Monitoring adverse drug reactions in children using community pharmacies: a pilot study

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Aims

To determine the feasibility of a community pharmacy-based parental adverse drug reaction (ADR) reporting system for children.

Design

Prospective study of parent-reported ADRs using a questionnaire issued to the parent or guardians of children 0–11 years of age collecting prescribed medicine for amoxicillin, and/or salbutamol, and collecting prescribed medicine for, or purchasing, paracetamol or ibuprofen suspension.

Setting

Seven community pharmacies in Grampian, Scotland.

Results

During a 4-week period 360 prescriptions or purchases for the study medications occurred. Two hundred and sixty-seven parents (85.5%) agreed to participate in the study. One hundred and six participants (40%) returned a total of 122 questionnaires. The demographics of responders and nonresponders including medication, age of child, and social status as assessed by the Depcat score were similar. There was no evidence of under-representation of any socio-economic group. Possible adverse events were detected using a symptom tick list and perceived ADRs using free text entry. Using the symptom tick list approach the most commonly reported symptoms were diarrhoea (28.9%) and tiredness (31.6%) for amoxicillin. The levels of diarrhoea and tiredness reported for ibuprofen, paracetamol and salbutamol were 15% and 20%, 7.4% and 18.5%, and 20% and 0%, respectively. Using the freehand section of the questionnaire 15 specific ADRs were reported by parents (12.3%). Eight children (21.2%) reported ADRs attributed to amoxicillin [diarrhoea ($n = 4$), fever ($n = 1$), anorexia ($n = 1$), hyperactivity ($n = 1$) and nonspecific ($n = 1$)], five to paracetamol [diarrhoea ($n = 3$), anorexia, irritability, crying and very angry ($n = 1$) and not stated ($n = 1$)], two to ibuprofen [diarrhoea ($n = 1$), not stated ($n = 1$)]. Only one off-label prescription was identified and this was for salbutamol syrup prescribed to a child under 2 years of age.

Conclusions

The prospective monitoring of paediatric ADRs, using a questionnaire issued to parents or guardians in the community pharmacies, is feasible.

Introduction

Children form a highly heterogeneous group in which drug pharmacokinetics and pharmacodynamics together with physiological development vary significantly with age, thereby placing them at a possible increased risk of adverse drug reactions (ADRs). Perceived barriers to conducting clinical studies in children have also led to a paucity of phase 3 and 4 clinical trial data. However, although the safety of medicines in childhood is of major public and regulatory interest, there is a significant lack of data and appropriate systems to facilitate drug safety monitoring in this population. Spontaneous reports of suspected ADRs to the Committee on Safety of Medicines by healthcare professionals are the main source of information used for regulatory pharmacovigilance in the UK. However, Medicines and Healthcare products Regulatory Authority figures confirm that over the 5 years from 1999 to 2003 only 7–18% of all yellow card reports referred to children (personal communication), suggesting that, just as in the adult population, ADRs are likely to be under-reported [1].

Although data are limited, ADRs are reported to be responsible for between 1.5 and 2.1% of paediatric hospital admissions [2, 3], and to occur in 2.6–9.3% of paediatric inpatients [4–6] and 1.5–11.1% of paediatric outpatients [7]. This situation is further exacerbated by the fact that most medicines prescribed to children are used off label [8–11], which in turn has been linked to an increased ADR frequency [3, 12, 13].

The investigation and detection of ADRs in children is problematic, due at least in part to the potential difficulty of a young child in verbalizing and describing symptoms that could be due to administered medication. There is a need for a mechanism for monitoring ADRs in the paediatric population, which is comprehensive, and easy to establish and sustain. We believed that such a system, relying on parental monitoring and reporting of suspected ADRs, could be operated via community pharmacies for both prescribed and over the counter medications (OTC).

We therefore sought to test and validate a community pharmacy-based method of ADR monitoring and reporting, suitable for both prescribed and OTC medicines. An adverse drug reaction questionnaire was supplied to parents or guardian purchasing, or collecting on prescription one or more of four specific medicines. We also planned to collect data in dispensing pharmacies to detect and assess levels 'off-label' prescribing, i.e. prescribing without the licensed restrictions in the Summary of Product Characteristics.

Because the medicines most frequently associated in the community with ADRs in children are antibiotics,

bronchodilators and vaccines [8, 14], we chose to investigate the frequency of parental ADR reports for prescribed amoxicillin, salbutamol, and prescribed or OTC paracetamol and ibuprofen suspension.

Methods

Data were collected over a 4-week period during November to December 2003 in seven community pharmacies in Grampian for all children under 12 years of age issued with a prescription for amoxicillin, salbutamol, paracetamol or ibuprofen suspension or for whom an OTC purchase of paracetamol or ibuprofen suspension was made. Subjects were recruited by a research assistant in each pharmacy who explained the study to the accompanying parent or guardian, and obtained informed consent. This individual also conducted a preliminary interview to obtain basic demographic data (age of child, post code, details of study medicines and any other medication currently being taken). Children were excluded if the accompanying adult was not the parent or guardian. A record was maintained of excluded subjects.

The parent or guardian was asked to complete a 5-day prospective diary (Figure 1) for each of the study medicines, recording dose and time of medicine administration, and any perceived ADRs. An extensive list of previously validated symptoms/ADRs was included as a prompt [15]. Completed diaries were returned in a reply paid envelope. The study was approved by Grampian Research Ethics Committee.

Basic descriptive statistics were performed. In order to identify any differences associated with socioeconomic status a deprivation score (Depcat) [16] was derived for each participant, from their post code (range 1 most prosperous to 7 least prosperous).

Statistics

Simple descriptive statistics were used to report frequencies; χ^2 was used to test for any association between age, Depcat score and level of response to the questionnaire. A *P*-value of <0.05 was considered significant.

Results

Over the 4-week period, 360 prescriptions and purchases for the study medicines were recorded, of which 30 were excluded (not parent/guardian accessing the medicine) and 18 missed (periods of high demand in the pharmacy). Of the remaining 312 events, 267 of the parents (85.5%) agreed to participate in the study. Two hundred and forty-one (90.3%) children were prescribed one, 23 (8.6%) children two, and three (1.1%) children

Name of medicine(entered by researcher) _____ Identification Number _____

Please complete this first page of the questionnaire every time that you give your child any of the above medicine

Day	Approximate time	Amount given
Day 1 Date _____		
Day 2 Date _____		
Day 3 Date _____		
Day 4 Date _____		
Day 5 Date _____		

After day 5 please turn to the second page of the questionnaire

1. Has your child's condition improved since starting this medicine?

☐ yes

☐ no

2. Do you believe that your child may have had any side effects from this medicine?

☐ yes

☐ no

If yes please describe the side effect in your own words in the box below.

3. Please tell us if you feel that your child has had any of the following since starting this medicine.

Skin rash	☐ yes	☐ no
Itchy skin	☐ yes	☐ no
Diarrhoea (loose bowel motions)	☐ yes	☐ no
Vomiting	☐ yes	☐ no
Squeamishness	☐ yes	☐ no
Hair loss	☐ yes	☐ no
Tummy pain	☐ yes	☐ no
Headaches	☐ yes	☐ no
Tiredness	☐ yes	☐ no
Irritability	☐ yes	☐ no
Hyperactivity or excitability	☐ yes	☐ no
Difficulty in sleeping	☐ yes	☐ no
Nervousness	☐ yes	☐ no
Cough	☐ yes	☐ no
Wheeze	☐ yes	☐ no
Nose bleeds	☐ yes	☐ no

Please tell us about any other symptoms

Thank you for completing this questionnaire. Please now put both pages in the stamp addressed envelope supplied.

Figure 1

Example of the patient questionnaire and data collection sheet

A novel community based method to monitor the frequency and nature of adverse drug reactions in a paediatric population: a pilot study

(Information to be obtained by interview at the point of consent)

Date _____ Patient Identification Number _____ Age of child _____ Gender ☐ male ☐ female

Postal Code or Street Name (if postcode not known) _____

Medication

	Formulation	Strength	Dose	Quantity	Prescribed or OTC	Reason for use
Amoxicillin					prescribed	
Salbutamol					prescribed	
Paracetamol					☐ prescribed ☐ OTC	
Ibuprofen					☐ prescribed ☐ OTC	

Previous Medicine Use ☐ no

	When used	Reason for use
Amoxicillin		
Salbutamol		
Paracetamol		
Ibuprofen		

Other medicines your child is on at present time (drug, formulation, dose):

Medicine	Formulation	Strength	Dose	Reason for use

Questionnaires given for ☐ amoxicillin ☐ salbutamol
☐ paracetamol ☐ ibuprofen

Figure 1

Continued

three study medicines. One hundred and six participants (40%) returned a total of 122 completed questionnaires (95 for one medicine, 9 for two, and 3 for three medicines). Differences between responders and nonresponders are described in Tables 1, 2 and 3. The response rates by drug (Table 1) were highest for ibuprofen (51.3%), followed by amoxicillin (44.2%), paracetamol (39.4%) and salbutamol (30.3%). However, although the numbers are small, there were no significant differences in the distributions of child age ($P = 0.2$) and deprivation scores ($P = 1.0$) between responders and nonresponders (Tables 2 and 3).

Of the 312 eligible events, 29% were for amoxicillin, 11% salbutamol, 46.5% paracetamol, and 13.5% ibuprofen (Table 4). Using the symptom tick list, 49.5% of all symptoms/adverse events were reported for amoxicillin, 35.8% for paracetamol, 9.2% for ibuprofen and 5.5%

for salbutamol. The most commonly reported symptoms/adverse events for amoxicillin were diarrhoea (28.9%) and tiredness (31.6%). The levels of diarrhoea and tiredness reported for paracetamol, ibuprofen, and salbutamol were 7.4% and 18.5%, 15% and 20%, and 20% and 0%, respectively. Although the number of parents reporting diarrhoea or tiredness was small when compared with the other three study medications, as expected amoxicillin use was associated with an excess reporting of diarrhoea of approximately 9%. Levels of tiredness were similar for all the study medications except salbutamol, which is a recognized stimulant.

Using the open comments section of the questionnaire, 15 (12.3%) completed questionnaires reported additional specific suspected ADRs: 21.2% of parents/guardians of children prescribed amoxicillin reported diarrhoea ($n = 4$), hot, very tired and not eating ($n = 1$),

Table 1

Comparison of responders and nonresponders by medicine

Medicine	Responders <i>n</i> (%)	Nonresponders <i>n</i> (%)
Amoxicillin	38 (44.2)	48 (55.8)
Ibuprofen	20 (51.3)	19 (48.7)
Ibuprofen OTC	13 (48.1)	14 (51.9)
Ibuprofen prescribed	7 (58.3)	5 (41.7)
Paracetamol	54 (39.4)	83 (60.6)
Paracetamol OTC	42 (41.2)	60 (58.8)
Paracetamol prescribed	12 (34.3)	23 (65.7)
Salbutamol	10 (30.3)	23 (69.7)

Table 2

Comparison of responders and nonresponders by age

Age	Responders <i>n</i> (%)	Nonresponders <i>n</i> (%)
<12 months	7 (25.9)	20 (74.1)
1 year	13 (52)	12 (48)
2 years	16 (50)	16 (50)
3	13 (40.6)	19 (59.4)
4	16 (48.5)	17 (51.5)
5	7 (35)	13 (65)
6	4 (22.2)	14 (77.8)
7	3 (18.8)	13 (81.2)
8	7 (43.8)	9 (56.2)
9	10 (55.6)	8 (44.4)
10	3 (23.1)	10 (76.9)
11	7 (41.2)	10 (58.8)

unable to eat very much, irritable, very angry and crying ($n = 1$), more hyperactive than usual ($n = 1$) and one nonspecific instance. The parents/guardians of 9.3% of children taking paracetamol reported diarrhoea ($n = 3$), unable to eat, very irritable, crying and very angry ($n = 1$) and not stated ($n = 1$); two ADRs were attributed to ibuprofen, diarrhoea in one child and the other not stated. Diarrhoea was reported three times for one child on three medications (diarrhoea with amoxicillin, ibuprofen and paracetamol) with the parent stating that any of the drugs could have been responsible. Two unspecified ADRs were reported for a further child on ibuprofen and paracetamol. In the single case of hyperactivity with amoxicillin, the parent noted uncertainty as to whether the reaction described was as a result of the

Table 3

Comparison of responders and nonresponders by deprivation category (based on post code)

Deprat score	Responders <i>n</i> (%)	Nonresponders <i>n</i> (%)
1	2 (40)	3 (60)
2	32 (42.1)	44 (57.9)
3	27 (35.1)	50 (64.9)
4	34 (41)	49 (59)
5	2 (28.6)	5 (71.4)
6	3 (50)	3 (50)
Missing	6 (46.2)	7 (53.8)

drug. Only one off-label prescription was identified and this was for salbutamol syrup prescribed to a child under 2 years of age. Currently using this type of questionnaire approach it should be possible to assess levels of off-label prescribing due to age, dose or formulation in children aged 12 years or less; however, it is not possible to assess the role of indication as a cause for such prescribing.

Discussion

This pilot study has demonstrated the feasibility of prospectively monitoring paediatric ADRs, using a questionnaire given out with prescriptions or OTC medicines to parents/guardians, via community pharmacies. A high recruitment rate was achieved and the process identified a number of recognized ADRs. These were primarily diarrhoea for amoxicillin, which is reported to occur in 5% of adults and 10% of children [17]. In the present study 28.9% of children reported diarrhoea using the tick list approach. However, if the reporting levels for diarrhoea for the other three medications are taken into account, amoxicillin would appear to be associated with an excess reporting rate of approximately 9%. The level of diarrhoea reported by parents as a specific ADR for amoxicillin, using freetext, was similar at 10.5%.

A common concern of this type of approach to ADR monitoring is that results might be biased by age or socio-economic group. However, the results of this study suggest that such bias is unlikely as there appeared to be no significant differences between the responders and nonresponders due to medication, child age or deprivation.

Although the initial parental take-up rate for this study was high, less than 50% of parents/guardians responded to the questionnaire. One of the possible

Table 4

Symptoms reported by parents since starting each medicine

	Amoxicillin (n = 38)	Ibuprofen (n = 20)	Paracetamol (n = 54)	Salbutamol (n = 10)
Skin rash	3	0	2	0
Itchy skin	0	1	1	0
Diarrhoea	11	3	4	2
Vomiting	1	0	1	0
Squeamishness	1	0	1	0
Hair loss	0	0	0	0
Tummy pain	3	0	0	1
Headache	1	0	0	0
Tiredness	12	4	10	0
Irritability	7	0	5	1
Hyperactivity or excitability	4	0	2	1
Difficulty in sleeping	4	0	2	0
Nervousness	0	0	0	0
Cough	5	2	10	0
Wheeze	2	0	1	1
Nose bleeds	0	0	0	0

explanations for this level of response is that paracetamol and ibuprofen suspension were purchased or prescribed prophylactically in anticipation of an event and not used during the study period. This issue could be resolved in future studies by including an item on the return questionnaire that established whether the medication prescribed or purchased was actually used.

Community pharmacies have been used successfully for the purpose of pharmacovigilance of OTC products [18–20] and represent a readily and easily accessible point of contact for the public where they not only obtain prescribed and purchased medicines but can also gain access to an expert in medicines use. It would therefore seem appropriate to utilize community pharmacies to heighten public awareness of ADRs and enhance the level of reporting in both exercises targeted at children or at-risk populations such as this, or through the established yellow card route.

Strengths and weaknesses

The approach used in this pilot study has limitations, the first of which was that despite a high initial take-up, less than 50% of parents or guardians returned completed questionnaires. Reported ADRs, using the tick list approach, may also have been primary symptoms or new symptoms, unrelated to either the index condition or the administered medicine. It is also unclear if this approach would pick up those more serious events resulting in medical intervention/hospitalization. How-

ever, there is no reason to suspect that parents would be any less active in reporting serious ADRs than medical staff. The questionnaire, however, would require modification with the inclusion of a specific section relating to the outcome of a reported ADR or need for medical intervention together with a request for parental contact details. In addition, the approach we have used is unable to detect ADRs which may remain largely asymptomatic such as full blood count abnormalities, or abnormal liver function tests. The described approach, however, also has several advantages, in that it is readily accessible to and involves the public, and that specific medicines of interest or specific at-risk groups could be targeted at particular times. However, the future generalizability of this approach will be determined only from larger scale studies.

Conclusions

Despite concerns about the use of medicines in childhood and, in particular, off-label and unlicensed prescribing, there appears to be under-reporting of paediatric ADRs using existing reporting systems. There is also a medical and political desire to improve public awareness, and participation in ADR monitoring. The ADR monitoring system reported here and based in community pharmacies can achieve these desired goals, and give rise to meaningful results with no evidence of socio-economic bias.

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