Health-related quality of life among children who have had adverse drug reactions

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Objective: **To compare health-related quality of life (HRQL) of children who have had multiple Adverse Drug Reactions (ADRs) to children who have had one ADR and to previously collected normative data on HRQL in healthy children.**

Design and setting: **This pilot study was conducted by interviews with parents of children who have had one ADR and parents of children with multiple ADRs, who live in South Western Ontario.**

Participants: **Forty two parents or guardians of paediatric patients who had attended the ADR clinic at the Children's Hospital of Western Ontario between 1997 and 2002.**

Main Outcome Measure: **HRQL scores as determined by the Child Health Questionnaire Parent-Form 50 (CHQ-PF50).**

Results: **In general, parents of children who have had multiple ADRs perceive that their children have lower HRQL than parents of children who have had one ADR or parents of healthy children. This trend was identified by the responses to the CHQ-PF50. Children with ADRs to multiple antibiotics scored lower than children with an ADR to one antibiotic in 11 of the 12 CHQ-PF50 sub-scales and lower than healthy children in 10 of the sub-scales. In particular, a statistically significant lower score in the general health perceptions sub-scale was noted among children with multiple ADRs, when compared to children with one ADR or to healthy children. Children with multiple ADRs had significantly more co-morbid conditions than the children with one ADR.**

Conclusions: **The findings suggest that children with multiple ADRs have lower HRQL when compared to children with only one ADR and to previously generated normative data in healthy children. This preliminary evidence indicates the need for further exploration of the impact of ADRs on HRQL in children. The role of co-morbid conditions also needs to be assessed.**

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Introduction

Adverse drug reactions (ADRs) are not uncommon in the paediatric population. In fact, they are a significant source of morbidity and hospitalisation among children. The incidence of ADRs in hospitalised paediatric patients is 9.5% and in paediatric outpatients is 1.5%[1]. Moreover, ADRs account for about 2% of total paediatric hospitalisations[2]. Although ADRs are a problem often encountered by paediatricians, to our knowledge, their effect on children's health-related quality of life (HRQL) has not yet been explored. Similarly, this question has not been previously examined in adults.

Children are often excluded from pre-commercial clinical trials, thus our understanding of ADRs in children comes primarily from post-marketing observations[2]. After the presentation of an initial-suspected ADR in a child, it is essential to document its occurrence and to investigate its aetiology. Anecdotal evidence from paediatric pharmacologists, who frequently evaluate children with ADRs, suggests that when ADRs are numerous in one child, that child and his or her family experience considerable stress and frustration. However, having only one ADR does not appear to cause children and families the same amount of anxiety. Our objective was to compare the HRQL among children with ADRs to multiple antibiotics, children with an ADR to one antibiotic, and children of the general population.

Methods

A pilot study was conducted to collect preliminary data, as HRQL among children with ADRs has not previously been studied. Subjects were recruited from a group of patients already identified at the ADR clinic at the Children's Hospital of Western Ontario as having a possible ADR to an antibiotic. Inclusion criteria included children who: were aged 5 to 17 years and identified by the ADR clinic at the Children's Hospital of Western Ontario as having a history of either an ADR to one antibiotic or three or more ADRs to different antibiotics; had seen a clinical pharmacologist within the past five years; had no major co-morbidity according to a chart review, such as seizure disorder or Trisomy 21, that would severely influence HRQL; and were living within a two hour driving distance from London, Ontario.

Our aim was to compare children with a history of an ADR to one antibiotic to those with reactions to several antibiotics. This would determine if there exists a cumulative influence of ADRs on HRQL. A database of children seen at the ADR clinic between 1997 and 2002 (approximately 400 children) was used to identify all children who met the eligibility criteria for the study. Forty children with a history of an ADR to one antibiotic and 40 children with a history of ADRs to multiple antibiotics were randomly selected. The parents of these 80 children were sent a letter explaining the study. This letter was followed by telephone contact to discuss the study, obtain consent and arrange an interview. Approval for this study was obtained from the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects.

HRQL Measures

HRQL refers to the specific influence of an illness or injury, medical treatment, or health care policy on an individual's quality of life [3]. Several instruments have been developed in the past decade which evaluate HRQL in children. These include both disease-specific measures and generic measures. Disease-specific measures are often used for the evaluation of interventions or for determining the impact of a particular medical condition. In contrast, generic measures are broader and allow for comparisons across disease groups or between patients and the general population. They lack the sensitivity of disease-specific measures, however[4]. A generic HRQL assessment tool, the Child Health Questionnaire (CHQ), was employed in this study to allow us to compare HRQL in children with ADRs to those in the general population. No disease specific measure has been developed for this population.

The CHQ was chosen for this study since it was designed specifically for children and thus measures concepts that are unique to this population[5]. The CHQ evaluates a child's physical, emotional and social well-being from the perspective of either the parent or the child; its validity and reliability have been demonstrated, and normative data are available[6].

In this study, one parent served as a proxy respondent for the child using the CHQ-Parent Form 50 (CHQ-PF50). Some of the children in this study were as young as five and the child self-report version is appropriate for children ten years of age and older[6]. Although there is some debate over the validity of proxy respondents[7], in the case of a child with one or more ADRs, assessing HRQL from the parent's perspective seems reasonable. It is the parent who is most familiar with the child's life and is often personally affected by their child's ADRs and the anxiety that frequently ensues. The collection of parental views is a first step in acquiring an understanding of the influence of ADRs on a child's HRQL. It is important that future research in this area attempts to obtain the child's perspective as well.

The CHQ-PF50 consists of 50 items organised into 15 sub-scales/items: (1) global health, (2) physical functioning, (3) role/social limitations due to emotional or behavioural difficulties, (4) role/social limitations due to physical health, (5) bodily pain and discomfort, (6) behaviour, (7) global behaviour, (8) mental health, (9) self-esteem, (10) general health perceptions, (11) change in health, (12) emotional impact on parent, (13) time impact on parent, (14) family activities, and (15) family cohesion.

The parent or guardian primarily responsible for each child's care was interviewed using the interview script provided in the CHQ's user manual. Each parent was also asked a series of questions regarding their child's health status (asked to identify from a list which health conditions their child had according to a health professional or a school official), the child's history of ADRs and related utilisation of health care services, and background demographic questions about themselves.

Data analysis

Raw data were entered into a database, and recoded and recalibrated according to instructions in the CHQ manual, using SPSS 11.0 for Windows. For each individual sub-scale, a transformed score between 0 and 100 was computed according to CHQ algorithms, with a higher score indicating higher HRQL. Then, using the means of the transformed scores for each of the sub-scales, physical and psychosocial summary scores were calculated using a linear T-score transformation algorithm outlined for the CHQ. This norm-based transformation method uses the means and standard deviations of normative data to generate these two summary scores[6]. This form of standardisation allows for easy comparison of CHQ scores among different groups of children.

Independent samples *t*-tests with two-tailed *P* values were used to compare the means among children with one ADR, children with multiple ADRs, and healthy children using published means and standard deviations for raw normative data. A P value ≤ 0.05 was used to signify a statistically significant difference. One-way ANOVA analyses were not conducted among the three groups of data since the raw normative data were not available.

Results

Description of the samples

Of the 80 parents originally contacted by mail, 42 participated in this study. Participants consisted of 21 with a child who had an ADR to one antibiotic (Group A), and 21 with a child who had ADRs to multiple antibiotics (Group B). Of the parents who did not participate; 21 were lost to follow-up (that is, had moved from the address on file and/or the telephone number on file was incorrect or out of service), five were lost to follow-up despite correct telephone numbers, five refused to participate, five agreed to participate but could not find time to be interviewed within the time constraints of the study, and one was excluded when the parent stated that the ADR had occurred in the subject's sibling. One child, with a history of an ADR to one antibiotic, was subsequently excluded from the study when the family moved, thus no longer meeting the inclusion criterion of living within a two hour driving distance.

Table 1 Child and parent demographics

	Children with one ADR	Children with multiple ADRs	Normative data[6]
Child			
% Female	38	71	45
Age (years), mean ± SD	11.0 ± 3.1	10.6 ± 3.4	11.5 ± 3.7
Grade, mean ± range	5.1 ± 3.0	5.0 ± 3.5	5.2 ± 3.6
First child (%)	38	43	–
Number of health conditions, mean ± SD	1.7 ± 1.6	3.1 ± 2.6	1.2 ± 1.2
Parent			
% Female	100	100	65
Age (years), mean ± SD	40 ± 6	41 ± 6	40 ± 7
% Biological parent	95	100	94
% Working full or part time	81	71	78
Highest level of education			
% Some high school or less	0	9	10
% Completed high school	33	29	29
% Vocational school or college	43	48	26
% University	10	9	22
% Professional	14	5	13
Marital status			
% Married	90	90	77
% Divorced	5	5	10
% Separated	5	5	3
% Other	0	0	10
Rac			
% Caucasian	100	100	83

Table 2 Incidence of co-morbid conditions in children as reported by proxy respondents

	Prevalence of co-morbid conditions		
	Children with one ADR, %	Children with multiple ADRS, %	Children from general US population[6], %
Chronic allergies or sinus trouble	33	48	18
Attention problems	14	33	19
Anxiety problems	0	33	5
Asthma	29	29	12
Behavioural problems	14	19	15
Learning problems	9	19	12
Sleep disturbance	0	14	2
Chronic musculoskeletal	9	9	3
Speech problems	9	9	12
Vision problems	14	0	19
Hearing impairment	0	9	4
Depression	5	5	5
Chronic respiratory	0	5	4
Developmental delay	0	5	3
Other chronic medical condition	29	43	5

The demographic characteristics of the children and their proxy respondents are summarised in Table 1. Among children with one ADR, 38% were female, compared to 71% of the children with multiple ADRs (P = 0.03). Children with multiple ADRs had more co-morbidities than the children with only one ADR (3.1 vs. 1.7, P = 0.033). The demographics of the children and parents comprising the normative general population sample (provided in the CHQ manual) are presented for comparison. It should be noted that this demographic information is for all American families sampled and not the sub-sample of Caucasian subjects used in our HRQL comparison, for which demographic data was not available.

The majority of children in this study had one or more co-morbid conditions. Specifically, 86% of the children with multiple ADRs and 71% of the children with one ADR had at least one health condition in addition to a history of ADRs. A summary of children's co-morbid conditions as identified by parents, from a standard list is found in Table 2. Other health conditions not included in the list but reported by parents include: migraine, eczema, dysmenorrhoea, musculoskeletal pain, Attention Deficit Hyperactivity Disorder, sensitive skin, plantar fasciitis, vesicoureteral reflux, Asperger Syndrome, Charcot-Marie-Tooth Disease, Ehlers-Danlos Syndrome, and mitral valve prolapse. Many of the children in the study had developed significant co-morbid conditions that were not previously recorded in the respective charts, since it may have been up to five years since they had seen a paediatric pharmacologist, and were therefore not excluded from the study.

Table 3 shows responses to a series of questions regarding the number of times the child had visited various health care facilities for a suspected ADR. Listed are the percentages of children who used specific health care services for an ADR suspected by the parent and, for those who had used a service, the average number of times used. It is evident that children with multiple ADRs accessed health care services more frequently than did children with one ADR.

Health-related quality of life

Mean CHQ sub-scale scores and summary scores for children with one ADR, children with multiple ADRs, and normative data are presented for comparison in Table 4. These CHQ data reveal that children with multiple ADRs scored lower than children with a single ADR in 11 sub-scales and lower than healthy children in 10 of the 12 sub-scales. One sub-scale, general health perception, demonstrated a statistically significant lower score among children with multiple ADRs when compared to the other two sample groups. The physical and psychological summary scores among children with multiple ADRs were lower than the scores of children with one ADR and healthy children.

Table 3 Child health care utilisation in relation to suspected ADRs

	Children with one ADR		Children with multiple ADRs	
	%	Mean number of visits	%	Mean number of visits
Visited family doctor/paediatrician	43	1.1	86	3.7
Visited walk-in clinic	5	1.0	16	1.0
Visited hospital emergency room	24	1.4	53	2.7
Admitted to hospital	5	1.0	16	1.0

Table 4 Mean CHQ-PF50 subscale and summary scores

CHQ-PF50 scale	Children with one ADR	Children with multiple ADRS	Normative Caucasian data
	Mean ± SD	Mean ± SD	Mean ± SD
Physical functioning	98 ± 4	95 ± 11	97 ± 11
Emotional or behavioural difficulties	94 ± 18	88 ± 20	94 ± 17
Role/social limitations of physical health	98 ± 7	90 ± 23	95 ± 16
Bodily pain and discomfort	81 ± 16	73 ± 29	82 ± 19
Behaviour	75 ± 18	73 ± 29	76 ± 16
Mental health	77 ± 15	74 ± 10	79 ± 13
Self esteem	86 ± 11*	80 ± 15	80 ± 18
General health perceptions	78 ± 16	64 ± 20**	74 ± 17
Emotional impact on parent	82 ± 23	73 ± 21	81 ± 18
Time impact on parent	93 ± 17	92 ± 12	89 ± 17
Family activities	83 ± 22	85 ± 11*	91 ± 17
Family cohesion	85 ± 19*	76 ± 22	73 ± 22
Physical summary	55 ± 5	50 ± 10	54 ± 8
Psychosocial summary	52 ± 10	50 ± 8	51 ± 9

* Statistically significant difference compared to normative sample.

** Statistically significant difference compared to one ADR sample and normative sample.

In contrast, the group of children with a single ADR scored higher than healthy children in 8 of the 12 CHQ sub-scales. In fact, the children with one ADR had a statistically significantly higher score than the healthy children in two sub-scales: self-esteem and family cohesion. The physical and psychosocial summary scores were higher among children with one ADR than the healthy children.

Discussion

The subscale scores generated using the CHQ-PF50 demonstrate that children with multiple ADRs tend to have a lower health-related quality of life as reported by parents when compared to children with one ADR and healthy children. The lowest score was obtained by children with multiple ADRs in the general health perceptions sub-scale, and this was significantly lower when compared to the other two groups. This sub-scale incorporates six questions on the CHQ-PF50 that address issues such as the parent's perception of the child's health in general, the child's health compared to other children, and whether the parent worries more about the child's health than other parents. Lower scores on this sub-scale supports the observation of paediatricians working with this group of children that in general, parents of children with multiple ADRs are more anxious about their child's health than parents of children with a history of one or no ADR.

Through anecdotal reports from parents, factors that may influence parental anxiety were identified. The parents of children with multiple ADRs commented that they expend a great effort to ensure this child sees the family doctor or paediatrician who knows the child's drug history, rather than any other physician, out of fear that this child might receive a potentially dangerous drug. Conversely, some parents stated that they avoid taking this child to the doctor at all, preferring to wait to see if the child will recover without the use of prescribed medication. An important point, made by one parent, was that ADRs tended to occur when a child is ill, and when a child reacts to one or more drugs, there is a fear that no drug will be tolerated. Moreover, it is usually the parent who must deliver the next potentially harmful drug to the child with a history of ADRs, generating feelings of anxiety, guilt, and powerlessness.

Children with multiple ADRs had more co-morbidities than children with one ADR. Since a generic measurement tool was used to assess HRQL in this study, it is not possible to differentiate the role of co-morbidities and ADRs. Children with multiple ADRs may have other associated health conditions that undoubtedly affect HRQL. A prospective study could evaluate the potential causal mechanisms for lower HRQL in these children. This study would require a large sample, a detailed assessment of co-morbidities, and multivariate analyses to simultaneously consider other relevant risk factors and co-variates.

There are several limitations to the interpretation of the findings from this study. Firstly, this was a small, retrospective cohort study. As previously noted, there is a need for a prospective study with a larger sample on whom comprehensive information on all potentially relevant data (other risk factors and co-variates) are collected to determine if in fact ADRs are a significant risk factor for lower HRQL after adjusting for all relevant factors. It is possible that general health status combined with socio-economic status account for the differences observed.

A further limitation related to this study's retrospective design is that in most cases, data were collected several years after the ADR had occurred.

Many parents indicated that their answers would have been different had the questions been asked at the time their child was sick and reacting adversely to medication. There is a need for a prospective study where data collection occurs at the time the child is seen in the ADR clinic. This would allow the investigator to systematically document the exact number of ADRs experienced by each child, their co-morbidities and past medical history for more valid comparisons. Additionally, asking HRQL questions at the time of the ADR or the first visit to the ADR clinic would enable a subsequent HRQL evaluation to be conducted at a later date to assess the long term effects of one or more ADRs.

Another limitation of this study is that subject eligibility was determined by a retrospective chart review. The information gathered from the ADR clinic charts was not standardised, and at times not up-to-date, making it difficult to determine the exact number of ADRs some children had experienced. Additionally, the normative data used for comparison in this study were from the United States, which might be different than data derived from a Canadian sample, given the contrasting access to health care services, among other disparities. As well, the female to male ratio among the three groups is quite different, due to differential loss to follow up. Finally, children's HRQL was assessed using proxy respondents. While this approach was reasonable in this pilot study, attempts should be made to also consider the perspective of the child in future studies.

This pilot study provides preliminary evidence that children with ADRs to multiple antibiotics may have a lower health-related quality of life in physical and psychosocial domains compared to both healthy children and to those with an ADR to only one antibiotic. Despite the limitations of our study, an interesting question is raised as to the reason for the lower HRQL that was observed. Our study supports the need for a larger prospective study that will allow for differentiation of the role of the multiple adverse drug reactions versus co-morbid health conditions on HRQL. If HRQL is in fact compromised, then the causal factors need to be investigated in order to provide appropriate comprehensive care to this unique group of children.

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