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Personalised medicine

Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population

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ABSTRACT

Acceptability of medicines for children is a challenge, yet critical to ensure adherence to treatment. There is very little literature on formulation factors that influence acceptability of medicines, particularly in the domiciliary environment. This pragmatic study was conducted at University Hospital Coventry and Warwickshire (UHCW) with the aim of identifying the prevalence and nature of oral formulation-related barriers to medicines administration in children suffering from long-term conditions.

This study used semi-structured face-to-face interviews with 221 parents/carers of children (0–18 years) and 57 young people (12–18 years).

Result: showed significant medicines refusal and manipulation in the domiciliary environment. Nearly one-third (71/232) of respondents reported medicines refusal. This was associated significantly with the age of child ($p = 0.016$), socioeconomic status (IMD 2010 score) ($p = 0.002$), taste ($p < 0.001$), texture ($p = 0.017$), and volume (of liquid/powder) or quantity (of solid dosage form) ($p < 0.001$). 29% (74/252) of respondents reported manipulating medicines. *P*-values are based on multivariable statistical analysis models.

This study has indicated that formulations prescribed to children with chronic conditions are not meeting the needs of a significant number of patients based on self-report. Age-appropriate medicines are required to provide suitable dose units with an acceptable taste for children. This study should aid pharmaceutical companies to prioritise paediatric formulation work.

1. Introduction

Approximately 200 million prescriptions are issued annually for children and young people in the UK (Costello et al., 2004). Previous studies have investigated medicines adherence in children, however these have not explored potential barriers to adherence in the domiciliary setting. In this paper, barriers are defined as obstacles that could result in non-adherence of medicines (e.g. forgetting, refuse, hard to swallow, etc.).

There is a paucity of studies investigating barriers to medicines administration arising from oral formulations (particularly those related to organoleptic and physical properties) in children with chronic conditions. Those studies reported previously are limited to specific disease groups, e.g. antiretroviral medicines in Human Immunodeficiency Virus (HIV) (Boni et al., 2000; Gibb et al., 2003; Goode et al., 2003; Marhefka et al., 2004; Pontali et al., 2001; Wrubel et al., 2005). Further studies compare the acceptance and flavour preferences of a spectrum of drugs from one class (e.g. antibiotics) using a "one-off" taste test method, commonly with the aid of a visual analogue scale (VAS) most often in healthy children or adults (Bagger-Sjöbäck and Bondesson, 1989; Chan et al., 1997; Cohen et al., 2009; El-Chaar et al., 1996; Samulak et al., 1996; Toscani et al., 2000).

The present study targets a large paediatric population suffering from different chronic conditions. The palatability of paediatric medicines is one of the most important formulation factors with potential to influence adherence to therapeutic

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regimens and outcomes (Salunke et al., 2011). It has been demonstrated that making medications more pleasing to the child can have a positive effect on compliance (Winnick et al., 2005). Refusal of a formulation was defined in the present study as, 'complete omission of a dose by intent on at least one occasion, including spitting the dose back out, and/or closing the mouth' and medicine manipulation was defined as 'a medicine physically adapted to facilitate medicines administration or for the purpose of giving a specific dose'.

The importance and incentive to study the palatability of paediatric formulations was discussed in the reflection paper (EMEA, 2006) and endorsed in the latest European Paediatric guideline on pharmaceutical development of formulations for paediatric use (EMA, 2013).

The aims of the present study were: (i) to identify the prevalence and nature of oral formulation-related barriers to medicines administration in children suffering from long-term conditions in a domiciliary environment; (ii) to identify the prevalence of children refusing formulations and also determine which formulation factors influenced oral medicines refusal and (iii) to evaluate the prevalence and nature of oral medicines manipulation by parents, carers and children in the domiciliary environment.

2. Materials and methods

2.1. Data collection tool

Understanding formulation acceptability in a domiciliary environment requires the use of alternative means of data collection compared to in-patient studies. A semi-structured interview was selected for this study to obtain the appropriate balance in data collection and subsequent analysis (Malim and Birch, 1996). During a semi-structured interview, the interviewer is able to show empathy and alter phrasing of questions in order to elicit detailed and considered responses from participants; these benefits have been previously shown to provide more detailed outputs (Gillham, 2000) and an increased response rate (Chambers, 2000) compared to paper-based questionnaires.

A multidisciplinary research team (Professor in Clinical Pharmacy, paediatric consultant and pharmacist) generated an outline of key problems with administering oral formulations to children; these issues were refined via four focus groups with healthcare professionals at the University Hospital Coventry and Warwickshire (UHCW) and Birmingham Children's Hospital (BCH). The data collected, in addition to self-report methodologies referenced in published studies (Medical Adherence Measure – MAM (Ingerski et al., 2009; Zelikovsky et al., 2008), Treatment Interview Protocol – TIP (Marhefka et al., 2004), Paediatric AIDS Clinical Trials Group PACTG questionnaire (NIAID)[1] and Morisky Scales (Morisky et al., 2008, 1986) were used to inform the design of the self-report semi-structured interview tool. The Young Persons Advisory Group (YPAG) at Birmingham Children's Hospital ($n = 12$ members) reviewed the tool to ensure that it was age appropriate.

The 13-item self-report tool (Supplementary file 1) used in the semi-structured interviews was designed to collect data exploring medicines adherence including medicines refusal (see Q5 in Supplementary file 1), medicines manipulation (see Q3a in Supplementary file 1) and barriers to medicines administration (see Q3b in Supplementary file 1) in parents, carers and children themselves. Open questions were used to elicit reasons for medicines refusal to avoid bias.

[1] NIAID, Pediatric AIDS Clinical trials group (PACTG), Pediatric adherence questionnaire: module 2 General reasons for non-adherence, QL5001.

A semi-structured interview was conducted by a single researcher (post-graduate pharmacist (RV) – not previously known to the patients) to minimise variation in approach and the responses were entered manually onto a structured data record during each interview. The interviews (maximum duration of 45 min) were conducted in a private area at the paediatric outpatients department at UHCW at times scheduled to coincide with routine clinical appointments. Ethical approval was granted by the South Birmingham REC and informed consent was obtained for all participants.

Participants were invited to provide demographic information in order to generate an Index of Multiple Deprivation 2010 (IMD 2010) score.

2.2. Qualitative analysis

Themes were identified using a frame-work analysis approach to form a coding spine. Thematic content analysis (Pope et al., 2000) was used to identify and group common themes,relating to medicines administration. Qualitative data was analysed using NVivo 8 software (QSR International).

2.3. Statistical analysis

Statistical analysis was conducted using generalised estimating equations to explore the relationship between independent variables (e.g. child age, IMD score, formulation type) and dependent variables with binary outcomes (refusal or manipulation).

Patient, participant and data on formulations were converted into categorical variables (see Tables 2 and 3).

Data analysis was performed on an individual medicine level facilitating comparisons between medicine specific variables (e.g. different medicine groups and formulations), which are not possible at a patient level. In order to account possible non-independence of data owing to any response correlation to medicines taken by an individual, univariable generalised estimating equations were used. The univariable analysis did not control for potential relationships between independent variables therefore multivariable analysis was also conducted using the combination of independent variables found to be significant ($p < 0.05$) for the dependent variables in the univariable model (medicines refusal, medicines manipulations). This generated odds ratios, 95% confidence intervals and associated p values. The data was analysed using SPSS version 20 software (IBM).

2.4. Study setting and study participants

A pragmatic approach was employed to identify and recruit participants resulting in a total of 1559 study invitation letters being posted to patients (via their parent/carer) due to attend follow-up paediatric clinics (1448/1559) or handed out on the paediatric wards (111/1559) at UHCW. Study interviews were conducted with parents or carers (if legal guardians) of children or young people, or with young people directly. The opportunity to assent and participate alone was given to 12–16 years old providing parent or carer consent was also obtained. Young people over 16 years of age were permitted to consent alone and encouraged to discuss the study with a parent or legal guardian before providing consent. It was necessary to include young people (those over 12 years of age), where appropriate as this sub-population reported increased personal management of their medicines administration. Parents or carers views were more useful for younger children where they may not have the cognitive capability to participate alone.