SHORT REPORT

Supply problems of unlicensed and off-label medicines after discharge

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Arch Dis Child 2006;**91**:686–688. doi: 10.1136/adc.2006.093724

A total of 709 unlicensed and off-label medicines were prescribed for 338 patients discharged from a paediatric hospital between 1 November 2003 and 31 January 2004. Thirty three per cent of patients had difficulty obtaining these medications in primary care which caused treatment disruption. The main problems were: (1) community pharmacies being unable to supply; and (2) GPs' refusal to prescribe.

In the UK, a Marketing Authorisation (MA) granted by the Medicines and Healthcare products Regulatory Agency (MHRA) provides assurance that the medication has been evaluated for its safety, quality, and efficacy. However, due to various financial, ethical, and technical reasons, many medications have not been tested in children,[1] and hence are not licensed to be used in children. The use of a medication outside the characteristics stated by the MA is given the term ''off-label'', whereas ''unlicensed medicines'' are medicines without MAs. It is known that paediatric patients seen by a specialist paediatric hospital often experience difficulties in obtaining unlicensed and off-label medications after discharge. However, no previous study has been conducted to investigate this issue.

This study aimed to identify the availability of unlicensed and off-label medications for paediatric patients and their carers in primary care, after discharge from a specialist hospital, Great Ormond Street Hospital (GOSH) for Children, London.

METHODOLOGY

The discharge prescription forms of patients leaving GOSH, London between 1 November 2003 and 31 January 2004 were reviewed by VY to extract information on: the patient's date of birth, full name, hospital identification number, telephone number, medications, date of dispensing, and the date of discharge. The *British National Formulary* (BNF)[2] and Summaries of Product Characteristics[3] were used to classify medicines as off-label or unlicensed. Following this, structured telephone interviews were conducted with the families by NB to investigate the availability of unlicensed and off-label medication in primary care after discharge. A second interview was conducted with some GPs by VY to establish whether there was a specific reason why they did not prescribe for a child. Telephone interviews with carers and GPs were conducted between February and July 2004.

The study was approved by the Audit Department of GOSH in order to improve the pharmaceutical care of the patients. As a result ethical committee approval was not required.

RESULTS

During the study period, 1894 patients were discharged with 5976 prescription items. Twelve per cent (709/5976) of the medications prescribed were either unlicensed or off-label and were given to 338 of the paediatric patients. Fifty nine patients were excluded at this stage (2 with overseas addresses and 57 who did not have a telephone number).

A total of 279 patients with UK addresses and contact telephone numbers were categorised into four main divisions of age:[4]

- Neonates (less than 1 month); 5 patients
- Infants and toddlers (1–23 months); 121 patients
- Children (2–11 years); 107 patients
- Adolescents (12–18 years); 46 patients.

After the first telephone interviews, it was established that 40 carers did not provide the correct contact number, 11 patients were from overseas, 7 were deceased, and 5 were inpatients. Nine carers could not understand or speak the English language and had difficulty in answering the questions. Consequently 63 patients were excluded from the interview.

Seventy two of 216 carers (33%) reported problems in obtaining medications after being discharged. The results of the telephone interview are summarised in table 1.

Twenty six carers reported that their GPs had refused to prescribe the appropriate medication(s); in total 15 GPs participated in the second interview. One GP was on holiday and another carer did not provide the correct contact number for the GP. The remaining patients were prescribed readily available medication at the time of the study, hence there would not have been any problem obtaining these medications in general practice. Therefore the team decided to exclude these GPs from the study. Table 2 shows the medications that the GPs refused to prescribe to the 15 paediatric patients and the reasons for their refusal to prescribe.

DISCUSSION

At present, we are not aware of any published study that has investigated the availability of unlicensed and off-label medication to paediatric patients in UK primary care. This is probably the first study to investigate this systematically. This audit established that one third of the paediatric patients leaving GOSH face some difficulties in obtaining unlicensed and off-label medications in primary care. Unfortunately, some patients experienced disruption in their treatment; this could be life threatening. For example, one patient was prescribed tacrolimus for prevention of graft rejection following a heart transplant. Failure to obtain this medication could result in organ rejection; therefore it is vital that treatment is not disrupted.

Pharmacy problems

It is understandable that pharmacies do not want to keep stocks of such medications, particularly ''specials'' products which usually have a very short expiry date. However, it is surprising to find that a number of pharmacies were unable to obtain these medications due to various reasons, such as being unable to locate the appropriate manufacturers, or manufacturers unable to produce the appropriate formulations. Many

Table 1 Results of the telephone interviews of patients

Questions	Responses	No.
(1) Have you encountered any problem in obtaining your medicines after your child was discharged from GOSH? (n = 216 respondents)	Yes	72
	No	144
If the answer to question 1 is yes, then continue with questions 2–4		
(2) Where does the problem arise? (n = 72 respondents)	GP refuses to prescribe the appropriate medication(s)	26
	Local pharmacy does not keep stock of the medication	19
	Pharmacy unable to supply the correct formulation	19
	Other	8
(3) Was the treatment disrupted because of not being able to obtain the relevant medication(s)? (n = 72 respondents)	Yes	18
	No	54
(4) How long was the treatment disrupted for? (n = 18 respondents)	<1 day	1
	1 day	6
	2 days	3
	3 days	2
	4 days	1
	5 days	0
	6 days	0
	>7 days	5

unlicensed medicines are extemporaneous products or ''specials'' products and many of them have to be prepared by specials manufacturers. Sometimes it is necessary to import foreign medicines. The lack of awareness of the availability and the sources of unlicensed medications among community pharmacists is due to the restrictions imposed by the Medicines Act. This prohibits companies promoting unlicensed or off-label use of medicines; consequently, community pharmacists are sometimes unable to locate the manufacturers. Although a new EU ''Better Medicines for Children'' regulation will give manufacturers the incentive to develop more paediatric medicines for in-patent drugs,[5] it is unlikely to have any significant effects on the off-patent drugs. Therefore, the availability problems are unlikely to be resolved in the foreseeable future. Further studies in community pharmacies should be conducted to identify ways to improve the supply; however, it is important to involve the MHRA in any future studies.

Table 2 General practitioners' responses

Patient	Medication(s)	Reason(s) for refusal
1	Sodium Bicarbonate	F
2	Growth Hormone, Melatonin	A, C
3	Ciclosporin, Melatonin	C, E
4	Methotrexate	C, E
5	Tacrolimus, Sodium Bicarbonate, Sodium Chloride	C
6	Tacrolimus	B
7	Albendazole	C
8	Thalidomide	C
9	Bisacodyl enema	C, D
10	Octogam	A
11	Epoetin injection	A
12	Epoetin injection	A
13	Tacrolimus	E
14	Short chain fatty acid	A
15	Bosentan*	A, C

A = too expensive to prescribe.
B = outside the prescribing guidelines for general practice.
C = inexperienced in prescribing medication for paediatric patients.
D = do not wish to take on board the extra responsibility.
E = do not have the facilities to monitor the pharmacokinetics or carry out the appropriate tests for the medication.
F = not enough information concerning the drug.
*Bosentan should be supplied by the hospital; it is not clear why this carer requested the GP to prescribe it.

General practice problems

The reasons for refusal stem mainly from the fact that GPs feel they do not have the relevant experience or expertise to prescribe to paediatric patients, particularly some with complicated cases. These are important and valid reasons for refusal to prescribe. In order to resolve the above problems, it is essential that the GP has access to sound information on any medication that he or she is to prescribe or administer, including the availability of the medications themselves. Making the BNF for Children available to all GPs is an important step towards tackling the problems in prescribing for children.

Other GPs have claimed that the medications some paediatric patients have been prescribed are too expensive to issue in primary care. Some GPs have also refused to prescribe because they do not have access to the correct equipment to monitor the pharmacokinetics. The above problems could be resolved by improving communication and shared treatment protocols.

Limitations of the study

GOSH is known to deal with complex cases and frequently treats children with serious and rare conditions. Therefore the results may not be common to other non-paediatric hospitals. However, other specialist paediatric hospitals in the UK are likely to encounter similar problems.

Conclusion

Children discharged from a specialist paediatric hospital frequently encounter problems in obtaining their unlicensed and off-label medicines in primary care. The results are likely to be applicable to other specialist paediatric hospitals. It is important to identify ways to improve the availability of these medications in primary care.

ACKNOWLEDGEMENTS

The authors wish to thank the participating families and GPs who took part in this study. Professor Wong's post is funded by a UK Department of Health Public Health Career Scientist Award.

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Funding: The School of Pharmacy, University of London

Competing interests: none declared

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Accepted 2 April 2006
Published Online First 22 May 2006

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ARCHIVIST

Vaccine against acute otitis media

The main bacterial pathogens in acute otitis media, which has its greatest prevalence among children less than 2 years old, are *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*. Plain pneumococcal capsular polysaccharide vaccines are not immunogenic in children under the age of 2 years but heptavalent conjugate vaccine is effective against pneumococcal disease due to vaccine serotypes. Now a new vaccine has been developed that contains 11 different pneumococcal polysaccharide serotypes, each conjugated to *H influenzae*-derived protein D. Protein D is an *H influenzae* cell surface lipoprotein that is highly conserved in both encapsulated and non-encapsulated strains of the organism and has proved effective in inducing protection against non-typable *H influenzae* in animal studies. The new vaccine has been assessed in the Czech Republic (Roman Prymula and colleagues. *Lancet* 2006;**367**:740–8).

A total of 4968 infants were randomised to receive either pneumococcal protein D conjugate vaccine or hepatitis A vaccine (controls) at 3, 4, 5, and 12–15 months of age and followed up to age 2 years. Data were analysed for 4907 infants. In the novel vaccine group there were 333 clinical episodes of acute otitis media and in the control group 499, a significant 34% reduction in the experimental group. Vaccine efficacy was 58% against acute otitis media due to vaccine serotype pneumococci and 35% against acute otitis media due to non-typable *H influenzae*.

The new vaccine provides protection against acute otitis media in children under the age of 2 years due to either of the two main bacterial pathogens. Its effectiveness against lower respiratory tract infections remains to be determined.