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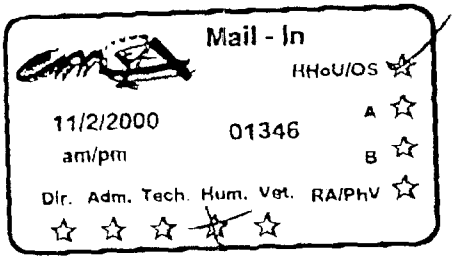
7 February 2000



→ Leng Heng
(Jassu Kat
is for you)
HD 14-02-00

R Bass
ICH Technial Coordination
7 Westferry Circus
Canary Wharf
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Dear Sir/Madam

We are grateful for the opportunity to make comments on this draft consensus guideline, the timing of which we welcome. We recognise the major problem of insufficient data to guide rational and evidence based prescribing in children. We consider that unless both positive incentives to test are given and failure to test is penalised, the current unsatisfactory state of affairs will never be rectified. We recognise that ethically adult data will be obtained first in all but drugs that are irrelevant to the adult population, for example growth stimulants. With regard to point 2.1, although in theory paediatric studies should not delay completion of adult studies, if a licence is granted for adults without strings attached such that paediatric data are also rapidly obtained, then there will be no incentive as at present, for the drug companies to obtain paediatric data. We are concerned by talk of "paediatric studies should be flexible" (point 2:3) because flexibility is often an excuse for inertia. With regard to (2.3.3), it is all very well to say that more studies would be expected after marketing, but unless these are funded they simply will not happen. With regard to 2.4.4 "Post marketing experience", we need to be very careful indeed that we do not rely on second class data that we would never dream of accepting in the adult population in order to inform paediatric prescribing.

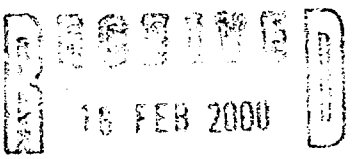
There are a number of practical points that need to be considered with regard to drug studies in children. End points have to be non-invasive and very different and may require techniques, for example the interrupter technique rather than the more direct FEV1. The need for one or twice daily formulation in order to obviate the need for teachers to give medications is also something that needs to be stressed. There are particular difficulties with regard to adolescents and pregnancy since many adolescents are sexually active and the subject needs to be approached very sensitively. A negative pregnancy test neither excludes pregnancy at the time it is taken nor excludes the possibility of pregnancy during the study.

You may be interested by an article written by one of us published recently in Clinical Research Focus, enclosed photocopy for your interest as well as European Study published in the BMJ (photocopy enclosed).

We hope these comments are taken in a constructive spirit. We welcome the initiatives being taken and would be happy to contribute further if that would be of value.

Yours sincerely

Dr Andrew Bush MD FRCP FRCPCH
Reader & Honorary Consultant in Paediatric Respiratory Medicine



Ms Jane Lamprill
Research Sister – Respiratory Paediatrics

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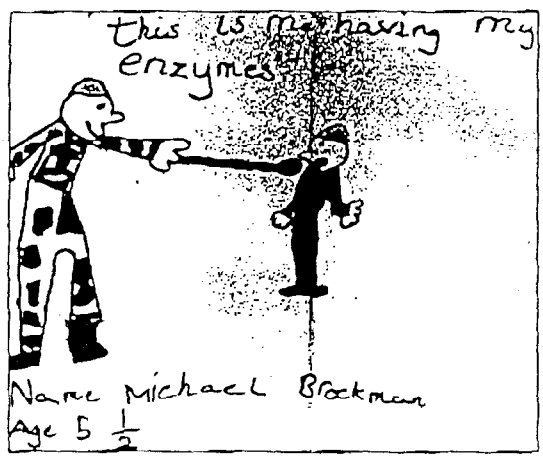
Trials of Paediatric Medicines

Jane Lamprill reviews an area that has been receiving increased attention recently - clinical trials and prescribing for children.

A seven year old boy, very keen to take part in an asthma study, carefully wrote his name in best joined-up writing beside his mother's on the consent form. Unfortunately, he signed as his football hero Peter Schmeichel, then burst into tears when we asked for his proper name. So we had a consent form with a pretend name on it, which the child wanted to use as his name, but which was also someone else's real name. Hello auditors!

The joys of working with children...and the trials? There has been debate in the recent academic press and media concerning medicines given to children which are off-label, off-licence and often without pharmacokinetic or safety data for the age group because clinical trials have not been done[1,2,3,4,5].



Michael taking his enzymes. Many children with cystic fibrosis cannot digest fat properly and need to swallow several capsules of enzymes before meals.

There are clearly potential safety and legal problems facing paediatricians and GPs who lack such prescribing information. Children are not small adults and errors can occur when adult drug dosages are adapted for paediatric use. Doctors are now often faced with intelligent, assertive parents wanting to be assured of safe treatment for their child.

However, there are significant obstacles to performing studies in children. Drug companies have to justify expensive paediatric trials to shareholders for relatively small financial returns compared to the adult market. These trials are subject to time consuming recruitment delays and fraught with ethical and practical difficulties.

How can this problem be tackled constructively and beneficially for all concerned? This article seeks to discuss some of the issues, link ethical considerations to practical advice about running paediatric trials and update as far as possible on the steps taken to remedy the situation.

What's the score?

Evidence from the Royal College of Paediatrics and Child Health (RCPCH, formerly British Paediatric Association) and the Association of the British Pharmaceutical Industry (ABPI)[6] given to the Government's 1997 Health Committee[7] caused ministers to be 'deeply concerned' and 'shocked that this situation existed, and we imagine most members of the public would share our reaction'. The anxiety was that many medicines for children are given 'in a route, formulation or dosage which has not been approved by the Medicines Control Agency' (MCA). The Department of Health confirmed to them that some paediatric medicines were not even licensed for human administration.

On the other hand, the MCA told the Committee that no evidence is known to them that 'any children have suffered harm as a result of a lack of child-specific testing and licensing'. This is possibly true, but one has to ask if the systems for reporting adverse events in children are adequate[1].

There are guidebooks on paediatric prescribing[8] compiled by paediatricians, based on years of clinical experience. 'Good doctors use both individual clinical expertise and the best available external evidence *and neither alone is enough*'[9] (my italics). But what do they do when no external evidence is available?

Randomised, controlled clinical trials have not been done on 90% of medications used in a Midlands neonatal Intensive Care Unit[2]. Paediatric dose calculations are usually based on body weight, or surface area, but without drug excretion data the timings may be too frequent and cause accumulation and toxicity, as neonates and babies have immature livers and kidneys. Alternatively, the very fast basal metabolic rate of older children may break down the drug too quickly, so efficacy is lost.

The Paediatric Vade-Mecum[8] states that 'dosage schedules are being constantly revised and new side effects recognised' and the reader is 'strongly urged' to refer to drug company instructions before administering any drugs mentioned. However, usually, no such evidence-based guidelines exist and children 'remain therapeutic orphans'[1].

It is interesting to note that Multicentre Research Ethics Committees are not required to include either a paediatrician or a parent. This is surprising, as the Office of Health Economics cites the prediction that in 2001 there will be 15.37 million people aged 19 and under in the UK[10]. This represents approximately 25% of the near future population who will not have a voice concerning critical health issues that affect them.

Paediatric clinical trials are not easy, but, if handled properly, can bring benefit for the drug company, investigator and, most importantly, the children and their parents. If industry and health professionals cannot find a way forward together, it is a near certainty that one will be imposed by the regulatory authority, almost certainly less satisfactory than one achieved by consensus.

Running paediatric trials

Ethics

Is it ethical to perform clinical trials in children?[11] Is it ethical not to and thus deny children the benefit of optimum treatment, or worse still, cause harm from unpredicted adverse events because trials have not been done?[1]

The main paediatric concerns for ethics committees are invasiveness of procedures, minimisation of risk and distress, and understanding informed consent.

Invasiveness

Pharmacokinetic studies require blood, but great care should be taken not to precipitate needle phobia, which could detrimentally affect all subsequent hospital visits[12]. Local anaesthetic cream and distraction should always be used. Better still, take the blood if the child has to have a cannula for clinical reasons anyway. Alternatively, blood can be taken under general anaesthetic during another procedure. Are there alternative, less invasive techniques such as urine, saliva or breath analysis? Note that neither children nor parents can give consent for a child to undergo any procedure that entails more than minimal risk for research purposes.

Natalie prepares to do an exercise test on the running machine. Note patches of local anaesthetic cream under transparent film on her arms, to prevent pain from venepuncture.

Table 1: How Paediatric Investigators can help drug companies

Pre-trial planning

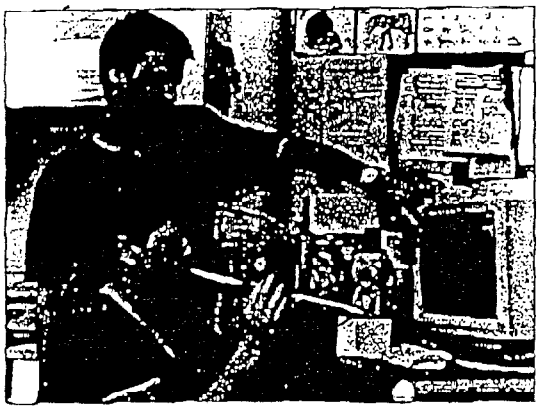
- Ensure a safe, child friendly environment with easy access to emergency equipment.
- Children cannot be paid to take part, so how will you give indirect incentives that are ethical? (making studies fun, giving an opportunity for education eg class project about disease area).
- Familiarise yourself with general principles of Good Clinical Practice (GCP) that drug companies must adhere to, especially CPMP paediatric guidelines[12].
- Don't do the study just for the money. How will it benefit the child?
- Paediatric studies are complicated to plan. Allow plenty of time for pre-study meetings to facilitate a smoothly run project.
- Screening failures can be higher in paediatric trials so be realistic about potential numbers of children.

During Study

- Tell parents/guardians to store drugs safely at home or away, out of reach of pets or other children.
- If medicine taken at school (eg asthma reliever) write to teacher about safe storage to prevent rest of class sharing the experience.
- Recruitment can be slower with children but remember time is money for drug companies. Slow studies can affect time to market and share price.
- Collaboration with other paediatric centres regarding recruitment techniques is very helpful.
- School holidays are a blessing and a curse. If it's a summer study, ring round parents early to establish when they are likely to be home or away to facilitate mutually convenient visits.

Safety and comfort

The Committee for Proprietary Medicinal Products (CPMP) states that 'every effort must be made to reduce known hazards,' and the Investigator must be aware of 'all relevant pre-clinical and clinical toxicity,' with trials carefully designed to minimise subject numbers and invasive procedures. They also recommend minimisation of distress and that only those experienced in working with children should perform such studies[13].



Natalie and Dr Payne demonstrating an exhaled nitric oxide (NO) machine. This is a non-invasive measure of airway inflammation. The dog's ears flap and it plays a tune when the correct expiratory flow rate is achieved.

The RCPCH have published ethical guidelines for children's research as a helpful reference[14].

Informed consent

Neither young children nor babies have the capacity to make informed decisions[15]. This puts great responsibility on the investigator and study site co-ordinator to ensure an explanation appropriate to age and maturation is given to parent and child, emphasising that the child need not fear disapproval if they change their mind and can withdraw from the study at any time.

Children's understanding of illness and hospitals is very different from that of adults. It also cannot be assumed that parents 'perception of their child's response will accurately reflect the child's feelings and needs'[15]. This can cause conflict if a child is growing towards autonomy: the parents may think taking part in a study is good for their child, but the young person may not want to participate.

Consent forms and information sheets need to be in clear language that is appropriate to the child's age and level of development. This can be tricky if the recruitment age is 6 to 18 years, necessitating junior and more advanced information sheets to satisfy both regulatory requirements[17] and the young peoples' need to fully understand their potential involvement in the study.

Living in the real world

Formulation and dosage need to be thought through carefully. Little children can be extremely wriggly and distressed when unwell. The practicalities of administering medication are just as important as the dose and formulation.

Oral drugs require easy administration, using a standardised measuring syringe. But it will not make any difference if the child spits it out because it tastes disgusting! Therein lies the dilemma, since it must not taste too nice either, or the child may take a swig in a quiet moment. Artificial sweeteners, additives and colourings may make some children hyperactive. For trial purposes, therefore, the liquid base needs to be the same in the placebo as in the active drug in case of reactions.

The British Dental Association recommends the use of sugar-free liquid medicines[18]. Salivation is reduced during sleep, so bedtime medicine can linger around the teeth causing decay. A parent will not want to have to ask a fractious child to clean his teeth again once settled!

Once or twice daily dosing is helpful, as many children are now cared for during the day by

Table 2: How drug companies can help paediatric investigator sites

Pre-trial planning

- Contact investigator at early planning stage; don't present them with an unworkable final protocol!
- Talk to a paediatric pharmacist early about formulation, packaging and labelling.
- Don't adapt an adult CRF: children are not small grown-ups.
- If possible, no blood tests. Keep invasive measurements to a minimum.
- Be as generous as ethically possible with travel and meal allowance for families giving up their time to help you, as they cannot be paid to take part.
- Provide a little rucksack to keep drugs and equipment together.
- Make diaries durable and child friendly eg with pictures.
- Ensure easy drug administration with clear instructions in big writing.
- Parents are busy and may have other children and commitments. Allow flexible time windows between visits.
- Longitudinal studies need to allow for growth on the case record form, especially since height is an indicator of lung function and dosage is often based on weight.
- A major reason for parent refusal is interference with the child's education. Timings need to be flexible to allow after school or weekend visits.
- Children do not tolerate long clinic visits - will you provide a television?!

During Study

- Always have staff available familiar with the study if the CRA is away, for urgent queries eg if child exhibits borderline entry criteria at screening. Children will not wait.

others. A child will take medicine more reliably and easily from its parents/guardians than from a succession of different staff. It can also be timed into the child's routine. Twice daily dosing can be done at home: children do not want to appear different from their peers and often feel singled out if they have to take medicine at school.

What do children feel about trials? Kathy Johnson's team at the Children's Mercy Hospital, Kansas City [19,20] surveyed 73 children aged 6-19 years who had participated in Phase I and II trials. Their results showed that 95% 'viewed participation as a positive experience'. 41.4% participated to help other children, 31.4% for age-related incentives (not allowed in UK), 12.9% thought it would be fun, 11.4% were seeking a 'unique experience' and 2.8% did not know why they helped. When asked about the worst moments, 28% did not have any, 23.8% did not like needles and 11.1% disliked the blood test. Other unpleasant things were horrid-tasting medicine and interruption of diet, sleep and normal routine.

A good team

The secret of success in paediatric trials is a good working partnership and strategy between drug company and investigator(s). Ways of ensuring a successful trial are suggested in Tables 1 and 2.

Good team; where are the supporters

Hart & Chesson[16] cite the 1991 Kings Fund report that states that children account for 25% of GP consultations and 30% of staff time in Accident and Emergency[21]. 'However, their needs are given insufficient priority by policy makers and health service professionals.' But how long will the Government and public stand for this?

Trials cost money[22]. The US Food and Drug Administration (FDA) had the original idea of offering incentives to pharmaceutical companies to provide paediatric clinical trial data[23,24]. With Government backing, they are allowing a six-month patent extension on all drugs also licensed for children, thus making paediatric trials very profitable. From April 1999, US drug companies will have to provide detailed labelling information[24], which will bring to public attention companies that are not 'child friendly'.

Dr Vas Novelli, Consultant Paediatrician at Great Ormond Street Hospital for Sick Children (GOS) wonders why the UK Government is not doing likewise and has the backing of 36 Members of Parliament and the Consumers Association which is also lobbying Parliament[24].

At the January 1999 Paediatric Clinical Trial conference in London[20], Professor Aynsley Green, Head of Research and Development (R&D) at GOS, advocated a consultative and synergistic approach-that Government, Academia, Regulatory Bodies and the Pharmaceutical Industry work together instead of in isolation. He was a founder member in November 1998 of The British Forum for the use of Medicines in Children with Professor Vallance, also of GOS. The RCPCH has agreed a new children's clinical trials unit at Birmingham Children's Hospital, in conjunction with Birmingham adult trials unit and the University. Professor Taunton Southwood, head of R&D is leading the team and aims to improve the number and quality of clinical trials in the paediatric age group. Dr Oomti Choonara at the Derbyshire Children's Hospital has recently helped to set up a European network for drug information in children, in which there are currently ten paediatric centres.

The first UK National Paediatric Formulary was published in June 1999 by the RCPCH[25]. Its three sections cover:

a) therapeutic guidelines

b) monograph information concerning dosages and +/- licence applications for specific age groups, and

c) dietary information regarding the special nutritional needs of very sick children.

Other information will be forthcoming from Joan Perou of ACRPI who is putting together a national information sheet in conjunction with GOS.

The European guidelines are changing[13]. A common guidance document for Europe, US and Japan is currently in preparation by the International Conference on Harmonisation (ICH). Designated as 'ICH/E11', this draft guideline is currently available for consultation[26]. It will come into operation six months after its final adoption by the CPMP, the EMEA's scientific committee.

Conclusion: A shared goal

There will be overwhelming demands for well-conducted trials in children. Our young football fanatic mentioned earlier has no idea all this is happening on his behalf. Now is the time to collaborate towards a shared goal: to produce workable and practical proposals to rectify the present haphazard state of affairs. In fairness to ourselves, the families and above all the children, non-evidence based paediatric prescribing cannot be allowed to continue. ❑

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Acknowledgement

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Papers

Survey of unlicensed and off label drug use in paediatric wards in European countries

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Abstract

Objective To determine the extent of use of unlicensed and off label drugs in children in hospital in five European countries.

Design Prospective study of drugs administered to children in general paediatric medical wards over four weeks.

Setting Children's wards in five hospitals (one each in the United Kingdom, Sweden, Germany, Italy, and the Netherlands).

Subjects Children aged 4 days to 16 years admitted to general paediatric medical wards.

Main outcome measure Proportion of drugs that were used in an unlicensed or off label manner.

Results 2262 drug prescriptions were administered to 624 children in the five hospitals. Almost half of all drug prescriptions (1086; 46%) were either unlicensed or off label. Of these 1086, 872 were off label and 164 were unlicensed. Over half of the patients (421; 67%) received an unlicensed or off label drug prescription.

Conclusions Use of off label or unlicensed drugs to treat children is widespread. This problem is likely to affect children throughout Europe and requires European action.

Introduction

Many drugs used to treat children in hospital are either not licensed for use in children or are prescribed outside the terms of their product license (off label prescribing).[1 2] Examples of use of off label drugs include diazepam rectal solution in children under 1 year (not licensed for age group), amiloride tablets in any children (formulation), or rectal injection of lorazepam for a child with an acute seizure (route). An example of unlicensed use is the preparation of a suspension from a tablet by the hospital pharmacy.

Considerable concern exists within Europe[3] and the United States[4 5] about the use of unlicensed and off label drugs in children. There is, however, little information available on the extent to which these types of treatments are used. The extent of use of unlicensed and off label drugs in the United Kingdom has been medical and surgical wards,[2] and a neonatal intensive care unit.[7] We wished to determine the extent of unlicensed and off label drug use in several countries within the European Union. This is important in view of the new European guidance on the clinical investigation of medicinal products in children.[8]

Methods

We studied a paediatric medical ward in each of the participating centres (Derby, United Kingdom; Uppsala, Sweden; Marburg, Germany; Bergamo, Italy; Rotterdam, Netherlands) prospectively for four consecutive weeks during 1998. The wards in Derby and Bergamo admitted mainly general paediatric patients, with Derby including children who had had surgery. The wards in Marburg and Uppsala had a mixture of general paediatric and respiratory cases (including cystic fibrosis). The ward in Rotterdam had the fewest general paediatric cases, containing children with cardiac, oncological, renal, and respiratory disease. Data on all patients admitted to the ward were collected by the investigator in each centre. The child's age, date of birth, weight, and diagnosis were recorded as well as details of all drugs administered (route of administration, dose, and indication for use). We did not include standard intravenous replacement solutions, flushes of 0.9% sodium chloride or heparin, blood products, oxygen, or drugs in clinical trials.

We assessed all drugs administered to determine if their use was unlicensed and off label using a previously described classification system.[1 2] Categories of unlicensed use were modification of licensed drugs (such as crushing tablets to prepare a suspension); drugs that are licensed but the formulation is manufactured under a special licence (such as a liquid preparation of a drug that is licensed only in tablet form); new drugs available under a special manufacturing licence (such as caffeine injections for apnoea of prematurity); use of chemicals as drugs when no pharmaceutical grade preparation is available; drugs used before a licence has been granted; and imported drugs (drugs imported from a country where they are licensed). Off label use included use of a drug in

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Table 1 Number of patients and prescriptions in each centre

	Derby	Uppsala	Marburg	Bergamo	Rotterdam	Total
No of patients	192	87	85	118	142	624
Age range	21 days-16 years	4 days-15 years	28 days-16 years	30 days-12 years	4 days-16 years	4 days-16
Prescriptions	798	185	224	398	657	2262
Mean No of prescriptions/patient	4.2	2.1	2.6	3.4	4.6	3.6
No (%) of prescriptions unlicensed or off label	239 (30)	57 (31)	91 (41)	264 (66)	385 (59)	1036 (4
No (%) of prescriptions unlicensed	58 (7)	8 (4)	8 (4)	1 (0.3)	89 (14)	164 (7)
No (%) of prescriptions off label	181 (23)	49 (26)	83 (37)	263 (66)	296 (45)	872 (39
No (%) of patients receiving unlicensed or off label treatment	109 (57)	37 (43)	46 (54)	101 (86)	128 (90)	421 (67)

Table 2 Five most frequently prescribed drugs (% of all prescriptions) in each centre

	Derby		Uppsala		Marburg		Bergamo		Rotterdam	
Rank	Drug	%	Drug	%	Drug	%	Drug	%	Drug	
1st	Paracetamol	21	Paracetamol	22	Paracetamol	9	Beclometasone	12	Paracetamol	
2nd	Ibuprofen	10	Cefuroxime	8	Cholecalciferol	8	Dipyrone	8	Heparin	
3rd	Salbutamol	5	Salbutamol	7	Cefuroxime	7	Salbutamol	8	Amphotericin	
4th	Cyclizine	5	Ibuproten	6	Salbutamol	7	Paracetamol	7	Pancreatin	
5th	Morphine	4	Cotrimoxazole	5	Xylometazoline	5	Amoxycillin	6	Spironolactone	

Table 3 Five most frequently prescribed off label drugs in each centre

	Derby		Uppsala		Marburg		Bergamo		Rotterdam	
Rank	Drug	No*	Drug	No*	Drug	No*	Drug	No*	Drug	No
1st	Cyclizine	38/42	Salbutamol	13/13	Budesonide	10/12	Beclometasone	47/47	Heparin	28/2
2nd	Salbutamol	27/42	Paracetamol	13/41	Salbutamol	8/17	Salbutamol	28/32	Pancreatin	17/1
3rd	Morphine	26/33	Cotrimoxazole	4/10	Xylometazoline	8/15	Paracetamol	26/28	Spironolactone	17/1
4th	Ipratropium	15/15	Betamethasone	3/5	Paracetamol	7/20	Betamethasone	21/38	Frusemide	16/1
5th	Diazepam	13/13	Acetylcysteine	2/4	Chloral hydrate	5/5	Amoxycillin	18/23	Tobramycin	15/1

*Number of off label prescriptions/total number of prescriptions for drug in centre.

summary of product characteristics—that is, at a different dose or frequency, in different clinical indications, in different age groups, administration by an alternative route, or in a formulation not approved for use in children.

The primary reference sources for determining licensed indications were the *Association of the British Pharmaceutical Industry's Data Sheet Compendium* in the United Kingdom; the *Swedish Physician's Desk Reference 1998* in Sweden; the *Rote Liste 1996* and *FachInfo* compact disc (1997) in Germany; the *Informatore Farmaceutico 1998* (national formulary) and technical leaflets in Italy; and the *Repertorium 98/99* and *Farmacotherapeutisch Kompas 1998* in the Netherlands.

Results

A total of 624 children were admitted to the general paediatric wards in the five participating centres and received 2262 drug prescriptions (table 1). The prescribing habits in the five centres differed greatly. Paracetamol was the most widely prescribed drug and analgesic in four of the five centres. Dipyrone was frequently used in Italy only. Salbutamol and cefuroxime were both widely used (table 2). Almost half of all drug prescriptions (1036) were either unlicensed or off label (table 1). Many more prescriptions were off label (872) than unlicensed (164). The results were remarkably similar in Derby, Uppsala, and Marburg. Use of unlicensed and off label drugs was greatest in Bergamo and Rotterdam, which had the highest percentage of off label prescriptions (66%) and Rotterdam the highest percentage of unlicensed prescriptions (14%).

Over half of the children (421; 67%) received an unlicensed or off label drug prescription during their stay in hospital. Analgesics and bronchodilators were among the five most frequently prescribed off label drugs in four centres (table 3). The commonest category of off label drug use was dose and frequency in three centres (Uppsala, Marburg, and Bergamo) accounting for more than half of off label use. In the other two centres (Derby and Rotterdam) dose and frequency accounted for 31-32% of off label drug use. The main category for off label drug use in Rotterdam was formulation. Formulation was also an important category in Bergamo but not in the other centres. Age was the commonest category of off label drug use in Derby (table 4). Table 5 shows examples of off label drug use. In Bergamo 53% of the children who received beclometasone were under 12 months old although it is licensed only for children aged 2 years and over in Italy.

Discussion

The drug use in the five paediatric wards differed. This is not surprising as each of the wards had different subspecialty interest and prescribing habits are different within each country.[3] Unlicensed drug use was highest in Rotterdam, which had the highest number of patients with complex diseases. Many of these children

pharmacy department to make them suitable for administration to children. Stability data are rarely available for such products, which are rendered unlicensed by this modification. Dipyrone is no longer available in many European countries because of the risk of agranulocytosis.[10] It is, however, widely used in Italy. About half of the children in each of the five countries received drugs that are either unlicensed or off label.

It is concerning that most bronchodilator drug prescriptions for children in hospital with asthma are off label, since this is a common condition for which there has been considerable research. The efficacy of bronchodilators in children under the age of 2 years is variable, especially in infants under the age of 12 months. A particular problem was the widespread use of inhaled corticosteroids in children under the age of 2 years (off label for age and dose); few data exist on the effect of inhaled corticosteroids on growth suppression in this age group. Studies are required to determine whether the off label use of bronchodilators is justified by good scientific evidence.

The most common reasons for off label use were that the medicine was prescribed at a different dose or frequency, in a different formulation, or in an age group for which it had not been licensed. There were also some children who received the drug for a different indication or by an alternative route. It is ironic that it is children who are most likely to receive medicines that are either unlicensed or used off label since the regulations for the licensing of medicines were introduced after cases of drug toxicity in the developing fetus (thalidomide) and newborn infant (chloramphenicol induced grey baby syndrome).[3]

Not all off label drug use is inappropriate. Drug toxicity is more likely with aminoglycosides if they are used in neonates as recommended by the manufacturers at intervals of 8-12 hours rather than at longer intervals. In many cases, however, the risk of off label drug use is not known because there are inadequate data. A recent study has shown that adverse drug reactions are an important problem in children after unlicensed or off label drug prescriptions.[11]

Key messages

- Many drugs are not tested in children, which means that they are not specifically licensed for use in children
- Licensed drugs are often prescribed outside the terms of the product license (off label) in relation to age, indication, dose of frequency, route of administration, or formulation
- Over two thirds (67%) of 624 children admitted to wards in five European hospitals received drugs prescribed in an unlicensed or off label manner
- 39% of the 2262 drug prescriptions given to children were off label
- The problem of off label and unlicensed drug prescribing in children is a European problem that requires European action

Table 4 Number (percentage) of off label prescriptions in each category for five centres

Category	Derby	Uppsala	Marburg	Bergamo	Rotterdam
Dose and frequency	66 (32)	53 (88)	59 (61)	255 (58)	96 (31)
Age	79 (39)	1 (2)	23 (24)	33 (7)	18 (6)
Indication	36 (17)	4 (7)	7 (7)	25 (6)	13 (4)
Route	24 (12)	2 (3)	3 (3)	49 (11)	4 (1)
Formulation	0	0	5 (5)	80 (18)	176 (58)
Total	205	60	97	442	307

Table 5 Examples of off label drug use

Drug	Off label use
Beclometasone	Used in infants under 12 months. Licensed for 2 years and over in Italy
Fluticasone	250 µg twice daily in 4 year old. Maximum dose 100 µg twice daily
Trimeprazine	Used as sedative in child with pneumonia. Licensed for urticaria, pruritus, and pre-anaesthetic medication
Rifampicin	Used for enzyme induction in infant with biliary atresia
Salbutamol	Used two hourly (12 times daily). Licensed for 4 times daily
Tobramycin	Used once daily in neonate. Licensed for twice daily

Reducing the risk

The new European guidance on the clinical investigation of medicinal products in children encourages pharmaceutical companies that wish to introduce new products to investigate these in children when clinically appropriate. Changes have also been made in the United States to encourage pharmaceutical companies to carry out clinical trials in children. These changes in regulations may improve knowledge for new products, although a recent study found little improvement in new drugs licensed in Europe.[12] However, a major problem remains with many existing drugs commonly used in children. Health professionals concerned about the lack of information regarding the use of drugs in children are in a difficult situation. They need to raise awareness of the problem in society as a whole without causing undue anxiety among parents.

To ensure that children are not exposed to unnecessary risks, controlled clinical trials are required to determine the most appropriate dose in children of different ages. A mechanism and infrastructure needs to be established to determine who will fund these trials. The European Network for Drug Investigation in Children has been established to try to improve this situation.[13] We feel that the European Union, national departments of health, and politicians as well as the European Medicines Evaluation Agency must take a more proactive role in getting drugs tested in children. If they fail to do so, children will continue to be denied the same rights as adults in relation to receiving treatment with drugs that have been fully tested.

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Difficulties with anonymous shortlisting of medical schoo applications and its effects on candidates with non-European names: prospective cohort study

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Abstract

Objective To assess the feasibility of anonymous shortlisting of applications for medical school and its effect on those with non-European names.
Design Prospective cohort study.
Setting Leeds school of medicine, United Kingdom.
Subjects 2047 applications for 1998 entry from the United Kingdom and the European Union.
Intervention Deletion of all references to name and nationality from the application form.
Main outcome measures Scoring by two admissions tutors at shortlisting.
Results Deleting names was cumbersome as some were repeated up to 15 times. Anonymising application forms was ineffective as one admissions tutor was able to identify nearly 50% of candidates classed as being from an ethnic minority group. Although scores were lower for applicants with non-European names, anonymity did not improve scores. Applicants with non-European names who were identified as such by tutors were significantly less likely to drop marks in one particular non-academic area (the career insight component) than their European counterparts.
Conclusions There was no evidence of benefit to candidates with non-European names of attempting to blind assessment. Anonymising application forms cannot be recommended.

Introduction

In the United Kingdom there is huge competition to study medicine, with in excess of 13 000 applications through the Universities and Colleges Admissions Service for just over 4000 places. A series of recent studies has found that the likelihood of success is less among applicants from ethnic minority groups than among white applicants.[1-6] A study based on 1991 entry indicated that the situation was improving.[5] Even so, when seven other mainly academic aspects of the ethnic minority group remained a significant predic of success. A recent study looking at all ho applicants for entry in 1996 and 1997 found a gre disadvantage for applicants from ethnic mino groups than previously.[6] This study was, howe limited for technical reasons by not being able include data on GCSE grades, which form a large p of the selection process and which were impor predictors of success in previous studies.[5]

Most unsuccessful applicants are rejected solely assessment of their application form—that is, at 'shortlisting' stage before being invited for intervie is during shortlisting that students from ethnic mi ity groups are believed to be disadvantaged.[3] application form contains no explicit reference to applicant's ethnic background, so it seems likely any discrimination must be based on the applica name. For this reason it has been suggested that whole of the shortlisting process be performed anc mously.[6]

We decided to assess the feasibility of asses forms anonymously within the current admissions tem of the Universities and Colleges Admissions S ice. In addition, we assessed the impact of doing s the shortlisting system we have used at Leeds scho medicine for the past four years.

Methods

Shortlisting process

Our shortlisting process involves each applica form being assessed separately by two of three ad sions tutors (including AL). A score from zero t points is awarded made up of four components inc ing career insight (4 points), non-academic activiti points), academic profile (4 points), and suitability medical career as described by the confide reference (6 points). When assessing applicat admissions tutors are unaware of the other selec score. The sum of the two scores then forms the