90 per cent of patients in neonatal intensive care units and 60 per cent of paediatric patients were exposed to unlicensed or “off-label” medicines. This situation arose because licensed medicines were designed mainly for adults and tended to be oral dosage forms in fixed doses. This was the explanation given by TONY NUNN (director of pharmacy, Alder Hey Children’s Hospital, Liverpool) in a lecture on unlicensed medicines given to children. In contrast, children’s dose requirements were very variable and liquid formulations were often needed. Pharmacists had responded by making extemporaneous or “magistral” preparations. The starting point was often licensed tablets or capsules that might be crushed or opened and made into a liquid medicine or made into capsules or powders. Segmented tablets were also used occasion-

ally. If there was no licensed product available, medicines might be made from pharmacopoeia-grade drugs or laboratory chemicals. The formulae for these preparations came from a variety of sources and the shelf-lives tended to be arbitrarily assigned. The scale of preparation was variable but for the items for which there was only a small demand, there was little evidence of quality assurance or good manufacturing practice (GMP), said Mr Nunn.

The practice of extemporaneous dispensing of medicines for children was investigated in a European survey conducted by pharmacists from Alder Hey Children’s Hospital, Liverpool and the Hôpital Robert Debré, Paris. Questionnaires had been sent to key individuals in children’s hospitals or units in 18 European countries. Twenty-one questionnaires had been returned from 16 countries. The results showed that there

were marked differences in practice. For example, there was a c

lear preference for liquid preparations in England, Ireland and Scandinavia, whereas capsules were made more often in Belgium, Croatia, France, Spain and Switzerland. Powders were most commonly used in Finland, Italy and Scotland.

Perhaps the most interesting finding from the survey was that many products were prepared when a licensed version already existed in another country. For example, 75 per cent of the “top 20” extemporaneously prepared liquids were available as licensed paediatric medicines in other European countries, and 30 per cent of powders and 75 per cent of capsules were also available as licensed paediatric medicine elsewhere, explained Mr Nunn.

Problems with import regulations and lack of knowledge about the availability of

licensed preparations both contributed to this problem.

A report on the use of unlicensed medicines in children has been sent to medicines agencies throughout Europe. It calls for licensed medicines to be used whenever possible. In addition, it proposes that the processes of obtaining suitable licensed medicines be harmonised throughout Europe and that a European collaboration to investigate the formulation and preparation of extemporaneous medicines be established.

— GENE THERAPY

Gene therapy was now in the explosive phase of development according to NICHOLAS ANAGNOU (professor of molecular biology, University of Athens). At present, there were more than 400 active protocols but most were phase 1 studies and only three were in phase 3.

There were now three approaches to gene therapy, namely gene substitution, gene replacement and gene modification. The first of these involved the introduction of a normal copy of the gene in the presence of the mutated gene. Gene replacement was a much more efficient process because it involved replacing the gene in the correct sequence. Gene modification could involve modifying other genes to alter the phenotypic expression of a cell, said Professor Anagnou.

The first prerequisite for gene therapy was a good vector. The ideal biological vector had to have a high transduction efficiency, that is, it had to transplant the new DNA fragments into as many cells as possible in order to ensure that its effects were seen. It also had to accommodate all the regulatory elements of the genome to ensure that it was correctly expressed. The vector should integrate into the genome in a stable way so that its expression was both sustained and regulated. Regulation was important, said Professor Anagnou, because unregulated expression, resulting in, for example, overproduction of a protein, could be detrimental. Sustained expression was desir-

able because it was now known that host cells sometimes modified the level of expression of a transducer gene, so that the effects appeared to wear off.

Professor Anagnou reviewed the properties of viral vectors. He said that they were used in gene therapy because of their high propensity to transfect cells (ie, cause the introduction of DNA isolated from a cell or virus into another cell). A typical viral vector was the Moloney murine leukaemia virus. This was an RNA virus that entered cells through receptors on the cell surface, then used its own reverse transcriptase enzymes to create double-stranded DNA that could enter the host cell nucleus. Because of this mechanism, this type of vector could only transfect dividing cells. The viral DNA was integrated into the genome of the host cell and reproduced in each daughter cell. This contrasted sharply with adenovirus vectors, which were able to enter cell nuclei, but did not integrate into the genome. As a result only 50 per cent of the daughter cells carried the transplanted material.

There were problems with the use of RNA viruses, said Professor Anagnou. For example, the therapeutic gene could integrate in the wrong place and end up producing too little or no protein at all. Equally, it could enter at a critical point and up-regulate the gene, causing protein overproduction. However, the major limitation was the inability to transfect non-dividing (post-mitotic) cells and this property was needed to tackle haemopoietic diseases such as thalassaemia.

The recent introduction of lentivirus vectors, derived from the HIV family of viruses, had been a major breakthrough. These viruses had a much richer genome than that of the Moloney murine leukaemia virus and this enabled them to enter the nuclei of non-dividing cells and integrate into the host cell genome. Neither retrovirus vectors nor lentivirus vectors could transfect resting cells (i.e. cells in G_0) and researchers were trying to find out more about the metabolic activity of resting cells in an attempt to understand the mechanisms involved.

Adenovirus vectors were smaller than the other types of virus vectors. Although they were able to enter the host cell nuclei, they did not integrate into the host genome. For this reason their effects were diluted at every cell division, and repeated treatments were needed. Adenoviruses could be produced more efficiently than retrovirus vectors — typical titres were 10^{11} virus particles per ml for adenoviruses compared with 10^6 virus particles per ml for retroviruses.

The third type of viral vectors were the adeno-associated viruses (AAV). These were small, simple viruses that had only two genes which could easily be replaced by therapeutic genes. The material was integrated into a specific area of chromosome 19. They were non-pathogenic and produced efficient gene

transfer. The main problem was that they could only carry a small amount of new genetic material. As understanding of viral biology improved, researchers were trying to develop a hybrid viral vector that would combine the benefits of easy integration, seen with the AAV, with the large payload of the adenovirus vectors, explained Professor Anagnou.

Gene therapy had a valuable application in cancer treatment and here, three different approaches were possible.

Corrective treatment relied on the introduction of a gene that corrected a defect, such as a suppressor gene. As this only worked in the cells that were transduced, it was only really satisfactory if all the cells in the tumour could be reached.

Cytotoxic treatment relied on a “bystander effect” such that cells adjacent to transduced cells were also killed. This was efficient because if as few as 10 per cent of tumour cells were actually transduced then the remainder would be killed by the bystander effect. An example of this effect was seen with the pro-drug ganciclovir. If a few cells had the enzymes required to activate ganciclovir by monophosphorylation, further phosphorylation, producing a lethal compound (ganciclovir triphosphate), would follow under the influence of other cellular enzymes. Ganciclovir monophosphate (“activated ganciclovir”) could pass between cells, and the lethal cascade would then occur in adjacent cells.

The third option was the use of immune effectors that activated the immune system.

— DEB ANALYSIS

Disturbance effect barrier (DEB) analysis was a helpful way of analysing complex systems and identifying the weak points, according to SVEN TERNOV (consultant, human-system interface design, Swedish Civil Aviation Administration) and

Table: Planning of treatment (post diagnosis)

Element	Doctor	Nurse
Operator task	Doctor orders new blood test before next dose of cytotoxic drug	Nurse makes out worksheet (The nurse's worksheet is more legible than the doctor's worksheet but the document has to be changed when the regimen is changed)
Disturbance	Wrong test ordered Patient identity mix-up	Template not updated Prescription is illegible Prescription is incorrect (but is still transferred)
Effect on system	Dosage not adjusted Delayed test result	Serious damage or death
Latent failures	No specific requirements about the level of competency of the prescriber Task not properly designed — resulting in a heavy cognitive workload	No procedures for updating the nurse worksheet Insufficient routines for the cytotoxic prescription sheet
Safety barrier analysis	Nurse may detect problem. A computerised procedure would be effective, especially if it prevented prescribing until the correct blood test result was available	No barriers in connection with the nurse worksheet The prescription chart needs to be clear and unambiguous so that there is no need for a nurse worksheet

ANNSOFIE FYHR (pharmacist, University Hospital, Lund). They had examined the handling of cytotoxic drugs, both in the pharmacy preparation area and at ward level, in the wake of a “near-miss” involving a ten-fold cytotoxic overdose.

“You can live happily with system failures (also known as latent failures) for many months,” said Dr Ternov, “but they are like unexploded bombs — and they contribute to medication errors”. Typical examples of latent failures include the following:

- faulty maintenance
- faulty lines of communication
- sloppy documentation
- failure to monitor properly
- a boss who made lots of procedures (that no-one followed)
- failing to learn from mistakes — and repeating them

Safety barriers were technical or administrative constraints which prevented human beings from making mistakes, or actually resolved errors before they harmed patients. It was relatively easy to design barriers for technical systems but it was more difficult to plan for the human element. For example, separate fittings for the different anaesthetic gases effectively prevented accidents. However, an incident at Malmö airport had underlined the unpredictable role of human beings: a cleaning lady had accidentally knocked a button in the control tower and the airport lights and the instrument landing systems were simultaneously inactivated.

Once a process had been chosen for DEB analysis, the first step was to map carefully the sequence of operator tasks. The next step was to consider possible “disturbances” for each task, considering the outcome of over-

or underperformance at each step and its effects on the stability of the whole system. Theoretical disturbances had to be validated through discussion with the staff involved. “People on the floor know a lot about the risks” said Dr Ternov. “They were often aware of near misses and were good at identifying latent system failures and inadequate safety barriers.”

“One thing you discover is the complexity of apparently straightforward processes,” continued Dr Ternov. He gave as an example the four distinct processes into which cytotoxic treatment could be broken:

- planning of treatment (after diagnosis had been made)
- prescribing (physical transfer of information)
- preparation of the cytotoxic injection
- administration of the cytotoxic injection

Taking the first of these, Dr Ternov showed how the process of prescribing a cytotoxic drug might be analysed (see Table).

In this example, blood test results were required before the next dose of the cytotoxic drug could be prescribed. Mistakes could occur at the stage when the blood test was ordered but the most serious latent failure in the system was the absence of a requirement for a specified level of competency for the prescriber. In other words, the system would not prevent junior or inexperienced prescribers from writing prescriptions for cytotoxic drugs. “If you do not specify a level of competence then you are asking for trouble,” said Dr Ternov. Furthermore, the task was badly designed in that it required the doctor to remember a lot of

detail. The next step in the analysis was to ask if there were any safety barriers in the system that could identify and correct an inappropriate prescription. The only barrier in this system was the nurse, who might identify such an error. However, a more effective barrier might be a computerised system which simply did not allow a prescription to be written until the correct blood test result was available.

This analytical process was repeated for all the sub-processes involved in giving cytotoxic treatment until a complete error-tracking diagram was constructed. It was then possible to show how long an error could persist before it was caught by a safety barrier. For example, said Dr Ternov, many prescribing errors were stopped at the preparation stage in the pharmacy. Errors (such as wrong dose, wrong patient) could also be introduced at this stage and these were usually stopped by the administering nurse. An important question to ask was whether there were any high-risk errors that could get right through the system, for example, if a doctor prescribed the wrong dose at the outset, could it pass undetected?

This analysis identified numerous latent failures in the system and these included:

- inappropriate procedures for transferring prescription details from the cytotoxic treatment manual
- inappropriate procedures for updating the cytotoxic treatment manual
- indistinct procedures for co-operation between the pharmacy and the wards
- lack of standardisation of equipment — several different types of intravenous pump were in use
- unsafe procedures for co-operation with the laboratories — there was a system to

fuzzy presentation of information, inappropriate methods and unsuitable working environments contribute to erroneous acts.”

During the discussion that followed, it emerged that approximately 50 per cent of the audience had experience of medication errors. One member of the audience also pointed out that the more one worked to improve the drug use process, the more errors one found, and so it was easy to form a negative view of the situation.

■ CYTOTOXIC RISKS

Cytotoxic contamination risks were discussed in a seminar conducted by PETER VAN BALEN (Netherlands Cancer Institute) and ULLA HULTSTRÖM (Östra Hospital, Gothenburg). They explored issues surrounding occupational exposure to cytotoxic drugs.

Handling of cytotoxics was just one part of risk management, according to Dr van Balen. Risk assessment was the essential first step because it was impossible to manage a risk if the size of the problem was unknown. Cytotoxic drugs were routinely prepared in clean rooms, but even with this level of protection, cyclophosphamide was still found in the urine of workers, and it appeared to be important because there was already evidence of reprotoxicity amongst oncology nurses.

Exposure could be monitored by both environmental and biological monitoring, and both were currently done in The Netherlands. Uptake of cytotoxic drugs by workers occurred mainly through the skin and by inhalation. Oral uptake was minimal. Monitoring of surrogate skin (as gloves or patches) gave an indication of the level of exposure. Gloves had been shown to carry up to 300mcg cyclophosphamide per pair, and the source for this was leakage of the drug during connection and disconnection operations.

Contamination of the floor in working areas was monitored by incorporation of a fluorescent dye. Widespread contamination was seen when this was done. The same approach could be used to check the performance of connectors — and it effectively revealed leaks. Another approach to tracking leaks was the use of technetium 99 (⁹⁹Tc) which often showed big inter-individual differences. Surface contamination could be monitored using cyclophosphamide, added Dr van Balen.

Respiratory exposure was a risk when there were aerosols, dust or drug vapours present. Aerosols or dust were a problem with cisplatin, cyclophosphamide, methotrexate and 5-fluorouracil whereas carmustine, cyclophosphamide, cisplatin epoxide and 5-fluorouracil were also known to vaporise.

Considering the risk of cancer, it had been estimated that an intake of 3.6–18mcg of

cyclophosphamide carried a risk of developing cancer of one in 100,000. This figure had been used to derive safe limits for workers in The Netherlands.

A prospective evaluation of a new cytotoxic preparation area had shown that after 12 months' operation there was extensive contamination — especially on door handles, keyboards, telephones and the fridge door handle. These results had prompted improved cleaning efforts. Dr van Balen said that originally ethyl alcohol alone had been used but this was more of a “spreading agent”. Normal soap, which had a pH of 10–12, was now used, and this had shown that good housekeeping worked.

Ms Hultström explained that in her hospital 6–8,000 cytotoxic doses were prepared annually, and they had systematically examined ways to make the processes safer. In one experiment, a quantitative assessment of leakage during preparation had been made using pertechnetate-labelled injections. Radiation levels on gloves and the workbench had then been measured. Pharmacists (who made cytotoxic injections at least once a week) obtained the best results. Experienced nurses were next best, followed by inexperienced nurses. Leakage was found to be more likely if the starting material was a dry powder, and the investigators assumed that this was because of the number of manipulations required. Closed-systems for injection preparation (such as PhaSeal, Carmel Pharma or filter spikes, Braun or Codan) were then introduced routinely for dry powder injections.

In another series of experiments, wipe-samples had been collected to measure surface contamination with cyclophosphamide and ifosfamide. The results showed no contamination on the floor, but contamination was present in the biological safety cabinet (BSC), and was heavy on the trolley where the prepared injections were placed. For cyclophosphamide, high levels were seen in the BSC, on the trolley and on the floor. They had been surprised to find a high level in the BSC on a day when no cyclophosphamide injections were made, said Ms Hultström. This had called into question their cleaning process which had relied originally on water or alcohol 70 per cent. Experiments suggested that a two-step process using first water and then alcohol, would be more effective, so this had been adopted.

As a result of this work, a number of changes had been made to the working routines in the pharmacy. PhaSeal Protectors or filter spikes had been introduced for the reconstitution of dry powders, and absorbent bench coating was now used both inside the BSC and on the trolley. Two pairs of gloves were used routinely, and the outer pair had to remain in the BSC. Furthermore, everything that had been inside the BSC was considered to be contaminated. In order to

check that samples had been sent, but no record that the results were ever returned

- insufficient written agreement about the extent of nurses' duties

“Nurses are doing what the doctors should have been doing, but there is no formal agreement for this and they are not paid to do it!” said Dr Ternov.

The investigators concluded that the combination of latent failures and lack of safety barriers gave rise to several major problems. An error of judgement by a doctor would be difficult to detect and the handling of information was not satisfactory. There were many errors in dose calculation and these were compounded by poor handwriting. Lastly, there was “interface fuzziness” between the roles of doctors and nurses, and between the pharmacy and the wards.

Two preventive measures were recommended. The first was computerisation as “many tasks were not well-designed for the human mind”. This could eliminate problems with information transfer, dosage selection, dosage calculations and could even provide a decision aid in connection with blood tests. The second was to double-check clinical judgements. “I cannot see any other way of enhancing safety,” said Dr Ternov. Radiologists had already adopted this approach, he added. However, the doctors at Lund University Hospital had been reluctant to discuss this point.

The results of this exercise had yet to be seen. So far, the number of incidents had not decreased but dialogue between all parties had improved and the pharmacy had been invited to give a talk on systems problems with cytotoxic drugs. Furthermore, a computerised system was shortly to be launched.

Dr Ternov concluded with “Ternov's law of human error”. He said, “Operators never act “wrongly”; they do what they believe is right based on the information available but

minimise contamination, the BSC was cleaned several times a day, the absorbent bench coat being replaced every two hours and the gloves every 30 minutes.

Surface contamination was rechecked after these measures had been introduced. The results showed that when the PhaSeal Protector was used, ifosfamide contamination was eliminated from the BSC, the floor and the trolley. Continual validation of routines was now the norm in her department said Ms Hultström, and constant reinforcement of the reasons for the routines was vital.

In the discussion, a member of the audience asked how products were handled, bearing mind the presumption that everything from inside the BSC was contaminated. Ms Hultström explained that the product was over-wrapped, but in effect, a contaminated product was sent to the ward, and this was a problem that had not yet been solved.

Asked about the sources of contamination the speakers said that some studies had shown surface contamination of manufactured products when they arrived in the pharmacy. There could also be contamination under the capsule of a vial. Leaks during preparation were probably the major source of contamination and this meant that working procedures needed to be good and that immediate cleaning, after an incident, was essential.

One questioner asked if there was really a relationship between the amounts of cytotoxic drugs handled and the extent of exposure. The speakers pointed out that there was significant inter-individual variation in leakages but that exposure to cytotoxic drugs was also possible for workers who did not directly prepare doses.

Asked what the real risks for staff were, the speakers said that three key studies had

shown that there was a risk of reprotoxicity and that this was a greater risk than that of carcinogenicity. Although it was not yet possible to demonstrate a dose-response relationship, the results could be used to devise control measures which would protect staff.

■ EAHP SURVEY

Only 32 per cent of hospital pharmacies in Europe provided an out-of-hours service, according to the second EAHP survey of hospital pharmacy. This was a shocking state of affairs said DAVID COUSINS (chief pharmacist, Southern Derbyshire Acute Hospitals Trust), a member of the EAHP Scientific Committee.

The survey, which was first carried out in 1995 and repeated in 2000, was based on 748 responses — a response rate of 27 per cent. No responses had been received from Ireland, Italy, Luxembourg or Portugal. The results showed that on average, there was one pharmacist for every 100 hospital beds, and in many countries the number of beds per pharmacist had increased since 1995. In Great Britain, the number of beds per pharmacist had decreased from 80 to 55 over this period. In contrast, there was one doctor for every four patients.

A typical pharmacy department was open for nine hours per day during the week. Thirty-two per cent provided out-of-hours services, and only 6 per cent had resident pharmacy services. (These were mainly in Great Britain, France, Greece and Spain.) The Netherlands and Spain dominated 24-hour unit-dose distribution services, with full medication profiles kept in the pharmacy. Dr Cousins wondered whether the other European countries could learn from The Netherlands and Spain because the benefits had been so significant.

More than 50 per cent of respondents said that their hospitals did not run intravenous additive services, and it appeared from the responses received that six countries (Finland, France, Greece, Hungary, Slovakia and Slovenia) provided no intravenous additive services at all. This did not sit comfortably with the increasing evidence of medication errors associated with intravenous therapy, said Dr Cousins. Many countries did not offer cytotoxic reconstitution services, but allowed these products to be made up on open wards by doctors and nurses. Dr Cousins called on the EAHP to make a clear policy statement on this issue. These countries needed help, encouragement and assistance to redress the situation, he said.

All pharmacies had computer facilities and 70 per cent had access to the internet. Dr Cousins suggested that in future the EAHP survey could be computerised.

CD-ROM versions of the full report will be sent to each head of delegation in the near future. Later in the year, a printed version will be produced.

Contributed by Christine Clark, freelance medical writer