Utility of routinely acquired primary care data for paediatric disease epidemiology and pharmacoepidemiology

Peter J. Helms,¹ Suzie Ekins Daukes,^{1,2} Michael W. Taylor,³ Colin R. Simpson^{1,3} & James S McLay²

Departments of ¹Child Health, ²Medicine and Therapeutics and ³General Practice and Primary Care, School of Medicine, University of Aberdeen, UK

Correspondence

P. J. Helms, Department of Child Health, Royal Aberdeen Children's Hospital, Westburn Road, Aberdeen AB25 2ZG, UK.

Tel: +44 (0)1224 552471

E-mail: p.j.helms@abdn.ac.uk.

Keywords

children, medicines, prescribing
disease epidemiology, primary care

Received

18 November 2004

Accepted

19 January 2005

Background

The majority of medicines prescribed for children are prescribed in primary care for common acute and chronic conditions. This is in contrast to prescribing in secondary care where the population of children admitted is small but where a large number of different medicines are prescribed to treat more serious and less common conditions.

Methods

Data on prescribing was extracted from the General Practice Administration System for Scotland (GPASS) for the year November 1999 to October 2000 and prescribing patterns for children aged 0–16 years expressed as percentages. A comparison of age specific consultations for asthma, as an example of a common paediatric condition, was also made between two separate general practice data sets, the General Practice Research Database (GPRD) and the continuous morbidity recording (CMR) subset of GPASS.

Results

Of 214 medicines investigated for unlicensed and off-label prescribing no unlicensed prescribing was identified. Off-label prescribing due to age was most common among younger and older children. The most common reasons for off-label prescriptions were, in order of frequency, lower than recommended dose, higher than recommended dose, below the recommended age, and unlicensed formulation. Age and gender specific consultations for asthma were similar in the two representative databases, GPRD and CMR, both showing disappearance of the male predominance in the teenage years.

Conclusions

Large primary care data sets available within a unified health care system such as the UK National Health Service (NHS) are likely to be broadly compatible and produce similar results. The prescribing of off-label medicines to children is common in primary care, most commonly due to prescribing out with the recommended dosage regimen.

Background

The majority of medicines used by children are prescribed in primary care and general practitioners (GPs) make use of relatively few medicines for the range of common problems presenting to them [1, 2]. This is in contrast to prescribing in secondary care where the number of children admitted is small, in total population terms, but where a large number of different medicines are likely to be prescribed to treat serious or rare conditions. It is estimated that 50–60% of children aged 0–16 years are prescribed at least one drug per year with this figure rising to 75–90% of infants and decreasing to about 40–50% of schoolchildren and adolescents [3–6]. From these reports it also appears that infants have the greatest number of different medicines prescribed. These high prescribing rates for infants correspond to the higher consulting rates in this age group and probably reflect an increased susceptibility to infections, a more severe course of infections, and greater parental and physician anxiety than in older children [3, 4, 7]. The most common medicines prescribed to children in primary care are systemic antibiotics, analgesics (primarily paracetamol), topical corticosteroids, antihistamines and antiasthmatics [1, 3–8]. Less commonly prescribed medicines are more likely to be a continuation of hospital initiated prescriptions for more serious or rare paediatric conditions.

The extent of paediatric unlicensed and off-label prescribing in primary care has been less extensively investigated than in secondary care. Variations between different countries are also likely and some studies have used different classifications of unlicensed and off-label prescribing thus making direct comparison difficult.

The most detailed studies of unlicensed and off-label prescribing in primary care so far reported in the UK include a 1-year study in a single practice for children aged 0–12 years [7] and a 1-year retrospective observational study in 161 Scottish general practices [8]. In the single practice study 10.7% of all prescriptions were either unlicensed or off-label with off-label prescribing far more common (10.5%) than unlicensed prescribing (0.3%). In both studies the most common cause of off-label prescribing was the use of doses out with the recommended range mostly accounted for by antibiotics at lower than recommended dose and by antiasthmatics at higher than recommended dose.

The UK health system is organized so that health care delivery is centred on general practice with referrals to specialists and routine hospital admissions organized at the GP level. All relevant patient information therefore is located in the offices of GPs including a record of all prescriptions, outpatient diagnoses and hospital referral

letters [9]. Consequently the information routinely entered onto general practice computers by GPs may be amalgamated from several practices to provide a source of data that can be used for research purposes. With over 95% of the population in the UK registered with a GP and the fact that individuals may only be registered with one GP at a time [10], general practice databases are population-based and include patients of all ages. With the ability to link patient information to prescribing and/or morbidity data general practice databases provide a unique opportunity to carry out large population-based epidemiological or drug safety studies rapidly and efficiently [11]. In order for general practice databases to be suitable to be used for research the data must first be validated to ensure accuracy, completeness and generalisability, i.e. the patients in the database are similar to other patients in the UK and the GPs that contribute to the database are similar to other GPs [11].

In the UK several general practice databases with wide geographical spread are currently used for epidemiological research including the General Practice Research Database (GPRD), the Mediplus/Torex database and the General Practice Administration System for Scotland (GPASS) database.

The GPRD was established in 1987 by the commercial company VAMP and since 1994 has belonged to the UK Department of Health and maintained by the Office of National Statistics. Following training and a trial period of data entry GPs supply data to the GPRD in return for a small fee and with strict quality standards of data entry [12, 13]. The database currently holds information on over 3 million patients in the UK and is broadly representative of the UK population although with a low representation from Scottish practices. The large size and extensive information recorded have facilitated many drug safety studies complementary to the UK yellow card pharmacovigilance scheme and has resulted in regulatory changes in the licensing of some medicines [10].

The MediPlus/Torex database is based on information from GPs using the Meditel general practice system and currently has data for about 1.8 million patients [14]. As with GPRD, the MediPlus/Torex database allows linkage of prescriptions to clinical diagnoses and the age and sex of patients and the data (particularly prescribing data) has been found to be accurate and reliable [14].

Most previous reports derived from UK general practice that are relevant to disease epidemiology and pharmacovigilance have been based on GPRD data sets. Other than demonstrating the amount of off-label and unlicensed prescribing, previous reports have provided less information on the variability between practices and

the main subtypes of such prescribing such as violations of recommended age limits or formulations. We therefore sought to identify the level and types of such prescribing in the GPASS practices and to establish the level of agreement between GPRD and GPASS for asthma presentations, this being one of the commonest chronic diseases of childhood.

Methods

Scottish data on patient consultations for asthma, were obtained from 47 general practices participating in the Scottish Continuous Morbidity Recording (CMR) project for all patients registered in April 1998 to April 1999 [15]. These CMR practices are representative of the age/sex and rural/urban mix of the Scottish population with 266 733 patients registered in the year of study and form a subset of practices using GPASS. Patient consultation rates for asthma (Read code H33 and below) [16] within the year were used as a measure of period prevalence. Repeat consultations were excluded. Similar data from the GPRD were available for 1991–95, originally derived for a respiratory epidemiology project funded by the UK Department of Health [17]. The GPRD is the largest source of information on primary care in the UK and covered between 3 and 6% of the population of England and Wales over this time period. Comparisons were based on the average yearly patient consultation rates for asthma (excluding patients who also had a diagnosis of COPD) (Oxmis codes used available on request from the authors). GPRD rates were based on 264 258 consultations for asthma, relating to 6 836 063 person years at risk [17].

The prescribing data used were extracted from GPASS, one of Britain's leading general practice systems. Established in 1984 using software originally developed by Dr David Ferguson, a Glasgow GP, GPASS is used by over 890 (84%) of general practices in Scotland [18]. GPASS software and support are provided free of charge to practices, making the computer hardware the only practice cost involved.

The generation of repeat prescriptions has been facilitated by the provision of a drug dictionary which helps standardize prescription information and includes an automatic generic substitution to reduce NHS costs [19, 20]. Patient morbidity is recorded using Read Clinical Classification Codes [16] which allow national standardization of the data.

The GPASS database is compiled by the Primary Care Clinical Informatics Unit (PCCIU) hosted in the Department of General Practice and Primary Care, University of Aberdeen from data supplied by GPs in Scot-

land using the GPASS system. Although primarily supplied to the PCCIU for the purposes of audit and feedback to the practices [19, 20] the data are also suitable for epidemiological research with information on between 1.5 and 2.8 million patients (depending on the year of study). Repeat prescribing data has been found to be both complete and accurate for practices contributing to the GPASS database while morbidity data has been shown to be accurate and to be approximately 75% complete [21, 22]. The prescribing of unlicensed and off-label medicines to children in primary care in the 161 general practices was investigated over 1 year from 1 November 1999 to 31 October 2000. All children aged 0–16 years were included in order to investigate any differences in the extent or nature of unlicensed or off-label prescribing with age.

The top 100 medicines prescribed to children were selected, making a total of 156 different medicines. In order to report the extent of unlicensed and off-label medicines within the most commonly prescribed drug classes a further 58 medicines were also investigated (lists available from authors on request). These 214 medicines accounted for 96.2, 93.8 and 90.4% of all prescriptions to 0–4, 5–11 and 12–16 year-old children, respectively.

Unlicensed and off-label use were identified by age, dose and formulation. Off-label prescribing according to indication or route of administration could not be investigated as information on diagnoses was not available from the GPASS database and the prescription information did not always specify the intended route of administration. In certain cases prescriptions were off-label for more than one reason, e.g. medicine prescribed below the recommended age and above the recommended dose for the older specified ages. In these circumstances off-label status according to age was given priority over dose which, in turn, was given priority over formulation.

The licensing status of the selected medicines was assessed using the summary of product characteristics (SPC) [23] and/or British National Formulary (BNF) [24] to determine the licence restrictions of each medicine. Children below the recommended age for a medicine or where no information was given regarding paediatric use were classified as having received an off-label prescription for that medicine due to age. Medicines that gave paediatric information with no specific age ranges were considered licensed for all ages.

Children prescribed medicines in a formulation not licensed for use when an alternative licensed formulation was available (e.g. salbutamol syrup prescribed to children below 2 years instead of the licensed inhaled

formulation) were classified as having received an off-label prescription due to formulation.

Children prescribed a dose outside the recommended range were classified as having received an off-label prescription due to either low dose or high dose.

Results

The pattern of consultations for asthma were similar in both CMR and GPRD although as can be seen the number of consultations was generally higher in GPRD (Figure 1). As expected a male bias was seen in both datasets although with a gender convergence in the teenage years.

No unlicensed use of medicines was seen in the GPASS dataset and the extent of off-label prescribing by participating general practice followed a normal distribution with an average of 24.6% and a range from 0 to 44% (Figure 2).

Significant numbers of registered children received an

off-label prescription within the range 20–35% over the age range 0–16 years (Figure 3). Off-label rates in those children with at least one prescription in the study year were highest in the first year of life but remained remarkably stable from 2 to 16 years (Figure 3).

The most common reasons for off-label prescriptions were, in order of frequency, lower than recommended dose, higher than recommended dose, below the recommended age, and unlicensed formulation.

Figure 1

Asthma consultations in CMR and GPRD practices. Boys (■), girls (■)

Figure 2

Off label prescribing by GPASS practice 1999–2000. Std. dev = 7.43, mean = 24.5, n = 161.00

Figure 3

Off label prescribing by child age for all registered children and for those with at least one prescription in the study year. Data from GPASS 1999–2000. Registered children (■), children with a prescription (◆)

Figure 4

Age trends for prescribing medicines to children below the recommended age. Data from GPASS 1999–2000

Formulation was the least common form of off-label prescribing and involved only 17 of the 214 medicines assessed. Off-label prescribing due to age was most common among younger and older children, following a U-shaped distribution over the whole child age range (Figure 4).

Discussion

Although the pattern of consultations for asthma were similar in CMR and GPRD datasets the generally higher concentrations in GPRD could in part be explained by the fact that the extracted data from GPRD were from an earlier period than those from CMR. During the period of 4–5 years between these collections, changes in the use of prophylactic therapy or in disease severity could have occurred. However, despite these possibilities, the similarity in gender specific consultation rates and the convergence of these rates in the teenage years would be compatible with the known ‘gender switch’ in disease prevalence that occurs in mid to late puberty [25, 26].

The prescribing of off-label medicines to children in primary care was found to be common although no unlicensed use of medicines was identified, possibly due to the fact that only the most frequently prescribed medicines 214 (93.4% of all medicines prescribed) were investigated. A previous study conducted in a single primary care practice in the UK [7] reported unlicensed use to be rare in primary care (0.3% of all prescriptions) suggesting that any unlicensed prescribing by GPs would be for uncommonly prescribed medicines and more likely to be initiated by hospital paediatricians.

We have previously reported that just over 26% of all children who received a prescription were prescribed at least one off-label medicine in a single year [8], approx-

imating to over 100 000 children in Scotland or if more than 1 million children if extrapolated to the whole UK. These figures are lower than those reported in studies of unlicensed and off-label prescribing in other European countries where 46–56% of children received at least one such prescription [27, 28] and may reflect regional differences in prescribing habits particularly with respect to the extent of unlicensed extemporaneous preparations used.

The prescribing of off-label medicines was not restricted to particular practices but was common in the majority (Figure 2). Only one practice did not prescribe off-label medicines in the study year and only a few had high off-label prescribing rates (44–46% of patients).

Some medicine classes had high proportions of off-label prescribing suggesting either a deficiency of licensed alternatives, suitable formulations or appropriate dosage regimens. These medicines included antihistamines, laxatives and systemic decongestants for 0–4 year-olds, antihistamines and cough preparations for 5–11 year-olds and antimigraine drugs for 12–16 year-olds [8].

There is clearly no one solution to solve the problem of off-label prescribing, as medicines are prescribed off-label for different reasons and in different child age groups. Previous studies in primary care have focused suggestions for improvement on the pharmaceutical industry suggesting that more clinical trials should be performed in children [7, 28]. However the present results suggest that the solution may also require other actions more centred on individual prescribers as evidenced by the wide range in off-label prescribing within practices (Figure 2).

Off-label prescribing due to age was, as expected, most common in young children particularly under 2 years (Figure 3). This finding is a likely consequence of the generally higher prescription rates in this age group and ethical and practical challenges in performing clinical trials in young children. A similar pattern was also seen in 16 year-olds (Figure 3) and is likely to be due to a not unreasonable conclusion by prescribers that medicines and doses used in adults would also appropriate at this age. However, the use of medicines in children below the recommended age and the extrapolation of recommended doses from adults or older children carries the risk of toxicity and unwanted side-effects from excessive doses or alternatively because of different drug handling and elimination may result in lack of efficacy. Even in teenagers, the effects of pubertal development and the different pace of such development in individuals could influence drug handling.

Medicines prescribed at lower than recommended

dose have been shown to be the most common cause of off-label prescribing for children of all ages involving over half of all medicines prescribed to children [7, 8]. As the use of medicines below recommended doses may lead to subtherapeutic treatment, and antibiotics were the most commonly prescribed group in this category, concerns about therapeutic response should be raised. Antibiotics have also been found to be the most commonly prescribed off-label medicines [8, 28].

In older children (5–11 and 12–16 years) the most common medicines prescribed at high doses have been found to be antiasthmatics (β_2 -adrenoceptor agonists and inhaled corticosteroids) [8]. This is likely to be as a result of a difference in dosage recommendation between the SPC and the 1995 (reported in 1997) British Asthma Guidelines that were current for the 1999–2000 data [29]. These guidelines recommended significantly higher doses of inhaled corticosteroids for the treatment of severe asthma than the SPC although they have now been revised using evidence-based methodology and are now in agreement with the SPC [30]. This example highlights a need for consistency between professional guidelines and prescribing information in order to minimize confusion.

It was not possible to assess the extent of prescribing for indications not included in the product licence as information on diagnoses, although available in the CMR subset, was not available in the larger GPASS data set. However if this could have been taken into account the extent of off-label prescribing would probably be higher than reported here. The selection of the 100 most frequently prescribed medicines, supplemented by a further 58 not in this list, but within one of the classes in the top 100, did not capture all prescribed medicines, hence underestimating the true level of off-label prescribing. The fact that no unlicensed prescribing was found for the 214 medicines assessed was also likely to be due to the initiation of such prescriptions by hospital-based paediatricians for rare diseases and indications. However as the focus of the present study was on prescribing in general practice non inclusion of such rare and unusual prescriptions would have only had a small effect on the observations made and conclusions drawn about general practice prescribing.

A further limitation was the lack of data on patient weight resulting in calculations for doses in $\text{mg kg}^{-1} \text{ day}^{-1}$ based on average weights for children of a particular age. However the number of medicines involving $\text{mg kg}^{-1} \text{ day}^{-1}$ dosage calculations was small and was only relevant to children under 12 years. In order to minimize this effect a weight range for each age was used rather than a single value.

The results of the present study are expressed in terms of patients prescribed off-label medicines rather than off-label prescriptions. Although the extent of off-label prescribing in terms of prescriptions would have added further detail, the focus on the individuals exposed to off-label prescribing in a single year is arguably more clinically relevant and identifies the population at potential risk or disadvantage. The risks of off-label prescribing in primary care have not been extensively investigated and there remains the potential for toxicity unwanted side-effects or ineffective treatment [31].

In conclusion, high quality routinely acquired data in primary care are becoming increasingly available and offer the potential for the study of disease epidemiology and pharmacovigilance. Large data sets available within a unified health care system such as the UK National Health Service (NHS) that offers universal health care at the point of need and in which general practitioners are effectively the 'gate keepers', are likely to be broadly compatible and produce similar results. The prescribing of off-label medicines to children is common in primary care affecting a large number of children.

Competing interests: None declared.

References

- 1 Straand J, Rokstad K, Heggedal U. Drug prescribing for children in general practice. A report from the More & Romsdal Prescription Study. *Acta Paediatr* 1998; 87 (2): 218–24.
- 2 Rylance GW, Woods CG, Cullen RE, Rylance ME. Use of drugs by children. *BMJ* 1988; 297 (6646): 445–7.
- 3 Schirm EBP, Gebben H, Sauer P, De Jong-van den Berg. Drug use of children in the community assessed through pharmacy dispensing data. *Br J Clin Pharmacol* 2000; 50 (5): 473–8.
- 4 Thrane N, Sorensen HT. A one-year population-based study of drug prescriptions for Danish children. *Acta Paediatr* 1999; 88 (10): 1131–6.
- 5 Cazzato T, Pandolfini C, Campi R, Bonati M. Drug prescribing in out-patient children in Southern Italy. *Eur J Clin Pharmacol* 2001; 57 (8): 611–6.
- 6 Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. *Eur J Clin Pharmacol* 2001; 57 (2): 159–65.
- 7 McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off-label prescribing of drugs in general practice. *Arch Dis Child* 2000; 83 (6): 498–501.
- 8 Ekins-Daukes S, Helms PJ, Simpson CR, Taylor MW, McLay JS. Off-label prescribing to children in primary care: retrospective observational study. *Eur J Clin Pharmacol* 2004, 1991–92; 60: 349–53.

- 9 McCormick A, Fleming D, Charlton J. Morbidity Statistics from General Practice – Fourth National Study. London: HMSO, 1995
- 10 Mann RD, Taylor MW, MacDonald TM, Jick H, Rawlins MD, Wood SM, Walter PC, Fletcher P. Databases for pharmacovigilance. What can we do? MBRF, 1996.
- 11 Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. *J Public Health Med* 1999; 21 (3): 299–304.
- 12 Walley T, Mantgani A. The UK General Practice Research Database *Lancet* 1997; 350 (9084): 1097–9.
- 13 Garcia Rodriguez LA, Perez GS. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998; 45 (5): 419–25.
- 14 Lawrenson RA, Coles G, Walton K, Farmer RDT. Characteristics of practices contributing to the MediPlus database and the implications for its use in epidemiological research. *Journal of Informatics in Primary Care* 1998; May: 14–18.
- 15 Simpson CR, Anderson WJ, Helms PJ, Taylor MW, Watson L, Prescott GJ, Godden DJ, Barker RN. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. *Clin Exp Allergy* 2002; 32: 37–42.
- 16 Saint_Yves IF. The read clinical classification. *Health Bull (Edinb)* 1992; 50 (6): 422–7.
- 17 Hansell A, Hollowell JNT, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999; 54: 413–9.
- 18 About GPASS. <http://www.gpass.co.uk> (accessed 03/2005).
- 19 The primary clinical information unit, university of Aberdeen, http://www.abdn.ac.uk/general_practice/research/special/pccdu-r/index.shtml (accessed 03/2005).
- 20 Ryan MP. A system for general practice computing in Scotland. *Health Bull (Edinb)* 1989; 47 (3): 110–9.
- 21 Milne RM, Taylor MW, Duncan R. An assessment of computing activity by GPASS users in Scottish general practice. *Health Bull (Edinb)* 1991; 49 (2): 152–60.
- 22 Whitelaw FG, Nevin SL, Milne RM, Taylor RJ, Taylor MW, Watt AH. Completeness and accuracy of morbidity and repeat prescribing records held on general practice computers in Scotland. *Br J General Pract* 1996; 46 (404): 181–6.
- 23 Association of the British Pharmaceutical Industry (ABP). Compendium of Data Sheets and Summaries of Product Characteristics. Datapharm Publications Limited, Epsom, Surrey, UK 1999.
- 24 British Medical Association Royal Pharmaceutical Society of Great Britain. British National Formulary, London 2000: 40 edn.
- 25 Wieringa MH, Weyler JJ, Van Bever HP, Nelen VJ, Vermeire PA. Gender differences in respiratory, nasal and skin symptoms: 6–7 versus 13–14-year-old children. *Acta Paediatr* 1999; 88: 147–9.
- 26 Osman M. Therapeutic implications of sex differences in asthma and atopy. *Arch. Dis. Child* 2003.
- 27 't Jong GW, Eland IA, Sturkenboom MC, van den Anker JN, Stricker BH. Unlicensed and off-label prescription of drugs to children: population based cohort study. *BMJ* 2002; 324 (7349): 1313–4.
- 28 't Jong GW, Eland IA, de Hoog M, Sturkenboom MC, van den Anker JN, Stricker BH. Unlicensed and off-label prescription of systemic anti-infective agents to children. *Paediatric Perinatal Drug Ther* 2002; 5 (2): 68–74.
- 29 The British Guidelines on Asthma Management. 1995 review and position statement. *Thorax* 1997; 52: S1–S21.
- 30 The British Guidelines on the Management of Asthma. *Thorax* 2003; 58(Suppl 1): i1–94.
- 31 Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002; 54 (6): 665–70.