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Developments in Oncology Research at the Pharmacy Department, Derriford Hospital, Plymouth

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tools. A post-column derivatization method after initial LC separation was developed for the determination of cisplatin and its monohydrated form (1). The pharmacokinetics were studied in guinea-pigs, mice and men.

The stability of cisplatin and its monohydrated compound has been determined by LC after addition of cisplatin to blood and plasma at 37°C (pH 7.5). The pKa for the monohydrated form was determined to be 6.56. Thus, at physiological pH the monohydrated complex is present mostly in an inactive monohydroxy form (2,3). The t½ for cisplatin and the complex were determined to be 1.43 and 0.36 h in blood, 0.88 and 0.26 h in plasma, respectively. It is interesting to note that cisplatin was more stable in blood than in plasma which was in line with our findings from in vivo studies in mice (4). It was also concluded that the monohydrated complex was formed to a small extent in blood despite its high Cl^--concentration in patients receiving 1 hour infusion of 100 mg/m^2 cisplatin (5). The volume of distribution for the complex in patients was smaller compared to cisplatin which might be due to the more lipophilic character of cisplatin (5). Organ distribution was demonstrated in perilymph and cerebrospinal fluid (CSF) in guinea pigs (6), and in blood, serum, kidney, liver, testis, brain and tumour in mice (4). There was a biphasic elimination from most tissues although there was a gradual accumulation in the brain. In tumours there was a delayed elimination of cisplatin compared with the other tissues (4).

The results of these studies increase the pharmaceutical chemical knowledge of practical handling as well as the understanding of the fate of cisplatin and its active metabolite in vivo.

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Pharmacokinetic research in oncology—One dose for all and all for one?

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How should doses of anticancer drugs be individualised for the patient? To date there are few instances where anticancer agents are individualised for the patient further than in relation to an estimate of the patient's body mass (eg weight or surface area). These descriptors of body mass are often poor predictors of the ability of an individual to clear a drug. Clearance, which is the most important pharmacokinetic parameter in determining dose, is also one of the most variable pharmacokinetic parameters, with variability often exceeding 5 to 10 fold between patients. A measure of clearance may be provided by the area under the concentration-time curve (AUC), which is related to both dose and clearance, and is a useful target for pharmacokinetic optimisation. In clinical practice the AUC has been found to be one of the most important descriptors of both effectiveness and toxicity for many anticancer drugs. An accurate method of estimating the AUC of an anticancer agent in an individual is, therefore, of considerable importance.

Variability in pharmacokinetic parameters may be categorised into three types. These are: 1) between patient variability, which describes the variability in a parameter across a population of patients, 2) between-similar patient variability, which describes the variability in a parameter within a group of patients that have similar characteristics (eg weight, renal function etc), and 3) within patient variability, which describes the variability within an individual during a course of treatment. An accurate method of characterising variability from these types is important for dose individualisation. Carboplatin is used as an example to describe these forms of variability and how these types of variability may be minimised in the clinical situation.

Greater involvement of persons knowledgeable in the area of pharmacokinetics in clinical trials of anticancer agents is required in order that the most appropriate dose may be achieved as early in therapy as possible. Pharmacists, with their background in clinical pharmacology, are likely to have a key role in this area. In the long term it is imperative that coordinators of clinical trials change from the use of dosing in relation to surface area or body weight to descriptors and surrogate endpoints, eg serum drug concentration monitoring, that are likely to be associated with a reduction in the sources of variability and therefore enhance accuracy of dosing.

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Clinical research

S. Dix

The speciality of oncology offers a variety of opportunites for pharmacy involvement in research. Research initiatives span from transalation, laboratory studies to clinical research protocols to drug usage evaluations. With a greater emphasis on the the multi-disciplinary approach to care, pharmacists are now essential team members in many oncology clinical research centers. Areas of pharmacy-related research include new approaches to enhance disease response and supportive care as well as pharmacoeconomic evaluations. Pharmacists are also involved in research on the use of individualized dosing of chemotherapeutic agents based on population or patient-specific pharmacokinetic parameters such as AUC based dosing of carboplatin or high-dose busulfan. Other areas where pharmacists have recently focused their research interests include the development and implementation of multi-disciplinary treatment algorithms to minimize over utilization of expensive agents. Drug interaction studies continue to provide an excellent opportunity for pharmacy-related research and have recently included an evaluation of the interaction between the new immunosuppressive agent, tacrolimus, and fluconazole in patients undergoing allogeneic transplantation. These studies are excellent examples of how pharmacists can initiate and participate in clinical and use such experiences to ultimately improve patient outcome.

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CONTRIBUTED RESEARCH PAPERS

Developments in oncology research at the Pharmacy Department, Derriford Hospital, Plymouth

G. Sewell

Derriford Hospital Plymouth is one of the largest single site hospitals in Europe and has recently attained UK Cancer Centre status. To meet the clinical and academic objectives of Plymouth Hospitals Trust, the University of Plymouth and the Cancer Centre, the Director of Pharmacy and the Director of Oncology created a senior Research and Technical Services Post combined with a Readership at the University's Postgraduate Medical School. This paper describes the establishment of a research facility with an emphasis on oncology, in the Directorate of Pharmacy, Plymouth Hospitals NHS Trust.

Facilities and Staff: A research laboratory equipped for pk/pd, drug stability/compatibility and drug delivery system studies was established within the Pharmacy Department together with research offices, and a practice research base. A postdoctoral scientist was appointed to assist in the supervision of research.

Research Projects: The following projects are in progress or have recently been completed: 1) Externally funded 3 year PhD, joint with Haematology Dept: Effect of cytokine modulation of mdr-1 phenotype on antracycline induced apoptosis in B-CLL. 2) Externally funded 2 year MPhil to evaluate the role of the hospital pharmacist in home-based ambulatory infusion and GP shared-care initiatives. 3) Development of dispersment medium for cytotoxic tablets to be given as a liquid dose. 4) Project by clinical trials pharmacist to determine the chemotherapy information needs of a) oncology patients, and b) their GP's. 5) Studies on the need for drug admixtures in palliative medicine, the compatibility of 2 and 3 drug admixtures and clinical outcomes/quality of life when admixtures, rather than multiple infusion devices, are used.

Conclusion: Research collaboration between the Departments of Pharmacy, Haematology and Oncology has been established. Several new clinical, biomedical and pharmacoeconomic studies are under development.

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Vincristine dose-related ototoxicity

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The lack of data on the possible effect of vincristine on the eight cranial nerve and recent reports of sensorineural hearing loss associated with this drug led us to conduct a prospective study on this issue.

Twenty-three patients treated with vincristine, because of lymphoproliferative disorders were checked before and after vincristine therapy. Testing included an evaluation of pure tone audiometry for air and bone conduction and speech audiometry for speech reception threshold.

We found no effect of the drug on hearing in our cohort patients, except on the only one who received a cumulative high dose of vincristine (24 mg) and showed a significant decrease on both PTA and SRT. Ototoxicity could therefore be a dose related side effect of vincristine.

Since audiometric studies are easily performed and inexpensive, it seems logical to recomend repeated audiogram testing of patients who are candidates for receiving high doses of vincristine. Such a policy could prevent sensorineural hearing loss on this selected population of patients.

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Improving the quality of cancer pain management in general practice

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Objectives: To apply the principles of academic detailing to disseminate specialist knowledge in cancer pain and to develop teaching materials for wider use by general medical practitioners.

Method: General practitioners in Melbourne and rural Victoria were recruited into the study through professional contacts, the Division of General Practice newsletters and random phone calls. Each general practitioner was visited on two occasions 6 months apart. At each interview, discussion of case histories was conducted by the project officer, covering 10 key issues. The interview required 20 to 30 minutes although up to 60 minutes was used at the doctor's request, with advice given being predetermined by a multidisciplinary panel. Between visits, the draft educational material was distributed for comment and feedback. Suggestions were incorporated into the final document which was printed as a booklet and distributed by mail prior to the second visit.

Results: Of the 105 general practitioners who commenced the study, 99 completed the program. The areas of cancer pain management most requested were modalities other than analgesics, how to assess pain, adjuvant therapy, differentiation of types of pain and choice of analgesics. From the case history discussion, education was especially required on the use of steroids, second line anti-emetics and non-medication options. All except four general practitioners increased their knowledge of cancer pain management, and all were pleased they had participated in the program. The educational booklet is available through the Drug Information Service at PMCI.

Conclusion: The principles of academic detailing were successfully applied to disseminate specialist knowledge from a teaching institution to general practitioners, with improvement in knowledge of cancer pain management by participating general practitioners.

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Population analysis of once-daily dosing of gentamicin in patients with neutropenia

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Aminoglycoside antibiotics are one of the antibiotics of choice in the treatment of patients with febrile neutropenia. However, there is little information on the pharmacokinetics of aminoglycosides in this specific patient group.

Aim: To determine the population pharmacokinetics of gentamicin given once daily in patients with febrile neutropenia.

Methods: Data were collected from 29 patients with febrile neutropenia receiving once daily gentamicin, for varying course lengths. Patient age, height, weight, lean body weight (LBW), gender, serum creatinine (SCr), creatinine clearance (ClCr), and serum drug concentration data were collected. Other nominal data was also collected, including severity of infection (if noted) and degree of neutropenia. An initial two-stage population analysis using a Bayesian dose individualisation program was performed to determine likely population values of the parameters. If these were different from typical values then a full population analysis was to be performed.

Results: Data for 13 female and 16 male patients were collected. Median age was 58 years (range 19 to 87 years). Mean (±standard deviation) demographic data follow: LBW (kg) = 65.7 (±9.9), ClCr (L/hr) = 5.4 (±2.0). Results of the two-stage approach follow (with a comparison to the general population values): Cl (L/hr) = 0.74 (±0.12) × ClCr + 0.007 × LBW, (0.82 (±0.31) × ClCr + 0.007 × LBW); Vd (L) = 0.28 (±0.05) × LBW, (0.25 (±0.06) × LBW).

Conclusion: The population values of Cl and Vd from the two-stage approach differ by only 10% from the general population values of Cl and Vd, therefore it was unnecessary to perform a full population analysis. Patients receiving gentamicin for febrile neutropenia may be considered pharmacokinetically similar to the population norm.

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Human resource issues in cytotoxic drug dispensing facilities

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It is almost two decades since concerns were first expressed about the safe handling of cytotoxic drugs. In Australia this resulted in the development of standards for a laminar flow cytotoxic drug safety cabinet and associated cleanroom for use in hospital pharmacies. Anecdotal evidence over the last ten or so years has suggested that there are human resource management issues with staff working in these facilities. We have conducted a study of these as part of a larger project on human resource issues in controlled environments.

In areas conforming to AS 2639 (Cytotoxic Drug Safety Cabinets—Installation and Use, 1983/1994) the cleanroom environment is controlled with differential air pressures with entry via a positive pressure air-lock. The technology has been paramount in the design of these facilities with human factors often given a lower priority. The nature of the technology becomes regulating, resulting in very formal procedures and work practices. Often staff work under conditions of

described (1 hour infusion in 250 ml NaCl 0.9% or Glucose 5% infusion bags or bottles).

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Safe preparation of an oral liquid formulation of mercaptopurine in the clinic and the home

M. Priston,[1] G. Sewell[1,2]

Introduction and Objective: This study investigated the provision of pharmacy-prepared sterile, single use dissolution/dispersion medium to convert a solid cytotoxic drug dose to an oral liquid presentation immediately before administration. This would obviate the need to prepare suspensions and would avoid concerns over occupational exposure during crushing of tablets, limited stability data, poor dose homogeneity on repeat use and the risk of microbial contamination of a preparation administered to immunocompromised patients.

Method: Initial studies investigated the dispersion of mercaptopurine tablets (10 mg) in a variety of media of 10 ml volume. Samples were withdrawn using an oral syringe at various time intervals and subjected to further dilution and assay using a stability-indicating HPLC assay. The fraction of drug in solution was determined in parallel studies by the introduction of a filtration step prior to dilution and assay.

Results: The diluent providing most complete dispersion of mercaptopurine was sodium bicarbonate 8.4%. Replicate experiments in which 5 ml of the dispersion was withdrawn for assay (equating to 5 mg dose) demonstrated excellent accuracy and homogeneity of drug content (x = 4.86 mg in 5 ml, S.D.=0.214 mg, C.V.=4.40%, n = 7). The mean recovery was 97.2% and recovery in all experiments was >90%. The fraction of drug dissolved in solution was 74% and the dispersion was stable for at least 4 hours at room temperature.

Conclusion: The provision of single-use screw cap containers with a sterile diluent for the dispersion of solid-dose cytotoxic drugs offers a safe and effective means of preparing a liquid presentation. Dose fractions are easily obtained using an oral syringe and disposal of remaining dispersion is safe and simple.

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Etoposide stability in ambulatory infusion pump with PVC drug reservoir

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Introduction and Objective: Although etoposide is a candidate for ambulatory infusion, poor drug stability and the manufacturers recommended maximum concentration in infusion of 0.25 mg^1 would necessitate either frequent changes of 'normal' volume pump reservoirs or the use of inpractically large pump reservoirs to deliver the required dose (typically 40 mg/m^2/day × 14 days). The aim of this study was to determine the stability and compatibility of a more concentrated (0.5 mg ml^{-1}) infusion (prepared from Vepesid injection, Bristol Myers) in the Graseby 9100 ambulatory pump.

Method: Duplicate Graseby 9100 medication cassettes containing etoposide infusion (0.5 mg ml^{-1}) were incubated at either 8° or 37° to replicate storage and in-use temperatures. Samples were withdrawn at various intervals and the drug assay (stability-indicating LC), pH, appearance, sub-visual particulates and moisture loss were determined. DEHP plasticiser (from the PVC infusion reservoir) was also quantified by LC.

Results: Over 7 days the infusions exhibited no drug loss with mean day 7 assay values at 8° and 37° of 100.1 and 101.8% of initial concentration respectively. There was no significant moisture loss or change in pH and subvisual particle count. However, by days 10 and 14 infusions stored at 8° had precipitated. DEHP was detected at all time points and by day 7 had reached concentrations of 38.5 and 91.0 μg ml^{-1} in infusions stored at 8° and 37° respectively.

Conclusion: Although etoposide ambulatory infusion (0.5 mg ml^{-1}) was physically and chemically stable for 7 days at 8° and 37°, leaching of plasticiser was significant and was attributed to Vepesid formulation excipients. The use of PVC-based pump reservoirs cannot be recommended and etoposide infusion should be administered from plasticiser-free containers and infusion devices.

Reference

1. *ABPI Data Sheet Compendium.* 1996-97; DataPharm Publications Ltd: London. P174.

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Production, and stability testing of concentrated morphine-HCl solutions for parenteral use

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In pain management, morphine-HCl is required in different concentrations ranging from 0.5 mg/ml for peridural application up to 40 mg/ml for portable infusion pumps. The saturation solubility of morphine-HCl is about 50 mg/ml. For the peridural route of administration the solution has to be unbuffered, free of preservatives and antioxidants and at a pH not less than 4. During autoclaving and storage morphine-HCl undergoes decomposition with the oxidative degradation products pseudomorphine and morphine-N-oxide. Oxidation in aqueous solutions depends on the hydrogen-ion-and oxygen concentration and is catalized by organic impurities. The preparation of the autoclaved solution has to take place under conditions that prevent shifting of the pH to the alkaline range, prevent the release of organic ingredients from the stopper material and assure the absence of oxygen in the aqueous solution.

The quality assuring analytical method was predictive for morphine-HCl in the presence of pseudomorphine and morphine-N-oxide. The feasibility of producing a heat-sterilizable morphine HCl solution for parenteral use ranging from 0.05%-4% in glass containers of different quality (type I and type II) was examined and a HPLC-based stability testing was performed. The following results were obtained: morphine-HCl solutions with a concentration up to at least 4% that are unbuffered and free of antioxidants are autoclavable and stable if filled in type I glass containers and sealed with teflon coated stoppers, the pH is adjusted at 4-5 and the solution is free of oxygen.

Under these conditions a rational large scale production of concentrated parenteral morphine is possible in the setting of the hospital pharmacy.

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Improved stability of carboplatin in the presence of α-hydroxypropyl cyclodextrin (αhpcd)

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Introduction and objective: The presence of nucleophiles (e.g. Cl^-) and pH>7 increases the degradation rate of carboplatin in solution.[1] Sources of nucleophiles include diluents, drug counter ions and excipients from drug admixtures. In admixtures with 5-fluorouracil (pH 8.5, contains OH^- ions) 16% carboplatin loss occurred in 24 hours at room temperature.[1] Prolonged ambulatory infusion and centralised preparation of chemotherapy admixtures require extended stability. This study investigated the effect of αhpcd inclusion complexation on carboplatin stability in the presence of nucleophiles.

Methods: Carboplatin was quantified using a stability-indicating LC assay. The solubility of carboplatin at 25° was determined in water and αhpcd solution (20% w/v). Carboplatin stability in the presence of (i) Cl^- 0.4 M and (ii) 5-fluorouracil admixture (5-FU 1g + carboplatin 100 mg L^{-1}) was determined in the presence and absence (control) of αhpcd (20% w/v) under controlled conditions.

Results: In 20% αhpcd carboplatin solubility increased by 51% indicating inclusion complex formation. After 192 hours in the presence of Cl^- (0.4 M) carboplatin complexed with αhpcd exhibited 8% drug loss (control = 62% drug loss). In the 5-FU admixture carboplatin with αhpcd lost 0% in 24 hours (control = 11% drug loss).

Conclusion: Formation of carboplatin inclusion complexes with αhpcd enhanced carboplatin stability in the presence of Cl^- ions and in 5-FU admixtures.

Reference

Sewell GJ, et al. Stability studies on admixtures of 5-FU with carboplatin and 5-FU with heparin for administration in continuous infusion regimens. *J Clin Pharm Ther.* 1994;19:127-133.

[1]Pharmacy Depart, Royal Devon and Exeter Hospital and [2]Pharmacy Department, Plymouth Hospitals NHS Trust and Postgraduate Medical School, Plymouth, UK.

Stability, and compatibility of admixtures of carboplatin and cyclophosphamide in glucose 5%

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Today, some patients suffering from advanced breast cancer are treated by autologous bone marrow transplantation following the administration of high-dose chemotherapy. Normally the treatment of these patients include a four day medication of continuous infusion with carboplatin, cyclophosphamide and thiotepa with frequent infusions of several other drugs. Simultaneous administration of all these drugs may cause compatibility problems. In order to make this administration more safe, we investigated the stability and compatibility of carboplatin and cyclophosphamide in dextrose 5% in PVC infusion bags.

To obtain optimal stability, only glucose 5% was used as diluting media due to the chloride ion induced degradation of carboplatin. Admixtures of the drugs at two different concentrations of carboplatin (0.1 and 0.4 mg/ml) and cyclophosphamide (0.75 and 3.0 mg/ml) were compounded in 1000-ml PVC infusion bags containing glucose 5%. Four bags of each concentration were prepared and stored at 4°C and 25°C. Analyses were carried out initially and after 1, 2, 4, and 7 days implying visually inspection for clarity and colour, pH and determination of the content of carboplatin and cyclophosphamide with a **stability indicating HPLC-method.**

After storage for 7 days at 4°C the content of carboplatin and cyclophosphamide was 99.4% and 97.0%, respectively, of the initial concentration. 7 days storage at 25°C caused a degradation of cyclophosphamide to 82.3% (0.75 mg/ml) and 86.8% (3.0 mg/ml), while the carboplatin content was still 96.6% of initial concentration.

After 2 days storage at 25°C the content of carboplatin and cyclophosphamide was found to be 99.7% and 96.5%, respectively.

In conclusion, a stability limit of 7 days at 4°C and 2 days at 25°C will yield a content of carboplatin and cyclophosphamide well above 95% of initial concentration.

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ASEPTIC PREPARATION AND SAFETY IN HANDLING CYTOTOXIC DRUGS

Safe handling of cytotoxic agents—A new approach to an I.V. administration system

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Many cytotoxic drugs have been found to be mutagenic and carcinogenic.The risk associated with occupational low level exposure has, however not been proven Therefore, without evidence to the contrary, risk is assumed to be present and we recommend a 'zero-exposure' guideline for our hospital. We observed that when the infusion line was connected to the cyto containing bags, spills with potential skin contact occurs in 25% of the cases. To avoid these spills we developed a new administration system based on a 'dry connection'. The system consists on (**a**) infusion bags with an injection port and a male luer lock connection port protected with a break-a-way (BAW) seal and (**b**) an infusion line with 3 female luer lock and 2 spike connectors.The bags containing cytotoxic drugs are prepared in the pharmacy and then transported to the ward. The nurse connects a standard infusion bag to one of the spikes in order to flush the administration set and one ore more cyto-bag(s) to the luer lock port(s). This is a dry connection since a BAW seal prevents direct contact of the cytotoxic drug with the connection point. Once connected, the BAW seal is broken and the cytotoxic drug can be infused. All empty bags remains connected and the set is discarded (after flushing with the standard infusion solution) if all luer lock connection ports are been used or at last after 24 hours. With this new system, we have eliminated the risk of contamination during administration, in conformity our 'zero-exposure' guideline.

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A comparative study of the cost, ease of use and safety of Onco-Tain™ and Onco-Vial™ in hospital pharmacy practice

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The objectives of this study were to compare the utilization cost, ease of use and safety of Onco-Tain™ (OT) a conventional containing cytotoxic agents and Onco-Vial™ (OV), a new system for cytotoxic drug withdrawal. The study was conducted at the pharmacy departments of PMCI and WMD. This was an open label randomised study of 168 consecutive preparations of 5-fluorouracil (5FU) (500 mg/20 ml) using either OT or OV. Eight pharmacists and four pharmacy technicians participated in the study. Following standardised training, each operator completed 14 randomised preparations. Time taken for each preparation and occurrence of any adverse events (e.g. needle-stick injury or cytotoxic spill) was recorded on a Dose Evaluation Form. On completion each operator independently evaluated each method of preparation for ease and safety of use. Economic evaluation of utilising OT and OV was conducted based on each institution's standard operating procedures. The average preparation time for doses using OV was 10.3% greater than the time for OT, which was statistically **significant ($P = 0.001$). The preparation time was found to depend** strongly on the dose being prepared, with the preparation time **increasing with larger doses. No needle-stick injuries were reported** with either method. One spillage occurred with OT. At PMCI, the total cost for preparing a 500 mg dose of 5FU was $5.56 for OV and $5.36 for OT. At WMD, the total cost for preparing a 500 mg dose of 5FU was $5.59 for OV and $7.94 for OT. Operators indicated a significant preference for OV in ease of drawing up, reductions in risk of spillage, aerosolisation and needle-stick injury; however operators did not perceive significant advantages of OT over OV for introduction of starting materials, reduction in the risk of breakage and disposal of materials. OV was preferred over OT on a number of evaluated parameters and offers potential cost savings in use of consumables.

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Guidance and follow-up of personnel during centralized preparation of cytostatics

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Each year approximately 27,000 intravenous cytostatics are prepared in the pharmacy of the University Hospital of Leuven. To achieve this 10 pharmacists and 20 pharmacy technicians are involved in a rotation system. On a daily basis 3 technicians prepare the cytostatics, ready to use, and one pharmacist checks the preparation according to the prescription. Three vertical laminar airflow cabinets are at their disposal in a separate cleanroom. Strict procedures regulate the entry of the cleanroom, the workmethods and the use of clothing.

Last year an unfortunate accident (broken glass) caused growing unrest among the personnel. This concerning incident has led to the idea of introducing a continuous follow-up of the people involved with the preparation of cytostatics.

Extensive information on determining low concentrations of cytostatics and their metabolites can be found in the literature.

polysorbate 80 vehicle, with 48 administration and extension sets with differing PVC contents.

Since a preliminary study had demonstrated no differences between the quantities of DEHP leached from 250 ml PVC bags into infusions of docetaxel or the vehicle (polysorbate 80) alone, this study was conducted using two concentrations of the vehicle (equivalent to those used in infusions of docetaxel 0.31 and 0.88 mg/ml). All infusions were prepared in 5% glucose and were delivered over 90 minutes. Duplicate infusion samples were analysed for DEHP content using a validated HPLC method (Lichrospher(column at 28°C; limit of quantification 0.5 (g/ml).

DEHP levels were either not detected or were below quantifiable limits during simulated infusions with 32 of the sets at either vehicle concentration. Levels above 0.5(g/ml were observed at the higher vehicle concentration only with three sets, and at both concentrations with 13 sets. The amount of DEHP leached was relatively low and only exceeded 5 (g/ml (the upper limit specified in the Taxotere(US registration dossier) with five of the administration sets and at the higher vehicle concentration.

In conclusion, the levels of DEHP leached with docetaxel infusion solutions vary between administration equipment, possibly due to PVC content. However, due to the short exposure time the amount of DHEP leaching was low and all PVC-free administration sets tested here were suitable for the infusion of docetaxel.

Am J Hosp Pharm. [1]1991;48:1520-4. [2]1993;50:1405-9. [3]1994; 51:2804-10.

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Compatibility of selected taxoid with PVC-based infusion equipment

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The surfactant polyoxyethylated castor oil used to formulate paclitaxel injection (Taxol( ) has been shown to cause leaching of the plasticiser diethylhexylphthalate (DEHP) from polyvinylchloride (PVC)-based infusion equipment (1-3) Docetaxel injection (Taxotere( ) also contains a surfactant (polysorbate 80) and the purpose of this study was to determine and compare the extent of DEHP leaching from PVC-based infusion equipment by docetaxel and paclitaxel solutions during both storage and simulated infusions over the recommended times (1 and 3 hours, respectively). Since a preliminary study showed that DEHP leakage was not significantly influenced by the diluent (0.9% NaCl or 5% glucose), each drug was prepared in saline at two concentrations (docetaxel 0.56 and 0.96 mg/ml; paclitaxel 0.3 and 1.2 mg/ml). Concentrations of DEHP in triplicate samples of infusion solutions were determined by HPLC (limit of detection about 1 (g/ml).

The amount of DEHP leached by both drug solutions when stored at room temperature for up to 8 hours increased with time and drug/vehicle concentration. At the higher concentration of docetaxel and paclitaxel the DEHP level in the infusion solution after 8 hours was 48 and 108 (g/ml, respectively. During simulated infusion of docetaxel, DEHP leaching was not markedly influenced by the brand of PVC infusion bag nor the concentration of drug/vehicle; the mean DEHP concentration at the end of the infusion was 10 (g/ml (range 9-14). With paclitaxel, there was a strong relationship between DEHP leaching and the drug/vehicle concentration; the DEHP levels after 3 hours was also 2 to 8 times greater than with docetaxel.

In conclusion, DEHP leaching, both during storage in PVC infusion bags and simulated infusion using PVC-based administration sets, is lower with solutions of docetaxel than paclitaxel.

Am J Hosp Pharm: [1]1991;48:1520-4. [2]1993;50:1405-9. [3]1994;51: 2804-10.

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Guidelines for high dose etoposide administration in bone marrow transplant patients

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High doses of etoposide (60 mg/kg) are used in conditioning regimes for bone marrow transplantation. Such conditioning is now included in the MRC UKALL XII protocol. There are practical and clinical difficulties associated with the administration of such regimes. We address these aspects and produce guidelines for the safe administration of this drug.

Objectives: 1. To identify an appropriate giving set for "neat" etoposide administration. 2. To compare the degree of plasticiser leaching from 2 different giving sets: a) Flogard IV solution set (Baxter) b) Low Adsorption set (Baxter) 3. To identify and quantify this plasticiser 4. To resolve practical problems associated with etoposide administration and to produce clinical guidelines.

Methodology: A high performance liquid chromatography (HPLC) method was developed to measure plasticiser released from intravenous lines exposed to etoposide for 4 hours. Two IV giving sets were compared. Guidelines were produced for high dose etoposide administration and used in the Bone Marrow Transplant Unit.

Results: Significant levels of a plasticiser-related substance were found in the solution taken from both lines. This subsequently turned out to be phthalic acid, bis (2-ethylhexyl) ester.

Conclusion: Significantly less plasticiser was stripped from the low adsorption set. Guidelines for the safe administration of high dose etoposide are needed. These have been produced and are being used effectively on our Bone Marrow Transplant Unit.

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PHARMACOKINETICS

Ifosfamide pharmacokinetics: Schedule dependency of enantioselective clearance

R. Davis,[3] M. Priston,[1] G. Sewell[1,2]

Introduction and Objective: Ifosfamide is marketed as a racaemic mixture of R- and S-ifosfamide enantiomers. We have previously demonstrated increased clearance of S-ifosfamide compared with R-ifosfamide following prolonged infusion of racaemic ifosfamide (1). This pilot study was undertaken to establish whether or not enantioselective clearance was dependent on the ifosfamide infusion schedule.

Method: Blood samples were taken over the infusion time-course from patients receiving either ifosfamide 1g/m^2/d × 12 days (Schedule A) or ifosfamide 1.5g/m^2 over 30 min × 5 days (Schedule B). Plasma ultrafiltrate was assayed for individual R- and S- ifosfamide using a column-switching LC method. Plasma concentration/time-course data for each enantiomer was modelled using Statis 3 pharmacokinetic software.

Results: The table (below) shows mean area under the curve (AUC) and clearance (Cl) values for R- and S-ifosfamide enantiomers. N/S = not significant.

	AUC (μg.h/ml)			Cl (ml/min)		
	R-ifo	S-ifo	p value	R-ifo	S-ifo	p value
Schedule A (n = 5)	1616	1201	<0.05	112	158	<0.2
Schedule B (n = 4)	499	492	N/S	34.4	35.2	N/S

Conclusion: The increased clearance and decreased AUC of S-ifosfamide was significant only in Schedule A (prolonged infusion). This schedule dependency may be attributable to hepatic P-450 induction. Preferential clearance of the S-enantiomer may reflect

increased metabolic activation to isofosforamide mustard or, conversely, enhanced 2- and 3-dechloroethylation to toxic side products. In either case this finding may be of clinical significance.

Reference

1. Powell S, Priston MJ, Sewell GJ. The pharmacokinetics of ifosfamide and its enantiomers in continuous infusion. *J Pharm Pharmacol.* 1992;44(suppl):1069.

[1]Department of Pharmacy, Plymouth Hospitals NHS Trust, [2]Postgraduate Medical School, University of Plymouth, UK, and [3]Arizona State University, Tempe, Arizona, USA.

Influence of weight, sex and age on the pharmacokinetic parameters of vancomycin

A. Aldaz, A. Idoate, C. Lacasa, J. Giráldez

A study was carried out of the influence of physiological factors such as weight, sex and age on the pharmacokinetic parameters of vancomycin (VAN) in a population of oncologic patients.

We assessed the pharmacokinetic parameters found in the course of the routine clinical care of 72 oncologic patients with solid tumors. All the patients included in the study presented normal liver and kidney function. The pharmacokinetic parameters (mean ± SD) of vancomycin in this population were obtained by the overall two-stage method using an earlier study involving oncologic patients.

Table I. Pharmacokinetic parameters of VAN as a function of weight (mean ± SD)

Group	N	V(L)	CL(L/h)	$k(h^{-1})$
Obese	9	48.7 ± 6.9	4.9 ± 1.8	0.103 ± 0.037
Normal W	58	41.2 ± 10.5	4.6 ± 1.8	0.112 ± 0.037
Low W	5	37.6 ± 10.5	2.4 ± 1.0	0.067 ± 0.032
Total	72	41.9 ± 10.4	4.5 ± 1.9	0.108 ± 0.038

TABLE II. Pharmacokinetic parameters of VAN as a function of age (mean ± SD)

Age (years)	N	V(L)	CL(L/h)	$k(h^{-1})$
<40	23	38.4 ± 7.6	5.3 ± 1.7	0.138 ± 0.028
40–60	40	41.7 ± 10.3	4.2 ± 1.9	0.099 ± 0.035
>60	9	51.7 ± 11.7	3.6 ± 1.2	0.070 ± 0.017

TABLE III. Pharmacokinetic parameters of VAN as a function of sex (mean ± SD)

Group	N	V(L)	CL(L/h)	$k(h^{-1})$
Female	42	38.5 ± 9.6	4.0 ± 1.5	0.107 ± 0.035
Male	30	46.6 ± 9.7	5.1 ± 2.1	0.110 ± 0.045

With regard to the volume of distribution (V), no significant differences were observed between the three weight groups when this parameter was expressed in L. Regarding sex, the differences observed in this pharmacokinetic parameter were significant for $P < 0.01$. Study of the volume of distribution (V) in the three age groups revealed significant differences ($P < 0.05$) between the oldest age group and the two others.

For the clearance of vancomycin (CL) the differences found between the mean values obtained are smaller than those for the volume of distribution, with significant differences ($P < 0.01$) between the patients with low weight and the other two weight groups when this parameter was expressed on the basis of ideal weight. As far as sex was concerned, significant differences ($P < 0.005$) were only found when the results were expressed independently of weight (L/h or mL/min). On the other hand, the significant differences found in the analysis of age ($P < 0.05$) were obtained when clearance was expressed on the basis of present weight (mL/min/presentW).

From the results of this study we can conclude that it is apparently necessary to increase the dosing intervals for vancomycin in geriatric patients with a view to avoiding the accumulation of this antibiotic, as well as the need for higher doses in obese patients and in men than in women.

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Effects of hepatic function on the pharmacokinetics of vancomycin in oncologic patients

A. Aldaz, A. Idoate, C. Lacasa, J. Giráldez

In a group of oncologic patients with solid tumors, we analyzed the influence of several variables on the disposition of vancomycin, focusing especially on hepatic function. The data concerning 154 patients with solid tumors were analyzed with regard to the descriptive variables shown in Table I.

Table I.

Qualitative		
Sex	Type of antibiotic treatment	
Diagnosis	Treatment with aminoglucosides	
Obesity	Kidney failure	
	Liver failure	
Quantitative		
Age (years)	PMO (kg)	Clcre in urine
Height (cm)	Serum creatinine	CLCGPA (mL/min)
Present weight (kg)	Total serum proteins	CLCGPI (mL/min)
Ideal weight (kg)	Length of aplasia	

Patients were classified with regard to liver and kidney function according to Miller's scheme (1981). The serum samples for each patient (Cmin 0–30 min pre-dose and Cmax 2 h after an i.v. infusion for 1 h) were analyzed by FPIA in TDx (Abbott). The pharmacokinetic parameters for this population were determined by the overall two-stage model, and the individual ones were calculated using the method developed by Sawchuk and Zaske (1976). The statistical analysis was performed using STATISTICA/W version 5.0 (StatSoft). The regression models for the pharmacokinetic parameters were obtained by multiple linear regression using the variables in Table I as the independent variables. Once the distribution function of each variable had been established, the values for the central tendency of the different pharmacokinetic parameters in the estimated subpopulations were calculated. The means were compared using ANOVA, and the Scheffé test was applied post-hoc with statistically significant differences for $P < 0.05$. The criterion for selection of the regression model was the square of the coeffient of adjusted multiple correlation (R^2_{ap}). The estimated models were tested by analysis of the residues.

No significant differences ($P < 0.001$) were noted between the pharmacokinetic parameters of vancomycin on the basis of liver function. On analyzing the estimated models of regression, both for Clvan and V, no differences were found on assessing the subpopulations obtained on the basis of hepatic function, with the exception of the independent term of the model of the volume of distribution. In patients with altered hepatic function, non-renal clearance higher than that found in patients without this complication was observed (20.8 mL/min and 3.9 mL/min, respectively).

In conclusion, in the population studied it was observed that

Oncology pharmacy facing ever increasing workloads. Patients too may benefit if waiting times for chemotherapy can be reduced as a result of shorter preparative times.

Reference

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Antiemetic therapy—Guidelines improve the cost-benefit ratio

A. Freidank,[1] P. Heinkele,[2] R. Radziwill,[1] F. Wegelin[2]

The control of chemotherapy-induced emesis and nausea has been improved with the introduction of 5-HT_3 antagonists. But delayed emesis and nausea, the therapy of moderately emetogenic regimen and the costs remain a problem.

The aim of this study has been to reduce the costs of antiemetic therapy without influencing the effectiveness of this therapy.

At a medical ward antiemetic regimens for low, moderately and highly emetogenic therapy have been established. At the day of chemotherapy 5-HT_3 antagonists (ondansetron or tropisetron) are used intravenously in combination with corticosteroids. Up to five days after chemotherapy the patients received metoclopramide and/or corticosteroids as oral medication. The success of the therapy has been documented by the patient with the help of record sheets. The sheet and the antiemetic medication have been handed to the ward with the chemotherapy by the pharmacy.

Up to now 24 patients with 52 cycles have been involved. 36 record sheets (69%) have been returned. Complete control of emesis has been found in 33 cycles (92%), complete control of emesis and nausea in 25 cycles (70%). Five cycles (14%) had been a highly emetogenic therapy. No difference between ondansetron and tropisetron has been seen so far. The cost of antiemetic therapy has fallen during two months from 12,412 DM in 1995 to 6,586 DM in 1996 (~50%).

The results show the possibility of reducing costs without influencing the quality of life. Guidelines for antiemetic therapy are helpful, and we will establish this system at our hospital.

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Oncological therapeutical chemoprotection: Pharmacoeconomic aspects of the treatment of head and neck cancer with amifostine

K. Domagk,[1] E. Di Martino, Ch. Breitsprecher, E. Werner

Amifostine represents a new and adjunct drug for the management of cancer patients receiving a combined radiochemotherapy. Clincal trials have demonstrated that amifostine can significantly reduce the cumulative renal and hematologic toxicities associated with cisplatin.

Our patients with head and neck cancer were treated with three cycles of 80 mg/m^2 Cisplatin (day 1) and 12 mg/kg 5-Fluorouracil (day 2-6) ± 740 mg/m^2 Amifostine. Comparison of the effects with and without pretreatment with amifostine indicated that patients pretreated with amifostine had fewer nephrotoxic and hematologic effects. The treatment with amifostine was well tolerated and no major side effects could be registered.

The discussion will focus on interpretation of pharmacoeconomics, especially the description and analysis of the costs and consequences of oncological therapeutical chemoprotection with amifostine in comparison to the common standards in our chemotherapy regimes.

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Drug Utilisation Review (DUR) programs—Is cost saving the only advantage?

K. Gandecha

Cost Saving is the aim and driving force behind many of the DUR activities. While cost saving is an important and attractive outcome, such programs often provide us with many other opportunities for more enduring improvements.

The Cancer Services Drug Committee has to date analysed the use of 3 main drugs/drug classes:

- 5HT3 Antagonists
- G CSF Preparations
- Octreotide (Sandostatin)

Cost savings have certainly been effected from the 1st two reviews but not from the last. Other outcomes have been review of our treatment protocol manual—with suggested standard antiemetic therapy and average cost for each protocol being included. A Drug Use protocol is also being completed for all high cost/high volume drugs to provide us with a baseline/reference for possible future DUR activities. A orientation/education program has also been implemented for all new medical staff in the Cancer Services.

In our experience, advantages of DUR—other than cost saving—have been very gratifying and have contributed greatly to the pharmacists role in a multidisciplinary team.

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Pharmacoeconomic evaluation of intravesical chemotherapy

G. Sewell,[1,2] R. Wastnage[1]

Introduction and Objective: In the UK superficial bladder cancer (SBC) is usually treated by intravesical instillation of either: epirubicin, mitomycin C or bacillus of Calmette-Guerin (BCG). These differ in mechanism of action, toxicity profile, basic drug cost and course length but there appears to be no overwhelming support for one agent over another. Pharmacy preparation costs also vary, partly as a result of differences in drug stability and also because BCG is a live attenuated vaccine and has been implicated in iatrogenic BCG meningitis arising from workstation contamination (1). UK regulatory authorities recommend a dedicated workstation (e.g. isolator) for BCG preparation which should be decontaminated after use. Some 70 new cases of SBC present annually in this institution. This study was undertaken to identify and compare costs for the 3 preparations in support of the drug selection process.

Method: Dose and course length can vary for these preparations and so calculations were based on normal literature values (1). Drug, consumable, nursing and clinic costs were calculated for each agent. Preparation times were determined from independent observations of the same experienced staff team for each instillation. Capital charge and depreciation costs were apportioned according to workstation occupancy.

Results: Cost per patient (standard doses) for epirubicin, mitomycin C and BCG were £905, £2285 and £971 respectively for a complete (standard) treatment course.

Conclusion: Analysis of overall cost (including clinical management) favoured epirubicin over BCG. Extended stability studies on epirubicin are in progress and these may, by facilitating batch preparation, widen the cost margin further.

Reference

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[1]Department of Pharmacy, Plymouth Hospitals Trust and [2]Postgraduate Medical School, University of Plymouth, Plymouth, UK.

Development of a pharmacoeconomics service in a provincial oncology centre

S.C. Malfair Taylor, L. Chow

Objective: To design and implement a formal pharmacoeconomics service which can be accessed by tumour groups to aid in decisions regarding guidelines, policies, and formulary requests, and which can be accessed by investigators wishing to perform a pharmacoeconomic analysis or add a pharmacoeconomic component onto a clinical trial.

Background: Pharmacoeconomics involves the application of economic evaluations to health care programs. Its purpose is to enhance the evaluation of traditional clinical data, reflect the economic impact of clinical choices, and assist in decision making about the appropriate use of health care resources. The actual pharmacoeconomic analyses incorporate the concepts of supply and demand together with factors such as clinical effectiveness and quality of life. The product is a descriptive analysis of the cost and impact of a particular drug therapy to the health care system, hospital, patient, or to society as a whole. The benefits of a pharmacoeconomc service include leading edge pharmacoeconomic research and evaluation for insight into formulary and drug benefit list considerations, and facilitation of enhanced incorporation of quality of life, cost effectiveness, and evidence based medicine into daily patient care. This means more cost-effective use of the drug budget and improved bargaining power for future budget considerations.

Methods: A review of the pharmacoeconomic literature was completed. Pharmacoeconomic and outcomes research conferences and symposia were attended. Data was synthesized to create a draft pharmacoeconomic proposal and template. This was informally circulated to establish interest in the service. Physicians preparing for clinical trials were approached to instill interest in adding a pharmacoeconomic component.

Results: The pharmacoeconomic service is designed to have an interdisciplinary team approach. It incorporates evidence based medicine and facilitates the collection and use of quality of life and patient satisfaction data to develop recommendations for cost effective use of individual drugs, categories of drugs, and/or drug regimens. Pharmacoeconomic analyses can be retrospective using the pharmacy database, or prospective in conjunction with clinical trials or daily patient care. The format of the pharmacoeconomic analysis is dependent on the question to be investigated and the setting in which the investigation is to be done. The pharmacoeconomic analysis template includes and describes how the pharmacist working on the service can coordinate and facilitate 1) meeting with key stakeholders to be involved with the pharmacoeconomic analysis to define objectives and initiate collaboration, 2) determining the desired perspective of the study such that the scope and the data requirements of the analysis can be defined, 3) determining the alternatives, 4) determining the outcomes, 5) selecting the appropriate method of pharmacoeconomic analysis, 6) determining monetary values, 7) identifying required resources, 8) establishing outcome probabilities, 9) incorporating decision analysis, 10) employing pharmacoeconomic manipulations: discounting, sensitivity analysis, and/or incremental cost analysis, and 11) presenting results.

Progress to date: The first pharmacoeconomic study protocol to utilize the service has recently been submitted for ethics approval and is due to commence at the end of February. The template was followed up to and including step 7. The pharmacoeconomic pharmacist has been named a co-principal investigator for the study.

Future plans: Upon receiving ethics approval, the pharmacoeconomics pharmacist will follow the remaining steps of the template, facilitate, coordinate and complete the study. Results wil be presented, submitted for publication, and used as part of a package to formally introduce the service widely throughout the entire provincial oncology agency.

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COMPUTER APPLICATIONS

ISOLATOR°, an Integrated SOftware for centraLized preparATion of cytOtoxic dRugs

J.-L. Cazin,[1,2] P. Gosselin[1]

Preparation of cytotoxic drugs in a centralized unit by oncology pharmacists is an assurance of quality. Now done is most countries, it tends to be associated with a computerized prescription.

Objectives: Our goal was to provide a tool for preventing medication errors and automating the information flow: physician prescription, pharmaceutical preparation and nurse administration, including maintenance of the equipment. The key features of this Windows software are: data security and maintenance of medical confidentiality, computerized prescription from the clinical units; real-time consultation about the statement of each preparation, using the computer network between clinical units and pharmacy; no more oral or fax medications orders, no transcribing in the pharmacy; systematic use of predefined lists: protocols, stabilities, incompatibilities. No free text typing; calculation of doses, cumulative doses; ability of a dose reduction (% or unit) or treatment transfer; guarantee of a pharmaceutical quality preparation for commercially available and investigational drugs; delivery, processing and validation of the order, double checking preparation, daily preparation report; validation of nurse administration; recording of potential incidents and behavior; producing of provisional schedule calendars of treatment; recording of the date and time of all actions of all participants; automated interface with the general bar-code inventory; planning of the production program; calculation of real cost and gain provided by centralized preparation; generation of calendars for maintenance; recording of results.

Conclusion: Designed for a multidisciplinary team, a preliminary version of ISOLATOR° was implemented in our 299-bed cancer center. As the pharmacist was integrated as a drug specialist member of the oncology team, the evolution was really made from a product-related pharmacy to a patient-oriented pharmacy.

Acknowledgments: Vincent Hourdequin (Computer Engineering, Paris).

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Extravasation treatment record database

J. Bingham, M. Dooley

Objectives: To establish an Australian database to record, analyse, and disseminate information on the extravasation of cytotoxic drugs.

Setting: Coordinated by Peter MacCallum Cancer Institute (PMCI) and involving oncology treatment centres throughout Australia.

Method: Existing PMCI records of extravasation were extracted from the Institute's Incident Database. Medical records for these patients were reviewed. A new data collection form was designed to capture relevant information on extravasation. Copies of the form were mailed to all Directors of Pharmacy and oncology pharmacists together with a covering letter. The project has also been promoted by letters to journals, and through oncology special interest groups. A database has been established at PMCI pharmacy using Microsoft Access. Retrospective reports have been entered into the database and new reports are entered as they are received. Selected non confidential data fields will be extracted from the database and incorporated into the Australian Drug Information (ANDIN) database for distribution to drug information centres participating in ANDINet. At regular intervals, the database will be reviewed and extracts and summaries published.

Results: The database currently consists of 124 PMCI reports and thirteen external reports received in the six months since the mailing. Encouraging support has been received from both oncology pharmacists and directors of pharmacy.

Conclusion: The success of the project on an Australia-wide basis

giving up his ability to make autonomous decisions. There can be a conflict between the autonomy of the moment, which Young describes as occurrent autonomy and the autonomy to preserve a life's plan, or dispositional autonomy. The same paradox does not arise if we place life on top of our hierarchy of values since there is no sense in which we would have to take life to preserve it. Another sense of autonomy is simply as an individual's right to make any decision about his life. We would all be able to exercise that right in full measure if we lived upon a desert island but in order to live together in a community we give up some of our autonomy for the good of the whole. It can be argued that our right to die could fall under that category if for example legislating for euthanasia for a minority of individuals had a detrimental effect on the wellbeing of other individuals in the same society. This is besides the fact that the right to die does not equate with the right to be killed since the latter involves a third morally independent party. An HVL policy may have to be defended against slippery slope arguments and may support such arguments in its defense. For example an HVL policy by allowing exceptions to an absolutist sanctity of life doctrine may be seen as the first step on the road to erosion of community value of life. Conversely, I may wish to support a slippery slope argument which contends that legislating for euthanasia would erode the community's respect for life. Finally, resource allocation at both macro and micro levels may limit the pursuit of an HVL policy.

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CONCURRENT PAPER SESSIONS

A. SAFE HANDLING OF ANTINEOPLASTIC AGENTS

Accreditation of aseptic cytotoxic preparation training course

M. Dooley

Training courses in aseptic cytotoxic preparation and clinical oncology pharmacy practice are offered by the pharmacy at the Peter MacCallum Cancer Institute. Pharmacists and technicians from Australia and overseas have participated in four or five day programs individualised to the needs of the participant. Following positive feedback a decision was made to apply to the Board of Education of The Society of Hospital Pharmacists of Australia (SHPA) for accreditation of the programs as continuing education activities. The first of three training programs to be developed for accreditation was the *Aseptic Cytotoxic Preparation for Technicians* program.

Objectives: The objectives were to fully document the training program for technicians and apply and obtain accreditation of the program as a continuing education activity by the SHPA Board of Education.

Method: The training program was reviewed, expanded and documented with consultation with the Peter MacCallum Cancer Institute Education Centre. A detailed application was submitted to the Board of Education.

Results: A fifteen module training program was developed. Performance criteria are documented for each module and the participant evaluated at the completion of each module. Assessment is performed by the senior pharmacist coordinating the module(s). An application for accreditation has been submitted. A certificate of successful completion will be issued to participants on completion of the program.

Conclusion: The *Aseptic Cytotoxic Preparation for Technicians* program offered by the PMCI pharmacy has been accredited as a continuing education activity by the SHPA Board of Education.

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Redevelopment of the pharmacy cytotoxic unit at Derriford Hospital: Four problems and a solution

G. Sewell, G. Kitto, J. Loving, M. Santillo

Introduction and objectives: The re-location of the Plymouth Cancer Centre from Freedom Fields Hospital to Derriford Hospital during 1997 will enable the transfer of cytotoxic reconstitution work for adult oncology patients from nursing staff to a pharmacy-based centralised service. Previously only cytotoxic doses for paediatric oncology and haematology patients were prepared by the Pharmacy Dept. The new work will result in a workload increase from 6000 to 28000 doses per year. Re-furbishment of the cytotoxic unit was necessary to increase the number of isolator workstations from the one existing Peteric isolator to three.

Problems: 1) Shortage of space. By incorporating a redundant aseptic suite exit corridor into the cytotoxic unit the area could be increased from 9.7 to 22 m^2. This was still not enough for 3 Peteric isolators. 2) External ducting of isolators. Ducting passed up through 7 floors and was fan assisted giving an extract of 850 m^3 hr^{-1}. With 1 × Peteric isolator this was at full capacity. Additional ducting would cost £45K. 3) UK regulatory authorities require isolator design improvements including interlock delay timers on transfer hatches. These could not be retro-fitted to existing Peteric isolator. 4) Financial restrictions.

Solution: Replace Microflow Peteric isolator (dimensions 2.9 × 0.86 m) and install 3 × Medical Air Technology Isomat isolators (dimensions 3.0 × 0.63 m) with extract rate of 180 m^3 hr^{-1} so all 3 isolators could be extracted by existing ductwork using a 3 into 1 manifold with a novel thimble arrangement to maintain room overpressure (+30pa) irrespective of the number of isolators in use. The Isomat isolators have interlock time delays and other safety/regulatory compliance features.

Conclusion: This solution has provided a cytotoxic facility with excellent circulation space, a better than class D environment and 3 isolators which are externally ducted and compliant with regulatory requirements. Use of new Isomat isolators in this situation provided savings of £25K over alternative schemes.

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Biological monitoring of antineoplastic drugs in urine of hospital pharmacy technicians and personnel of oncology departments*

A. Pethran, K.H. Hauff, R. Schierl

In order to evaluate the risk to health of personnel exposed to antineoplastic agents the incorporation of drugs was quantified by detering the urinary concentration (load factor). In addition, induction of micronuclei in peripheral blood lymphocytes will be studied (effect monitoring), for correlation with the urinary excretion of cytostatic drugs. Additionally wipe proofs and air samples will be done to determine exposure doses.

Subjects and Methods: Nearly 100 participants handling cytostatic drugs in central preparation in hospital pharmacy or by contacting patients in oncology departments at 14 hospitals in Germany were included in the study starting in December 1995 for a 3 year period. All participants collected their urine during 24 hours in separate PE bottles. The samples were stored at −20°C until analysis. At the same time blood samples of all participants will be screened for micronuclei. Workplace and work history are known, amount and number of preparations in the week of urinary sampling is registered. Cyclophosphamide and ifosfamide were determined using high resolution gas chromatography/mass spectrometry. Quantitation of the drugs is performed using internal standardisation in the concentration range of 100 pg to 40ng/ml of urine. Platinum was analysed via anodic stripping voltammetry. The limit of determination is about 2 pg absolute or 2 ng/l for 1 ml urine sample size, respectively. Platinum concentrations are related to creatinine values.

Results and Discussion: We analysed more than 400 urine