Quarterly number of reported cases of paralytic poliomyelitis. The horizontal lines represent the mean and 95% confidence limits of the mean number of cases per quarter. The three vertical arrows represent pulse vaccination with oral polio vaccine.

polio has not been controlled by regular age-specific immunisation through fixed centres, even in towns with over 60% coverage with three doses. Control was achieved in this campaign as a result of the wild polioviruses in circulation being replaced

by the widespread pulse of vaccine viruses.⁵ Pulse immunisation will increase the coverage rate as well as the seroconversion rate, presumably owing to the circulation of vaccine viruses.⁴ Thus some children who were missed in the pulse campaign may also become immunised. As a result the circulation of wild polio-viruses would be interrupted and the incidence of poliomyelitis in the community would fall.^{4 5}

This study shows that polio can be controlled in small geographical units. As more resources become available the area covered can be increased until the whole nation achieves control over polio.

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Clinical Topics

Development and operation of a pharmacy-based intravenous cytotoxic reconstitution service

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Abstract

An intravenous cytotoxic reconstitution service has proved extremely popular with both medical and nursing staff. Since the pharmacy has taken over the responsibility for presenting these medicines in a readily usable form, many potential hazards to inexperienced medical staff have been eliminated, and much time and money have been saved. The pharmacists are in an excellent position to offer advice on many aspects of cytotoxic treatment and are well equipped to spot prescription errors. They are often asked to supply information concerning rates and methods of ad-

ministration as well as compatibility data of different diluents with various cytotoxic agents. The eventual objective of the service is to provide reconstituted cytotoxic drugs for all patients in the pharmaceutical district receiving chemotherapy. As it is not practical to have pharmacists available 24 hours a day, some form of batch production of syringe-loaded drugs could be used. In the immediate future the practicality of storing syringe-loaded drugs in a deep freeze (at -20°C) with rapid thawing will be considered.

Introduction

The past 20 years has seen an explosion in the introduction of effective cytotoxic agents for treating malignant disease (fig 1). Not only has the number of agents increased, so has the frequency with which they are used.

Until relatively recently chemotherapy tended to be used only in specialised units on small numbers of patients with rare tumours. With the growth of chemotherapy as an adjuvant to surgery and radiotherapy, however, and with the advent of multicentre clinical trials in common malignancies, these drugs are now prescribed much more widely. This increased use may produce an unduly heavy burden on medical and pharmaceutical

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resources. It has therefore become necessary to establish facilities to prepare and administer these drugs efficiently, safely, and accurately.

FIG 1—Availability of clinically useful cytotoxic agents by five-year periods.

Prescriptions for intravenous cytotoxic treatment are traditionally dispensed by supplying a convenient number of the manufacturer's original packs to obtain the doses required. Often these packs do not contain the exact dose, and in most cases the drug is presented as a sterile freeze-dried powder requiring reconstitution. The task of reconstituting and presenting the required dose has largely been abandoned by the pharmacist and left to the junior doctor or sometimes the nurse.

Only in the past few years have a few pharmacists started to consider the requirements for safe handling and suitable methods of dispensing intravenous cytotoxic drugs.¹⁻⁷ We attempt to describe the requirements, how they were achieved in practice by developing a pharmacy-based intravenous cytotoxic drug dispensing service, and discuss some proposals for future developments.

Problems of reconstitution

The task of reconstitution is time-consuming and has several associated hazards:

DRUGS

Many cytotoxic agents are known or suspected to be carcinogenic, mutagenic, or teratogenic.⁸⁻⁹ These effects have been shown in animals,¹⁰ and certain drugs have been implicated in the development of secondary tumours in patients treated by chemotherapy.¹¹⁻¹³ What is not known is the effect of long-term low-level exposure to cytotoxic drugs on those people who regularly prepare and administer them. Falck *et al.*¹⁴ reported detection of mutagenic activity in urine concentrates of nurses working on a cancer unit, but the significance of this was questioned by Lassila *et al.*¹⁵ It must be emphasised that the study of the long-term potential hazards to those preparing these agents is at a very early stage and as yet little work has been done. Some of the drugs are corrosive if spilt on to the skin or mucous membranes and can be particularly damaging to the eyes.^{1,16} The hazard arising from inhaling aerosol droplets that may be produced during the reconstitution procedure must also be considered. It is thus advisable to take precautions to protect both the operator and environment when handling anticancer agents; spillage must be dealt with promptly and effectively.

WARD ENVIRONMENT

Intravenous cytotoxic drugs are usually reconstituted in a ward area with the associated risk of contaminating the injection before ad-

ministration. Many patients receiving cytotoxic treatment are more prone to infection than the average hospital patient as they are often myelosuppressed and have impaired immunity.

STAFF

Cytotoxic drugs are usually given by busy junior doctors who consequently may not have time to prepare and administer these drugs until the evening. By then more senior staff have often gone off duty and the junior doctors themselves are tired. In addition, staff preparing these drugs will often still be in training and are not always fully aware of the hazards outlined above.

The Royal College of Nursing Oncology Nursing Society has supported the view that in clearly defined circumstances the care of the cancer patient may be enhanced if a nurse were responsible for both establishing intravenous lines and administering intravenous cytotoxic drugs. Suitably trained specialist nurses in intravenous treatment could well alleviate some of the pressures on busy, junior medical staff by performing such tasks.

Developing a pharmacy-based intravenous cytotoxic drug dispensing service

FACILITIES

During October 1980 a new sterile products unit was built and commissioned at the London Hospital (Whitechapel). The unit functions chiefly as an aseptic dispensing unit rather than a manufacturing unit. Each room in the unit has a high efficiency particulate air (HEPA) filtered air supply, and consequently the quality of the air in the unit complies with BS5295 (class 1). The upgrading was necessary as the type of work carried out had changed dramatically in recent years. Limited small-scale manufacturing is undertaken in this unit—for instance, ampoules and eye-drops—while the main

FIG 2—Reconstitution of cytotoxic drugs within a vertical downflow, laminar flow safety cabinet (Howie class 2 type, supplied by Microflow Pathfinder Ltd).

function is dispensing intravenous feeding mixtures, intravenous additions, and intravenous cytotoxic drugs. Intravenous cytotoxics are reconstituted by pharmacy staff in a vertical downflow, laminar flow safety cabinet (Howie class 2 type) supplied by Microflow Pathfinder Ltd (fig 2). This type of cabinet gives a high degree of protection for the operator as well as providing a class 1 (BS5295) working environment suitable for preparing intravenous doses. The hazards of using horizontal laminar flow cabinets for this type of work have been reported.¹⁷

METHOD OF PREPARATION

Cytotoxic drugs are reconstituted by members of the sterile products unit after they have received intensive training in aseptic technique. Many intravenous cytotoxic agents are obtained by the pharmacy as sterile, freeze-dried powders inside rubber-capped glass vials. The reconstitution process entails aseptically transferring a quantity of diluent into the vial and removing an equal quantity of air to avoid a build up of pressure in the vial. If the pressure inside the vial is allowed to increase there is a risk that: (1) the syringe and needle may separate; (2) aerosols may spurt from the vial when the needle is removed; and (3) the rubber top may split or even blow off. It is undesirable to use "bleed needles" when reconstituting as you do not want cytotoxics to leak from the vial.

All staff working in reconstitution procedures are made aware of the hazards of handling these agents and are informed of the action necessary if an accident occurs—for instance, dropping a vial, self-injection during preparation, etc. Figure 3 shows a "flow diagram" of the reconstitution procedure.

FIG 3—Flow diagram of reconstitution procedure.

DOSE PRESENTATION

During the initial stage of the service reconstituted cytotoxic drugs were presented as dissolved powders in their original vials. The doctor would then withdraw the appropriate dose from the vial before administering it to the patient.

After consultation with the medical staff concerned it was decided that the ideal presentation of the drugs would be for the pharmacy to provide the appropriate patient dose in a labelled disposable syringe,

sealed with a sterile blind hub. Syringes were thought to be more appropriate than other administration systems, such as minibags, as most intravenous cytotoxics in this hospital are injected "down the line" of a fast-running intravenous infusion.

Dispensing in syringes eliminates further hazards to medical staff as the dose is already removed from the vial. The only manoeuvre necessary is removing the blind hub and replacing it with a needle. Whenever appropriate, drugs, such as cisplatin and methotrexate, are added to infusion fluids.

As the pharmacy are now syringe loading the drugs, several patient doses may be removed from a vial. This reduces the number of drugs wasted and represents a considerable financial saving.

All syringes are given a 24-hour maximum expiry time when they are sent to a ward. Each syringe is labelled (fig 4).

STORE IN FRIDGE	
mg	
in	
ml	
Expires:	
hrs	
on	
Patient's name:	
Ward	
pharmacy, London Hosp.	

FIG 4—Example of a syringe label.

A written instruction is sent to the ward requesting the return to the pharmacy of unused syringes as soon as possible. Whenever possible, returned syringes that are still in date are relabelled and used for another patient. The contents of syringes that cannot be reused immediately are returned to their original vials if the correct storage conditions have been observed on the ward.

STABILITY DATA

Manufacturers of cytotoxic drugs were contacted and asked to supply stability data for their products after reconstitution. In many cases the expiry time could be considerably extended beyond that suggested in the data sheet if the product had been stored in a controlled environment (table).

Whenever possible, cytotoxics are reconstituted in advance and loaded into syringes as prescriptions are written. All cytotoxics are reconstituted to a standard concentration and to eliminate errors in the pharmacy a worksheet is used (fig 5). The worksheet is completed on receipt of a prescription and, as may be seen, specifies standard concentration and appropriate diluent.

WORK LOAD

The work load figures are shown graphically (fig 6). The increase in work from September 1980 corresponded to the arrival of a basic-

Expiry times for commonly reconstituted cytotoxics stored at 4°C in the dark

Drug	Time (days)	Reference
Adriamycin	7	Hoffman <i>et al</i> ¹⁸
Cyclophosphamide	6	Kirschenbaum <i>et al</i> , ¹⁹ Brooke <i>et al</i> , ²⁰ and manufacturers' information
Vinblastine	30	Data sheet
Vincristine	14	Data sheet

grade pharmacist, responsible for further developing the cytotoxic reconstitution service at this hospital.

A pharmacist was available until 7 pm Monday to Friday to dispense cytotoxic prescriptions that arrived late in the pharmacy. With an extra member of staff intravenous cytotoxic prescriptions could be dispensed for outpatients as well as inpatients, and it is the outpatients that largely represent the increased work load since September 1980. In the immediate future we intend to look at the practicality of storing syringe-loaded drugs in a deep freeze (at -20°C) and using rapid thawing (perhaps using a microwave oven) when they need to be dispensed.

Advantages of a pharmacy-based intravenous cytotoxic drug service

There are several advantages of this service.

(1) Intravenous cytotoxic agents are reconstituted and dispensed under laminar flow conditions in a cabinet that provides protection for the operator as well as for the product.

(2) Intravenous cytotoxic agents are reconstituted and dispensed by highly trained pharmacy staff, who are aware of the hazards associated with handling these agents.

(3) Because of 1 and 2, handling of these agents on the wards is considerably reduced, as dry powders are rarely dispensed. The pharmacy service is currently reconstituting 98% of all intravenous cytotoxic agents prescribed.

(4) Dispensing preloaded syringes has three main advantages:

(a) Minimum handling by the doctor is required before these agents can be administered to the patient.

(b) The risk of accidental overdosage is eliminated as the exact patient dose is dispensed.

(c) Much money previously wasted may be saved.

(5) A considerable amount of house officers' time is saved as

FIG 6—Number of intravenous cytotoxic doses prepared each month from January 1979 to September 1981.

the pharmacy has assumed responsibility for the dispensing and presentation of these agents. Questionnaires issued to all house officers using the service asked them to indicate whether they considered the service to be (a) essential, (b) useful, or (c) superfluous. All replies indicated that the user considered the service to be essential.

(6) Since the appointment of a full-time basic grade pharmacist few reconstituted cytotoxics are wasted. Returned syringes are reused whenever possible, and several patient doses can be removed from one vial. It is estimated that £5000 (from a total bill of £47 500 a year for intravenous cytotoxics) is being saved due to the more efficient method of dispensing.

(7) It has been found useful to have a member of the pharmacy staff with a special interest in and knowledge of cytotoxic drugs. Liaison between medical staff and pharmacy has been greatly improved. Newly available agents have been swiftly and safely introduced into clinical use because of the pharmacist's special access to the drug manufacturers and link with the regional drug information service. The same links have allowed rapid resolution of any difficulties.

(8) Having a member of the pharmacy staff specially interested in cytotoxic drugs has allowed drug usage to be monitored and likely future demands anticipated. Owing to the increased efficiency medical staff have participated more readily in multi-centre clinical trials, which in the past they might have been reluctant to do because of the expected demand on medical time.

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Cytotoxic reconstitution work sheet							
Patient _____		Ward _____		Doctor _____			
Date required _____		Time required _____					
Cytotoxic agent	Prescribed dose	Stan conc	Vol req	Pack size	Diluent	Vol used	Batch No
Adriamycin		2mg/ml		10mg 50mg	5ml WFI 25ml WFI		
Cisplatin		1mg/ml		10mg 50mg	10ml WFI 50ml WFI		
Cyclophosphamide		20mg/ml		100mg 200mg 500mg 1gram	5ml WFI 10ml WFI 25ml WFI 50ml WFI		
Dactinomycin		0.5mg/ml		0.5mg	1ml WFI		
Doxorubicin		5mg/ml		20mg	4ml WFI		
5-Fluorouracil		25mg/ml		250mg	10ml		
Methotrexate		25mg/ml		25mg	1ml, 50mg/2ml, 250mg/10ml		
Mitomycin C		6mg/5ml 30mg/30ml		2mg x3 10mg x3	5ml WFI 30ml WFI		
Mustine		1mg/ml	Dry	10mg	10ml WFI		
Vinblastine		1mg/ml		10mg	10ml Diluent		
Vincristine		0.2mg/ml		1mg 2mg	5ml Diluent 10ml Diluent		
Vindesine		1mg/ml		5mg	5ml Diluent		
Other cytotoxic drugs supplied from dispensary (inc TIA's)							
Busulphan _____				Folic Acid _____			
CCNU _____				Melfalan _____			
Chlorambucil _____				Procarbazine _____			
Cytosine Arabinoside _____				Thioguanine _____			
Prescription checked by _____				Method checked by _____			
Raw materials checked by _____				Prepared by _____			
Final check by _____				Entered into regime file by _____			

FIG 5—Cytotoxic reconstitution work sheet.

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Lesson of the Week

Acute tuberculous lymphadenopathy in an immunosuppressed patient

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Patients who receive immunosuppressive drugs for non-malignant disorders develop mycobacterial infections more often than untreated individuals.¹ Active pulmonary tuberculosis has been found in patients with systemic lupus erythematosus (SLE) who are treated with high doses of corticosteroids.² We report on a patient with SLE who was receiving immunosuppressive treatment and presented with an acute tuberculous cervical lymphadenitis.

Case report

A 53-year-old woman was admitted with a two-day history of swelling in the left side of the neck and a one-day history of pain on swallowing. SLE had been diagnosed in 1960 and had mainly affected the skin and to a lesser extent the joints. She had been receiving prednisolone 15 mg daily and azathioprine 100 mg daily for several years with no problem. She was a smoker and had mild shortness of breath on exertion; there was no history of cough, sputum, night sweats, weight loss, or contact with tuberculosis.

The physical examination showed a large, erythematous exquisitely tender swelling of the left side of the neck, and vitiligo secondary to skin destruction related to SLE over the face (figure). Her temperature was 38°C and pulse rate 80 per min. Examination of the chest was normal. The results of investigations showed haemoglobin 11.3 g/dl; white cell count $5.7 \times 10^9/l$ ($5700/mm^3$), with a differential count of neutrophils 82%, lymphocytes 14%, and monocytes 4%; platelet count $233 \times 10^9/l$ ($233\,000/mm^3$). Many acid-fast bacilli were seen in a sample of fluid aspirated from the swelling in the neck. *Mycobacterium tuberculosis* was cultured from this specimen and was

Tuberculosis lymphadenitis in an immunosuppressed patient may be acute and resemble an acute pyogenic bacterial infection

The patient on the second day after admission to hospital, showing an erythematous swelling on the left side of the neck and skin destruction on the face.

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sensitive to streptomycin, aminosalicylic acid, isoniazid, rifampicin, thiacetazone, cycloserine, pyrazinamide, and prothionamide. A chest x-ray examination showed patchy diffuse consolidation in the right upper zone and a dense area of consolidation just below the left first rib with an area of possible cavitation. X-ray films of the neck showed no evidence