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Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children

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Background: The need to use unlicensed and off label drugs in children due to the lack of suitable, licensed formulations with appropriate prescribing information creates many problems on an everyday basis for healthcare professionals, carers and children.

Patients and methods: This prospective study was designed to examine the incidence and nature of unlicensed and off label prescribing, in paediatric oncology patients with acute lymphoblastic leukaemia and other malignancies. Inpatient and outpatient prescriptions were analysed for a 4-week period.

Results: All patients received at least one unlicensed or off label drug. Fifty-five per cent of prescriptions were licensed, 19% were unlicensed and 26% were licensed drugs used in an off label manner. Unlicensed preparations were used in 40% of prescriptions for cytotoxic agents, due to a lack of commercially available formulations suitable for the paediatric patient. These drugs included mercaptopurine and methotrexate which have been used in the treatment of paediatric leukaemia for many years, their efficacy having been demonstrated by on-going Medical Research Council trials.

Conclusions: It is disappointing that drugs, which are the mainstay of therapy for paediatric leukaemia and other malignancies, are unavailable in appropriate licensed formulations to facilitate their administration to children. This needs to be urgently addressed.

Key words: chemotherapy, children, leukaemia, off label, unlicensed

Introduction

When a new drug is discovered the pharmaceutical company involved must follow the drug licensing process. Evidence demonstrating that the drug is safe, effective and of high quality is submitted to the regulatory body. If the evidence provided is satisfactory then a marketing authorisation is issued. This allows the company to market the drug according to the specific details contained in the licence in terms of patients, ages, indications, doses, routes of administration, contraindications and warnings. Many drugs used to treat children are not licensed, that is, they are unlicensed drugs. These drugs have not been subjected to the scrutiny provided by the licensing process. Others are prescribed outside the terms of the marketing authorisation, this is termed off label prescribing; that is, in ways not approved by the regulatory bodies [1–5]. This may be in terms of the age of the patient, dose prescribed, route of administration or the indication which the drug is used for.

Twenty-five per cent of prescriptions in paediatric medical and surgical wards in UK hospitals are unlicensed or off label [2]. Forty-six per cent of prescriptions for children in hospitals across Europe are unlicensed or off label; 67% of these patients receive at least one unlicensed or off label prescription [4].

The situation is more pronounced in specialised areas. Ninety per cent of babies in neonatal intensive care receive unlicensed or off label drugs; 65% of prescriptions are unlicensed or off label [5]. Seventy per cent of children in paediatric intensive care receive unlicensed or off label drugs [1].

A US study reported 56% of oncology patients receiving at least one off label drug during their treatment [6]. This caused widespread problems of financial reimbursement by health insurers who would not pay for off label therapy, leading to a significant number of oncologists changing their preferred treatments for prevalent forms of cancer. Paediatric oncology is a specialised area with relatively low patient numbers, treated with complex drug regimes. This study aimed to explore the incidence, nature and implications of unlicensed and off label drug use in this patient population.

Patients and methods

Information was collected prospectively from prescriptions for all paediatric oncology inpatients and those seen as outpatients at the Queen's Medical Centre, Nottingham, UK, over a 4-week period. Details recorded included the following: the patient's hospital number, date of birth, weight, surface area, diagnosis, drugs administered, formulation, date and route of administration,

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dose, frequency and indication for use. As in previous studies [2], the use of the following drugs was not recorded: standard intravenous replacement solutions, flushes of sodium chloride 0.9% or heparin to maintain the patency of intravenous and arterial lines, blood products (other than albumin), topical local anaesthetic agents and oxygen therapy.

All prescriptions were analysed to determine whether they were used in a licensed, unlicensed or off label manner. A classification system described and used in previously published studies was used [7]. A course of a drug, or a drug given as a single one-off dose was termed a prescription episode.

The primary reference source used was the current Data Sheet Compendium produced by the Association of the British Pharmaceutical Industry (ABPI) [8]. Alternative sources of information included the package insert, and the British National Formulary [9] since most information in these sources conforms to that in a drug's licence. The paediatric drug reference book *Medicines for Children* also provided useful information [10]. The manufacturer of the product was contacted where information was unavailable or ambiguous.

Results

Data were collected for 51 patients. Twenty-eight patients (55%) were being treated for acute lymphoblastic leukaemia (ALL). Eight patients (16%) were undergoing treatment following relapsed ALL. The remaining 15 patients had other diseases including neuroblastoma (3), non-Hodgkin's lymphomas (5), osteosarcoma (2), retinoblastoma (2), Wilms' tumour (2) and rhabdomyosarcoma (1). The median age of the children was 5.3 years (0.6–16.3 years).

The patients received a total of 569 prescription episodes with the median number of prescriptions being 10.5 (range 2–32) per patient; 76 different drugs were given. All patients received at least one unlicensed or off label medicine. The maximum number of unlicensed and off label drugs prescribed for a single patient was 13. Fifty-five per cent of prescription episodes were licensed medicines used in a licensed manner, 19% were unlicensed, 26% were off label. Table 1 shows the overall license status of prescriptions and highlights cytotoxic drugs in further detail.

Unlicensed prescriptions

Categories of unlicensed prescriptions identified include the following.

Modifications to licensed drugs. Eighty-nine prescriptions (16%) were medicines prepared by modifying licensed products. Eighty-four of these were cytotoxic preparations involving mercaptopurine, methotrexate, thioguanine and etoposide for oral administration. This was necessary when the drug was only available commercially as a solid dose form (i.e. a tablet or capsule) or an injection. An oral suspension was needed for a child to be able to swallow the drug, or to provide a preparation for administration of a paediatric dose. These were prepared in the pharmacy department of the hospital. Techniques involved crushing tablets, opening capsules and removing the contents or withdrawing the contents of an injection vial. The resulting powder or liquid was mixed with a suitable suspending agent to produce a liquid formulation. This manipulation of the original licensed product produced an unlicensed preparation.

'Special' formulations of licensed drugs. The remaining 17 unlicensed drugs were 'special' formulations of drugs produced on a 'named patient' basis by pharmaceutical companies. The majority were low strength tablets of mercaptopurine and thioguanine to facilitate administration of a paediatric dose. Such formulations have not been subjected to the licensing process, have not undergone clinical trials and are therefore unlicensed.

Forty per cent of cytotoxic prescriptions involved the use of an unlicensed formulation.

Off label prescriptions

Categories of off label drugs identified included those administered to patients of different ages, in different doses, by alternative routes and for indications not included in the licence.

Table 1. License status of prescriptions

License category	No. of prescription episodes (% total) (n = 569)	No. of cytotoxic agent prescriptions (% cytotoxics) (n = 240)
Licensed	314 (55)	126 (53)
Unlicensed		
Modification in pharmacy	89 (16)	84 (35)
'Special' formulation	17 (3)	13 (5)
Off label[a]		
Dose	119 (21)	12 (5)
Age	39 (7)	18 (8)
Indication	7 (1.2)	2 (1)
Route	2 (0.4)	0 (0)

[a]Some drugs were off label for more than one reason, therefore totals are greater than 100%. Many of the drugs were prepared in the pharmacy aseptic services unit and presented to the ward as ready to administer dose forms. These are officially unlicensed preparations but have not been classified as such, since this reflects good pharmaceutical practice rather than being a direct consequence of unlicensed and off label prescribing.

Off label dose. One hundred and nineteen prescription episodes (21% of total prescriptions) were off label in terms of the dose prescribed. Thirty-two episodes were due to co-trimoxazole being prescribed for prophylaxis of *Pneumocystis carinii* pneumonitis on a three times weekly basis on Mondays, Wednesdays and Fridays. The licence states that administration should be on consecutive days.

Twenty-seven off label doses were for ondansetron. They were off label because the prescribed doses were different to those licensed, and the intravenous route was used more frequently than recommended in the licence.

Other examples include higher than licensed doses of nystatin suspension as prophylaxis against candidal infection, in accordance with UK Children's Cancer Study Group (UKCCSG) recommendations. Higher than licensed doses of gentamicin were required in order to achieve therapeutic serum concentrations.

Off label age. Thirty-nine prescriptions were off label for age because paediatric use is not licensed. Examples include etoposide and carboplatin, widely used in a number of UKCCSG trials. Other common examples include chlorphenamine injection, ranitidine injection, cyclizine injection and amiloride solution.

Off label indication. Seven prescriptions were prescribed for off label indications. These included cisplatin for osteosarcoma; this is not a licensed indication despite being advocated by UKCCSG protocols. Other examples included lorazepam being used to treat anxiety and insomnia, cyclizine injection to treat chemotherapy induced nausea and vomiting and trimeprazine used for insomnia. None of these indications are included in the licence.

Off label route. Two prescription episodes were off label in terms of the route of administration. Hydrocortisone injection was administered intrathecally, although the licence recommends intravenous and intramuscular administration.

Table 2 details the drugs prescribed and their license status. Unlicensed and off label prescribing in relation to patient age is shown in Table 3. Although patient numbers are small, the use of off label drugs seems to be more pronounced in children under 12 years of age. The use of unlicensed medicines appears to be higher in the older patient group.

Discussion

A limitation of the study is the patient population. The majority of patients were being treated for ALL. Other malignancies were seen in 29%, giving an insight into unlicensed and off label prescribing in non-leukaemic malignancies. No brain tumour patients were seen in the time period studied but it is likely that a

Table 2. Unlicensed and off label prescriptions according to drug class

Drug class	No. of prescriptions (% total) (n = 569)	No. of unlicensed prescriptions	No. of off label prescriptions[a]
Cytotoxic	240 (42)	97	32
Antibiotic	99 (17)	0	57
Antifungal	17 (3)	0	10
Antiviral	4 (0.7)	1	0
Anti-emetic	49 (9)	0	33
Corticosteroid	48 (8)	0	2
Analgesic	47 (8)	0	5
Laxative	13 (2)	0	3
Electrolyte supplements	12 (2)	2	0
Sedative	6 (1)	1	5
Antihistamine	6 (1)	0	5
Diuretic	5 (0.9)	2	5
Antacid	4 (0.7)	0	4
Folinic acid	4 (0.7)	1	1
Allopurinol	3 (0.5)	2	0
Urokinase	3 (0.5)	0	1
Salbutamol	2 (0.4)	0	0
Emollient	2 (0.4)	0	0
Antitussive	2 (0.4)	0	1
Sucralfate	1 (0.2)	0	1
Filgrastim	1 (0.2)	0	1
Gabapentin	1 (0.2)	0	1

[a]Some drugs were off label for more than one reason.

Table 3. Unlicensed and off label prescriptions according to age group

Age group	Total no. of prescriptions	Unlicensed prescriptions		Off label prescriptions		Licensed prescriptions	
		n (reason)	% Total for age	*n* (reason)	% Total for age	*n*	% Total for age
28 days –23 months (*n* = 2)	22	1 (special)	5	6 (dose) 1 (age)	31	14	64
2–5 years (*n* = 24)	282	3 (special) 49 (modified)	18	57 (dose) 21 (age) 2 (indication) 1 (route)	28	151	54
6–11 years (*n* = 18)	215	6 (special) 33 (modified)	18	47 (dose) 15 (age) 5 (indication) 1 (route)	28	117	54
≥12 years (*n* = 7)	50	7 (special) 7 (modified)	28	9 (dose) 2 (age)	8	32	64

NB. Prescriptions could be off label for more than one reason.
'Special', 'special' formulations of licensed drugs produced by a pharmaceutical manufacturer.
'Modified', modifications to licensed drugs by the pharmacy department.

similar situation would be seen. The treatment regimes often include etoposide and carboplatin, which are not licensed in children, as seen above, and cisplatin which is not licensed for use in brain tumours.

Sixteen per cent of prescriptions required the pharmacy department to modify commercially available products in order to provide a preparation which the child could swallow and suitable to deliver the paediatric dose. The majority of these were oral cytotoxics, such as mercaptopurine, methotrexate, thioguanine and etoposide. These agents have been the mainstay of treatment for ALL since 1980 and are likely to remain so. It is disappointing that formulations suitable for children have not been licensed in all these years. Acute lymphoblastic leukaemia is the commonest childhood cancer with approximately 600 new cases each year in the UK alone. As treatment is required for 2 or 3 years, sustained use of such preparations is guaranteed; lack of demand would therefore not appear to excuse this omission on the part of the pharmaceutical industry.

Compliance with therapy is of major importance in these patients. Acute lymphoblastic leukaemia maintenance therapy involves taking a complex regime of drugs for either 18 or 30 months. Non-compliance has been suggested to be a major factor contributing to the 20–30% of ALL patients in the UK who relapse unexpectedly months or years after completion of treatment [11]. Many factors are known to influence compliance; the availability of palatable, easy to administer paediatric preparations can only help [12]. Preparations produced in the pharmacy department are limited in terms of palatability and stability due to a lack of information regarding appropriate flavouring and preservative agents. The resulting suspensions are often unpleasant to take and have short shelf lives.

Improvements in written information is sought on a national scale by providing patient information leaflets (PILs) with prescription medicines as these are known to improve patient satisfaction and knowledge [13]. The drug company PIL reflects the licence for the drug. The use of unlicensed drugs means that a PIL is unlikely to exist. For off label drugs, the PIL may provide inappropriate and confusing information. This potential avenue to improve compliance therefore becomes unavailable.

The manipulation of cytotoxic drugs in the pharmacy department is not without risk despite the precautions of protective clothing and use of vertical airflow cabinets currently employed. Infertility and miscarriage have been associated with cytotoxic drug handling in nursing and pharmacy personnel [14, 15]. This could be more safely done by the pharmaceutical industry with their superior facilities and resources to protect the personnel involved.

'Special' formulations of drugs, such as low strength tablets of mercaptopurine, are a preferable alternative to pharmacy preparation of liquids for children who can swallow small tablets. They facilitate administration of the low doses small children require. In addition, they allow fine-tuning of doses in accordance with clinical trial recommendations. Unfortunately, the manufacturer has discontinued their supply together with other low strength cytotoxic tablet formulations [16, 17]. This decision was made without consulting the medical and pharmacy professions involved in the care of these children and is disappointing. Guidelines issued jointly by the ABPI and the Department of Health make recommendations for the timescale and conduct of notification of product discontinuations. These may reduce the risk of this situation being repeated in the future [18].

Off label use was most common with antibiotics and antiemetic agents. Prescribing of ondansetron was based on recommendations from an established paediatric dose reference [19]. The licence recommends in children a single intravenous dose of 5 mg/m^2 followed by 4 mg orally twice daily. Many children require more than one intravenous dose due to being unfit to tolerate oral medication; this is off label. Doses were needed three times daily as the children were not controlled with twice daily dosing; this was also off label.

Many paediatric dose reference sources are available, most written by hospitals reflecting local practice and experience rather than sound, scientific evidence. They have been essential to paediatric healthcare professionals for many years due to the lack of licensed drug information but often offer conflicting advice. This situation has improved since the publication of the peer reviewed book *Medicines for Children* [10]; however, this is no replacement for information based on controlled clinical trials in the paediatric population.

Off label use of drugs in terms of age involved several drugs. Despite etoposide and carboplatin having been recommended in UKCCSG national trials for many years, the manufacturers state that "safety and effectiveness in children have not been established" and "specific dose recommendations for use in children and infants cannot be made due to insufficient use in paediatrics at this time" [8].

Every patient received between 1 and 13 unlicensed or off label drugs. This does not imply that such prescribing is anything but appropriate. The majority of patients are treated in trials and are closely monitored, treatment is centrally co-ordinated and long-term follow-up is carried out. Data are regularly reviewed and treatment protocols amended. Such trials have been successful in improving the prognosis for children with malignancies. They are the best way of addressing dilemmas such as the problems of chronic toxicity and late sequelae, which tend to be of less concern when treating adult malignancies [20].

The pharmaceutical industry should have access to the information generated by these trials, as a means of licensing their products for use in children. In return, they should produce stable, palatable formulations of drugs in strengths appropriate for the safe administration of children's doses with suitable patient information to support their use.

Highest use of off label drugs in the under 12-year-old age groups is to be anticipated. Many manufacturers consider children over 12 years of age to be adults and therefore would apply adult dose guidelines to these patients. The higher proportion of unlicensed prescriptions in this age group suggests that this is an incorrect assumption. Many of these patients are not able to take adult designed formulations, and therefore require modifications to licensed medicines or 'special' formulations to provide drugs that they can take and that are appropriate to their dose requirements. There is much discrepancy between age classifications and corresponding dose recommendations in paediatric drug licences. Age groups seem to be arbitrarily chosen and vary between manufacturers. This has been addressed in two notes for guidance containing international agreement on age classifications, which the pharmaceutical industry should follow [21, 22].

Increased awareness of the problems caused by the lack of appropriate paediatric dose information and suitable preparations for administration of medicines to children is gradually stimulating change. In the US, the Food and Drug Administration Modernisation Act (FDAMA) was introduced in 1997 [23]. This provided economic incentives in the form of 6 months extension of existing patent protection on drugs for which the manufacturer conducted paediatric studies in accordance with the Act's requirements. The FDA strengthened this action with the Final Rule in 1998 [24]. This legally requires that manufacturers of certain new drugs conduct studies to provide adequate labelling for their use in children. Such drugs include those likely to be used in a substantial number of children, or those offering a 'meaningful therapeutic benefit' to children over existing treatments. The effects of this legislation to January 2001 have done much to generate clinical studies and useful prescribing information for children [25].

The US National Institute of Child Health and Human Development has provided funding to establish a Paediatric Pharmacology Research Unit Network [26]. Collaboration between the research units making up the network, the FDA and the pharmaceutical industry is encouraged, the primary objective being to increase the number of drugs licensed for use in children until all drugs used for children are licensed.

In September 1997 'European Guidance on Clinical Investigation of Medicinal Products in Children' was published [21]. This provides useful advice to the pharmaceutical industry regarding when and how drugs should be tested in children. The document carries no legislative power, and a recent study suggests that it is not having a significant effect [27]. However, in December 2000 the European Union Council recognised paediatric medicines as a high priority and invited the regulatory body to identify measures to ensure that children have access to medicines that have been shown to be suitable for their use. This resulted in the publication of a consultative document 'Better Medicines for Children' which has been written with the aim of improving the availability of suitable medicines for children [28]. It is hoped that this will result in legislation and other action to improve the situation in Europe.

The licensing process offers the best reassurance that medicines are safe, effective and of a high quality. Unlicensed medicines and those used in an off label manner are not supported by the reassurances this system provides. Co-operation between the pharmaceutical industry, regulatory authorities, healthcare professionals and parents/carers involved in the care of paediatric oncology patients is essential, and urgently required, in order to end this denial of children's rights to safe and effective, high quality drug therapy.

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