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The prescribing of analgesics and non-steroidal anti-inflammatory drugs in paediatric primary care in the UK, Italy and the Netherlands

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly prescribed drugs which are frequently used for the treatment of various painful conditions. However, particularly for the paediatric population, there is a lack of information on effectiveness, safety and appropriate formulation resulting in off-label use and undertreatment.

The aim of this study was to investigate the prescribing patterns of non-steroid anti-inflammatory drugs and opioids in children and adolescents in three European countries.

A retrospective cohort study was conducted using the same protocol in three primary care databases: Pedianet (Italy), IPCI (Netherlands) and IMS Disease Analyzer (UK). User prevalence rates were calculated for opioids (N02A) and non-steroidal anti-inflammatory drugs (NSAIDs) (M01A) based on ATC therapeutic and chemical levels and stratified by country, age and gender.

The prescribing prevalence for NSAIDs was lower in the Netherlands compared to Italy and the UK. Ibuprofen was the most frequently prescribed drug in this group in Italy (20.8 users/1000 PY) and the UK (30.6 users/1000 PY) whereas diclofenac was dominant in the Netherlands (1.7 users/1000 PY). Among opioids, codeine and codeine combinations were most commonly prescribed; only little use was seen for other drugs.

There is a great variety of different NSAIDs and opioids prescribed to children in Europe in primary care. This is due to a varying availability of drugs in different countries but also because of differing prescribing attitudes, reimbursement scheme and a lack of data on the effectiveness of individual drugs. Further research into the rationale for prescribing these drugs to children is clearly needed.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly prescribed drugs which are frequently used for the treatment of various painful conditions. Although pain is a common condition in children; it is frequently under-treated in this population [1–4].

A number of non-steroidal anti-inflammatory drugs (NSAIDs) are available on the European market and used for various indications such as fever, post-operative pain and inflammatory disorders such as juvenile idiopathic arthritis (JIA) and Kawasaki disease. Although generally well tolerated these drugs are associated with serious adverse reactions such as upper gastrointestinal ulcers and/or bleeding, nausea, diarrhea, hypersensitivity reactions and renal failure [5]. A study of adverse drug reactions to simple analgesics in a children's hospital in Australia, revealed three times as many reports for NSAIDs as for paracetamol over the same timeframe, in a comparable age range [6].

Opioids are predominantly used for the management of moderate to severe pain such as post-operative and cancer pain or in

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; JIA, juvenile idiopathic arthritis; EMEA, European Medicines Agency; TEDDY, Task Force in Europe for Drug Development for the Young; IPCI, Integrated Primary Care Information; GP, General Practitioner; ICH, International Conference of Harmonization; ATC classification, Anatomic Therapeutic Chemical Classification; IMS-DA, IMS Disease Analyzer.

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Table 1
Total number of children and person-years (PY) contributed to the study from each country.

Age group	IMS-DA (UK)		IPCI (Netherlands)		Pedianet (Italy)		Total	
	Children no.	PY no.	Children no.	PY no.	Children no.	PY no.	Children no.	PY no.
0 < 2 years	95,060	106,248	25,694	36,599	56,000	87,421	176,754	230,269
2–11 years	262,306	855,678	62,326	158,879	103,195	296,139	427,827	1,310,696
>11 years	229,959	683,900	40,364	87,078			270,323	770,978
Total[a]	444,822	1,645,827	101,559	282,557	129,487	383,560	675,868	2,311,944

[a] Number of children in various age groups does not add up to total as one child can contribute to more than one.

sickle cell disease [7]. These drugs can induce a long list of adverse drug effects, such as constipation, nausea and vomiting, respiratory depression and potential drug misuse; hence physicians often hesitate in prescribing these drugs to children.

There are various drugs available for the treatment of pain, however, a recent workshop organized by the European Medicines Agency (EMA) concluded that there is a need to harmonize paediatric pain management in Europe through specialists and academia, and to further educate all concerned physicians in recognising and treating pain [8].

Unfortunately, there is very little information about the prescribing of NSAIDs and opioids in children. In response to this information evidence gap, the TEDDY network (An EU Commission-funded network of paediatricians and academia) conducted this study with the aim to characterize the prescribing pattern and trends of NSAIDs and opioids in primary care in children in Italy, the Netherlands and the UK. These data will provide much needed information to allow the paediatric healthcare professionals, researchers and regulators to develop future studies and guidelines to improve pain control in children.

2. Method

A retrospective cohort study was conducted using the same protocol in three primary care databases: the Pedianet database in Italy [9–11], the Integrated Primary Care Information (IPCI) database [12–16] in the Netherlands and the IMS Disease Analyzer (IMS-DA) database in the United Kingdom (UK) [17–19].

The Pedianet database comprises data on about 180,000 children provided by 105 primary care paediatricians. The IPCI database contains information from electronic patient records of 400[1] GPs covering more than 1,000,000 patients. The IMS-DA database in UK comprises longitudinal patient data which capture primary care interventions made by the GP on 3 million anonymous patient records provided by 570 doctors.

All three databases comprise patients' complete automated medical records from physicians in primary care settings. In all three countries children need to be registered with a GP (the United Kingdom and The Netherlands) or a paediatrician (Italy); hence all three databases are population based. Data are recorded for children and adolescents aged 0–18 years in The Netherlands and the United Kingdom, whereas data were available only up to the age of 14 years in Italy. Prescribed drugs in the Pedianet and IPCI databases are coded based on the World Health Organization (WHO)-Anatomical Therapeutic Chemical (ATC) classification (WHO, 2008). Prescriptions held in the IMS-DA database are coded based on the ATC classification issued by the European Pharmaceutical Market Research Association (EPhMRA, 2008). The age and sex distribution for all three databases is representative for the country of origin. All three databases have been characterized [20] and used in paediatric research previously [9–13,21,22]. Comparative studies have been previously conducted and demonstrated that data are comparable in all three databases [22,23].

2.1. Study population

The study population was comprised of all children aged less than 18 years from the UK and the Netherlands. In Italy, children are usually transferred to adult physicians between 13 and 14; therefore data were censored at the age of 11 years to allow direct comparison. All patients must have a database history of at least 6 months, or were born during the study period (1 January 2000–31 December 2005).

Each child was followed from the start of the study period or the date of registration with the primary care practice (whichever was the latest), until the child left the practice or the end of the study period whichever came first.

The number of children in the study population and the person-time of follow-up of each child was calculated and stratified by calendar year and age group. Age was assessed on 1 January of each year and grouped according to the guidelines of the International Conference of Harmonization (ICH) as <2 years, 2–11 years and ≥12 years [24]. Details of the study population are shown in Table 1.

2.2. Data extraction and analysis

Based on the ATC classification system drugs belonging to M01A (non-steroidal anti-inflammatory products) and N02A (opioids) were considered in the analysis. In addition all codeine prescriptions with an indication for pain were retrieved from the ATC category R05 in both IPCI and Pedianet as R05 is the only WHO ATC code for codeine. The EPhMRA ATC Classification used in IMS provides different codes for codeine used for pain and codeine products for cough so only prescriptions related to a pain indication were included. All combination products containing at least one opioid component were classified as opioids.

Prevalence was defined as the number of subjects with at least one prescription of the respective drug class or drug during the year of investigation divided by the total number of person-years attributed during that year of investigation. Person-years were used as the denominator for calculating prevalence due to the dynamic natures of age and the population of the databases. Prevalence was stratified by country, age and gender. The 95% confidence intervals (CIs) around the prevalence estimate were calculated based on a Poisson distribution. A χ^2 (Cochran-Armitage) test for trend was used to examine yearly trends of drug prescribing. Analyses were carried out using Stata/SE version 9.1 (Statistical Software: Release 9.1, College Station, TX).

3. Results

The total study population consisted of 675,868 children generating 2,311,944 person-years (PY) of follow-up (Table 1). Over the 5-year period a total of 124,514 prescriptions were issued for non-

[1] At the time of data collection 150 GP's contributed data to the database.