SHORT COMMUNICATION

Drug Saf 2011; 34 (4): 307-317
0114-5916/11/0004-0307/$49.95/0

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Dose Variations Associated with Formulations of NSAID Prescriptions for Children

A Descriptive Analysis of Electronic Health Records in the UK

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Abstract

Background: NSAIDs, particularly ibuprofen, are commonly prescribed for children but there is limited published research on real-life prescribed doses for this class of drugs.

Objective: The aim of the study was to investigate if variations in NSAID doses prescribed to children can be explained by patient age, indication, dosage form, type of NSAID or year of prescription.

Study Design: Recorded daily doses for drugs within the 'Anti-rheumatics, non-steroidal plain' anatomical classification were studied. First prescriptions of a distinct NSAID substance within 13-month time periods in a patient's history were included. To enable grouping and comparison of NSAIDs, doses were analysed as prescribed daily doses (PDDs) relative to the adult defined daily dose, stated as the relative PDD (rPDD) in this study. Multiple regression analysis was performed with the rPDD as the response variable, and age, indication, dosage form, NSAID substance and year of prescription as the explanatory variables.

Setting: Prescriptions from the Intercontinental Medical Statistics (IMS) Health Disease Analyzer database containing electronic health records of general practitioners in the UK issued from 1988 to December 2005.

Patients: Data for children aged 2–11 years with NSAID prescriptions including daily dose information.

Results: A total of 21 473 first prescriptions for 19 695 patients were studied. The vast majority of prescriptions were for ibuprofen (n = 20 855), which were therefore analysed separately. The other NSAID prescriptions were grouped (n = 618), containing diclofenac, indometacin, mefenamic acid, naproxen and piroxicam ('NSAID group'). The rPDD varied considerably with dosage form in both the ibuprofen and NSAID groups. In particular, tablets/capsules were

prescribed at higher doses than liquid dosage forms. In the NSAID group, naproxen was prescribed at noticeably higher doses. The rPDD varied only slightly with age in both groups. Prescriptions indicated for rheumatic disease were associated with lower doses than other indications in the NSAID group. The rPDD was not influenced by year of prescription.

Conclusions: This study shows a correlation between higher prescribed NSAID doses and tablet/capsule formulation, and highlights the need for careful choice of dose formulation when prescribing medicines for children.

Background

Pharmacokinetic and pharmacodynamic properties of a medicine vary in growing children with respect to age, body composition, maturity of drug elimination pathways and organ development.[1,2] The optimal dose for a child must therefore be calculated for each individual, depending on age, weight, body surface area and/or disease. Not all medicines used in children have been tested in this population,[3-5] and child-specific recommended doses are thereby not always available. If the medicinal product is labelled for children, the age ranges for when increments of doses are recommended sometimes varies, even for similar products.[6,7] This adds to the complexity of prescribing a suitable dose of medication for the child. It might not be surprising that dosing errors are a common type of medication error in children.[8,9]

It is encouraging that children's specific needs with medicine usage have appeared on the agenda with respect to regulations for developing medicines used in children.[10-12] Another important improvement is the introduction of the *British National Formulary for Children* (BNFC), where authoritative and best-practice guidance is compiled concerning medicines used in children, including medicines not licensed for this population.[13]

The availability of a suitable dose formulation is imperative to facilitate correct measurement of the dose and to increase the possibility that the child accepts and is able to take the medicine.[14,15] Developments within the area of age-appropriate dose formulations have also been initiated recently.[16-18] In a study on pharmacy dispensing records in the Netherlands, Schirm et al.[19] showed that many children are prescribed oral formulations that are not always appropriate for their age.

With this background, we aimed to investigate if prescribed dose variations could be explained by patient age, indication, dosage form, type of medicine and time of prescription. The study focuses on NSAIDs because of the limited available published research on real-life prescribed doses in children for these medicines despite them being commonly used in this population.

Methods

Intercontinental Medical Statistics (IMS) Health Disease Analyzer

Prescription data was extracted from the Intercontinental Medical Statistics (IMS) Health Disease Analyzer database,[20] which includes electronic health records completed by general practitioners (GPs) in the UK. Records for over 2 million anonymous patients were available in the dataset used in this study. The database is updated monthly and contains patient demographics, prescription details, and information about medical problems and diagnoses. Data quality is maintained by the presence of data quality markers in the database, and collated information from the markers is used as feedback to the GPs; this helps to improve data quality in the database.[21]

Prescription Inclusion Criteria

NSAID prescriptions for children between the ages of 2 and 11 years, recorded from 1988 until the end of 2005, were used. Prescriptions of NSAID substances within the European Pharmaceutical

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Marketing Research Association (EphMRA) anatomical classification M01A1 (Anti-rheumatics, non-steroidal plain) with oral or rectal dosage forms were included, irrespective of indication for use. Substances prescribed for more than 20 patients were used: diclofenac, ibuprofen, indometacin, mefenamic acid, naproxen and piroxicam. Each patient's complete prescription history was used, but to limit the number of repeat prescriptions the analysis was restricted to first prescriptions of these specific NSAIDs within a 13-month period. If the patient had been prescribed, for example, ibuprofen twice, a gap of more than 13 months between the two prescriptions was necessary in order for the second prescription to be included in the analysis. One patient could be counted more than once if prescribed more than one NSAID substance, and be represented in different age groups.

Dose and Dosage Form Evaluation

In order to calculate the prescribed daily dose (PDD), a strict criterion was set for each prescription to include strength, amount (e.g. 'one tablet') and frequency (e.g. 'twice daily'). Prescriptions recorded with an unspecific amount, or frequency given with 'as directed' or 'as needed' were excluded from the analysis. The dosage forms were grouped into 'liquid' (suspension, syrup), 'tablets/capsules' (e.g. tablets rapid, retard, soluble, dispersible, forte, melt and capsules), 'suppositories' and 'granules'. To be able to group and compare the different NSAID doses in the statistical analysis, the PDD was given as a proportion of the adult defined daily dose (DDD), which is the daily assumed average maintenance dose for a substance used for its main adult indication based on adults weighing 70 kg, according to the WHO Collaborating Centre for Drug Statistics Methodology.[22] The statistical result is therefore given as a proportion of the adult DDD, denoted *relative* PDD (rPDD) in this paper. The rPDD was calculated using the following adult DDDs: ibuprofen 1200 mg, diclofenac 100 mg, indometacin 100 mg, mefenamic acid 1000 mg, naproxen 500 mg and piroxicam 20 mg.[22] If the PDD was ibuprofen 300 mg, then the rPDD was 0.25 of the adult DDD (300/1200) in this study. The rPDD was used with the only intention to present and analyse data in this study and not to suggest that an adult DDD is a good benchmark to determine what an appropriate dose would be for a child, since that is a much more complex issue.[2,23]

Statistical Evaluation

Descriptive statistics were generated using Microsoft Access® and Excel®. The vast majority of prescriptions were for ibuprofen, therefore these prescriptions were analysed separately from the rest of the NSAIDs. The NSAID group, excluding ibuprofen, will be referred to as the 'NSAID group' containing diclofenac, indometacin, mefenamic acid, naproxen and piroxicam prescriptions. For both groups, multiple linear regression was used to determine the influence of age, indication, dosage form, type of NSAID substance and time of prescription on the rPDD. The prescriptions in the IMS Health Disease Analyzer are linked to a defined medical problem coded with the Read terminology, referred to as 'indication' in this study. The variable related to indication, included in the regression analyses, denotes whether or not a prescription was indicated for rheumatic disease, which could be suspected to be associated with the prescribed dose. Time of prescription (measured in years from the first of all prescriptions) was included to detect any influences on the prescribing pattern over time. The analyses were performed with the statistical software R.[24] Details on the variables used in these analyses are given in table I.

Results

Between the years 1988 and 2005, 35 803 first prescriptions of a NSAID were extracted. After exclusion of 12 154 prescriptions with dosage instructions limited to 'use as directed' or 'unknown', and 2170 prescriptions with unspecific amount or frequency in the dosage records, plus six erroneous prescriptions belonging to four patients, a total of 21 473 first prescriptions for 19 695 patients remained and were included in the analysis. There were 20 855 prescriptions in the ibuprofen group and 618 in the NSAID group.

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Table I. Outcome and explanatory variables used in the statistical analyses

Variable	Unit	Type	Possible values
Outcome variable			
rPDD	Proportion of adult DDD	Numerical	Positive, real-valued
Explanatory variables			
Age	Years	Numerical	Positive, real-valued
Time of prescription	Years (from 10 June 1988)	Numerical	Positive, real-valued
Dosage form		Categorical	Tablet/capsule, liquid, suppositories, granules
Substance[a]		Categorical	Diclofenac, indometacin, mefenamic acid, naproxen, piroxicam
Indication		Categorical	RA, others

a Only used in the analysis of the NSAID group.

DDD = defined daily dose; **RA** = indications related to rheumatoid arthritis; **rPDD** = relative prescribed daily dose.

The number of prescriptions by substance, dosage form and age group (2–3 years, 4–5 years, 6–8 years and 9–11 years) is shown in table II. Most prescriptions were for ibuprofen liquid formulation, followed by ibuprofen tablets/capsules and thereafter diclofenac and mefenamic acid tablet/capsule prescriptions. Liquid was by far the most commonly prescribed dosage form in the ibuprofen group (89%), while tablets/capsules were more commonly prescribed for the other NSAIDs (76%).

Regression Analyses

The major finding was that in both the ibuprofen and NSAID groups, the rPDD varied considerably with the prescribed dosage form. In particular, tablets/capsules were prescribed at much higher doses than liquids. The mean adjusted difference in rPDD between tablets/capsules and liquids was 0.17 in the ibuprofen group and 0.75 in the NSAID group (95% CIs were 0.17, 0.18 and 0.67, 0.83, respectively). These were substantial differences, especially for the NSAID group, which may be realized by converting the mean adjusted rPDD difference into corresponding differences in real doses: an rPDD of 0.75 corresponds to diclofenac or indometacin 75 mg, mefenamic acid 750 mg, naproxen 375 mg or piroxicam 15 mg.

In the ibuprofen group, the rPDD increased with age at a modest rate of 0.02 per year (95% CI 0.02, 0.02), whereas in the NSAID group the rPDD decreased slightly with age (the estimate was –0.01 per year, with a 95% CI of –0.02,

Table II. No. of prescriptions by type of NSAID, dosage form and age group

Substance	Dosage form	Total	Age			
			2–3 y	4–5 y	6–8 y	9–11 y
Ibuprofen	Tablet/capsule	2201	11	19	108	2063
	Liquid	18652	4296	3907	4933	5516
	Granules	2	0	0	0	2
Diclofenac	Tablet/capsule	227	9	15	34	169
	Suppositories	23	5	9	3	6
Indometacin	Tablet/capsule	8	2	0	2	4
	Liquid	7	1	2	3	1
Mefenamic acid	Tablet/capsule	162	3	3	2	154
	Liquid	79	6	9	23	41
Naproxen	Tablet/capsule	48	2	7	6	33
	Liquid	40	3	5	12	20
Piroxicam	Tablet/capsule	24	2	2	3	17

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–0.00). Timing of prescription was not associated with rPDD in any of the groups. Furthermore, a small increase in rPDD, although not statistically significant, was seen in ibuprofen prescriptions indicated for rheumatic disease compared with other ibuprofen prescriptions (mean adjusted difference 0.02, with a 95% CI of –0.01, 0.05). For the NSAID group, however, the rPDD was lower for prescriptions indicated for rheumatic disease than for other indications. The mean adjusted difference was –0.15 (95% CI –0.26, –0.03), an effect greater than for ibuprofen.

Finally, in the NSAID group the rPDD varied with the prescribed substance; in particular, naproxen was prescribed at noticeably higher doses than all other substances. The mean adjusted difference in rPDD between prescriptions of naproxen and indometacin, the substance with the second highest doses, was 0.36 (95% CI 0.17, 0.55). Complementary details of the results from the two multiple linear regression analyses for ibuprofen and the NSAID group can be found in the online supplementary material (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A39).

Review of Prescribed Daily Doses by Dosage Form and Age Groups

Box and whisker plots with median and mean values for the rPDD by dosage form and age group, are displayed in figures 1 and 2 for the ibuprofen and NSAID groups, respectively. Compared with liquid dosage forms, tablet/capsule prescriptions had a higher median and mean rPDD in all age groups in both the ibuprofen and NSAID groups, which is coherent with the results from the regression analyses. The difference was most noticeable among the preschool children (ages 2–5 years). The median rPDD for preschool children with tablet/capsule prescriptions was equal to the adult DDD in the ibuprofen group but higher in the NSAID group (1.5 times the adult dose). For tablet/capsule prescriptions, preschool children also had higher median rPDD than the older age groups.

Box and whisker plots with median PDDs in milligrams for tablet/capsule or liquid dosage forms by each substance and age group are shown in figure 3. For substances with both tablet/capsule and liquid prescriptions, this figure shows a consistent pattern of higher doses for the tablet/capsule prescriptions. This further affirms the results of the regression analyses in this respect. When stratifying the data by substance, dosage form and age group, it resulted in few prescriptions for some of the groups. For all substances but piroxicam, the tablet/capsule doses were higher for the preschool children compared with the older age groups.

The tablet/capsule prescriptions for the 2- to 5-year-olds were further reviewed. Of all 75 tablet/capsule prescriptions (including ibuprofen), 54 prescriptions were equal to or higher than the recommended adult DDD: ibuprofen (n = 23), diclofenac (n = 16), naproxen (n = 8), mefenamic acid (n = 5) and indometacin (n = 2). The indications for these prescriptions were mostly muscle or skeletal problems, of which two were specifically for juvenile arthritis and gout. In 28/54 prescriptions, indication for use was specified. Of all 8318 prescriptions with *any* NSAID and dosage form for the 2- to 5-year-olds, these 54 prescriptions of tablets were the only ones with an rPDD equal to or higher than the adult DDD. The patient records for these 54 prescriptions were reviewed to determine if they were suggestive of overdose; however, no indicative pattern of problems following these prescriptions was found to support this possibility.

Across all age and dosage form groups there were 15 prescriptions with an rPDD of two times or more the adult DDD, all of which were of tablets or capsules; 11 prescriptions of naproxen, 1 of mefenamic acid, 2 of piroxicam and 1 ibuprofen prescription. Of the prescriptions with specified indications (8/15), joint or skeletal pain was most commonly listed.

Discussion

The rPDD varied considerably with dosage form for both the ibuprofen and NSAID groups. In particular, tablets/capsules were prescribed at higher doses than liquid dosage forms. In the NSAID group, naproxen was prescribed at noticeably higher doses. The rPDD varied only

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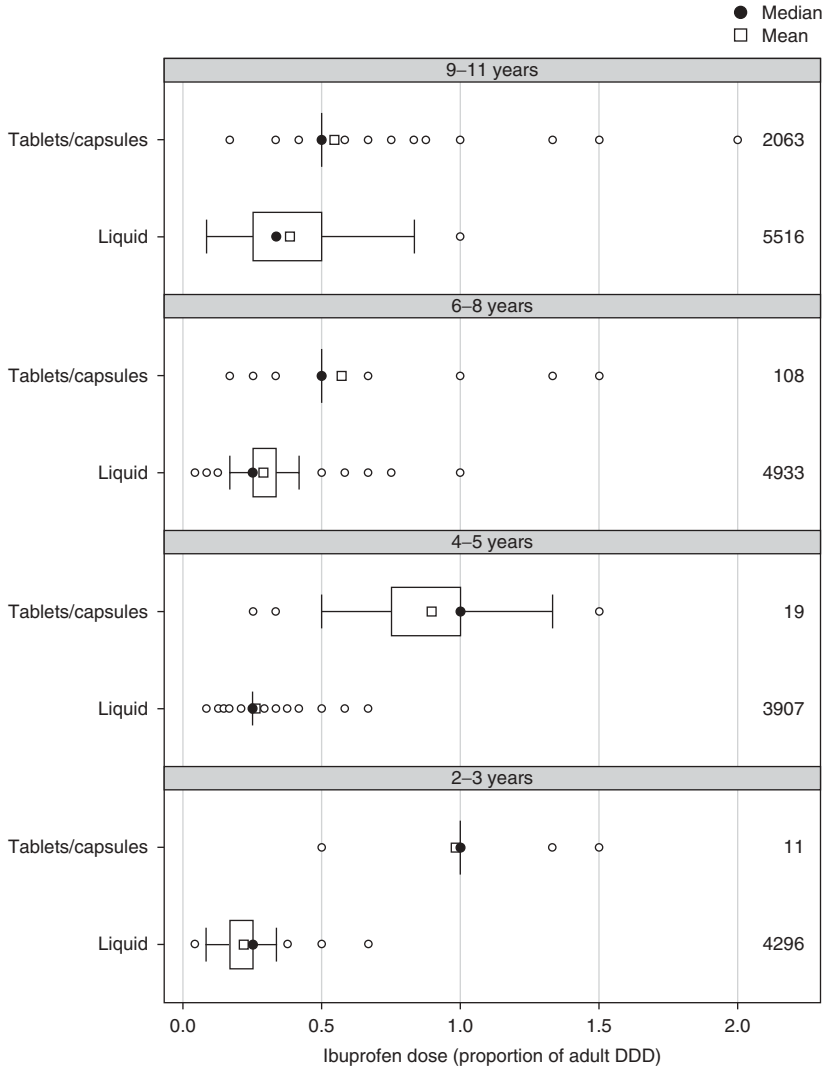

Fig. 1. Relative prescribed daily doses (rPDDs; proportion of adult defined daily dose [DDD]) for the ibuprofen group by dose formulation and age group. Upper and lower box limits denote third and first quartiles (Q3 and Q1, respectively); upper and lower whiskers denote the highest observation still within 1.5 times the interquartile range from Q3 and the lowest observation still within 1.5 times the interquartile range from Q1, respectively. Outliers are denoted by unfilled circles. Numbers to the right indicate the number of prescriptions for the respective groups. The two prescriptions of granules in the 9- to 11-year-old group are not included in the graph because of the low count. The PDD for these two prescriptions was ibuprofen 1800 mg (1.5 times the adult dose).

slightly with age in both groups. Prescriptions indicated for rheumatic disease were associated with lower doses than other indications in the NSAID group. The rPDD was not influenced by time of prescription.

The difference in rPDD between the tablet/capsule and liquid prescriptions was most noticeable for the preschool children (ages 2–5 years), both in the ibuprofen and NSAID groups, although the number of prescriptions was small. The median rPDD was 1 and 1.5 times the adult DDD compared with 0.25 times the adult DDD in prescriptions of a liquid formulation. All 2- to 5-year-old children with an rPDD that was the

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same or above the adult DDD had prescriptions of tablets or capsules. Further investigation of the consequences of these higher rPDDs for the preschool children in this study was done by reviewing recorded medical events within 1 month after the NSAID prescriptions, but no systematic pattern was suggested. This might be explained by the fact that none of the ibuprofen, diclofenac and naproxen prescriptions, which constituted most of the prescriptions for these preschool children with higher doses, exceeded the maximum recommended daily doses, as stated in the BNFC for ibuprofen (2400 mg from 4 years of age), diclofenac (150 mg) and naproxen (1000 mg).[13]

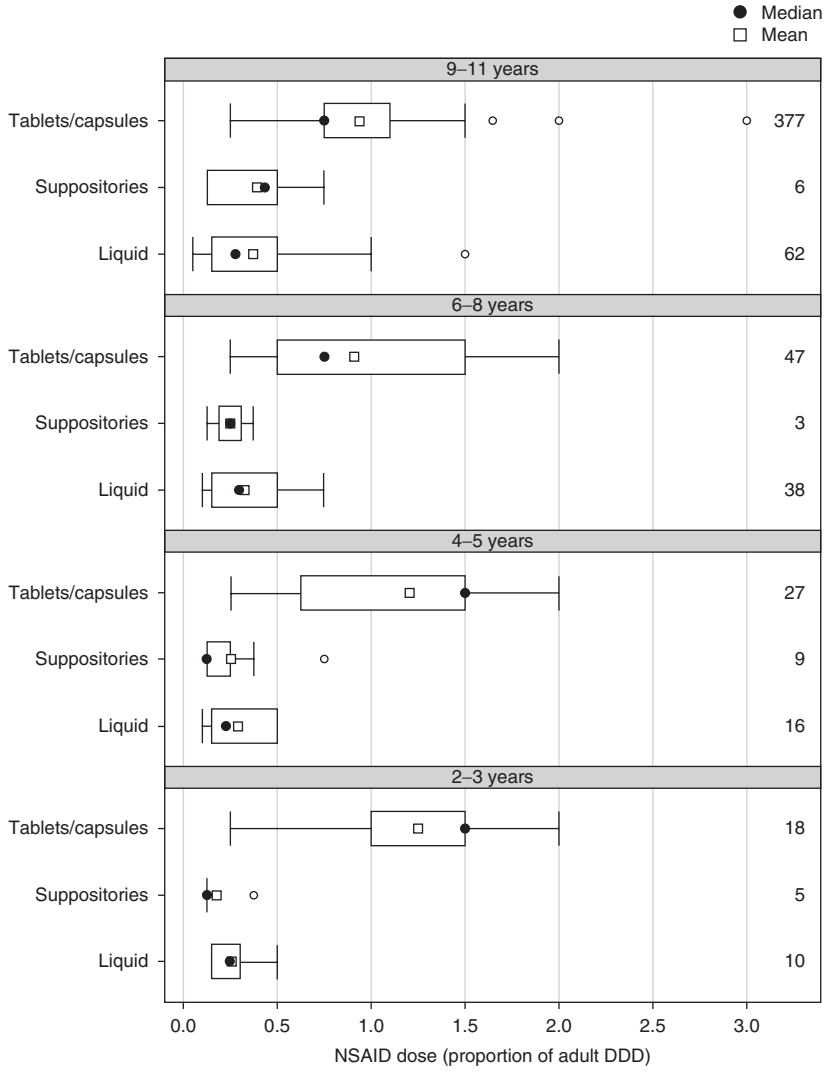

Fig. 2. Relative prescribed daily doses (rPDDs; proportion of adult defined daily dose [DDD]) for the NSAID group, excluding ibuprofen, by dose formulation and age group. Upper and lower box limits denote third and first quartiles (Q3 and Q1, respectively); upper and lower whiskers denote the highest observation still within 1.5 times the interquartile range from Q3 and the lowest observation still within 1.5 times the interquartile range from Q1, respectively. Outliers are denoted by unfilled circles. Numbers to the right indicate the number of prescriptions for the respective groups.

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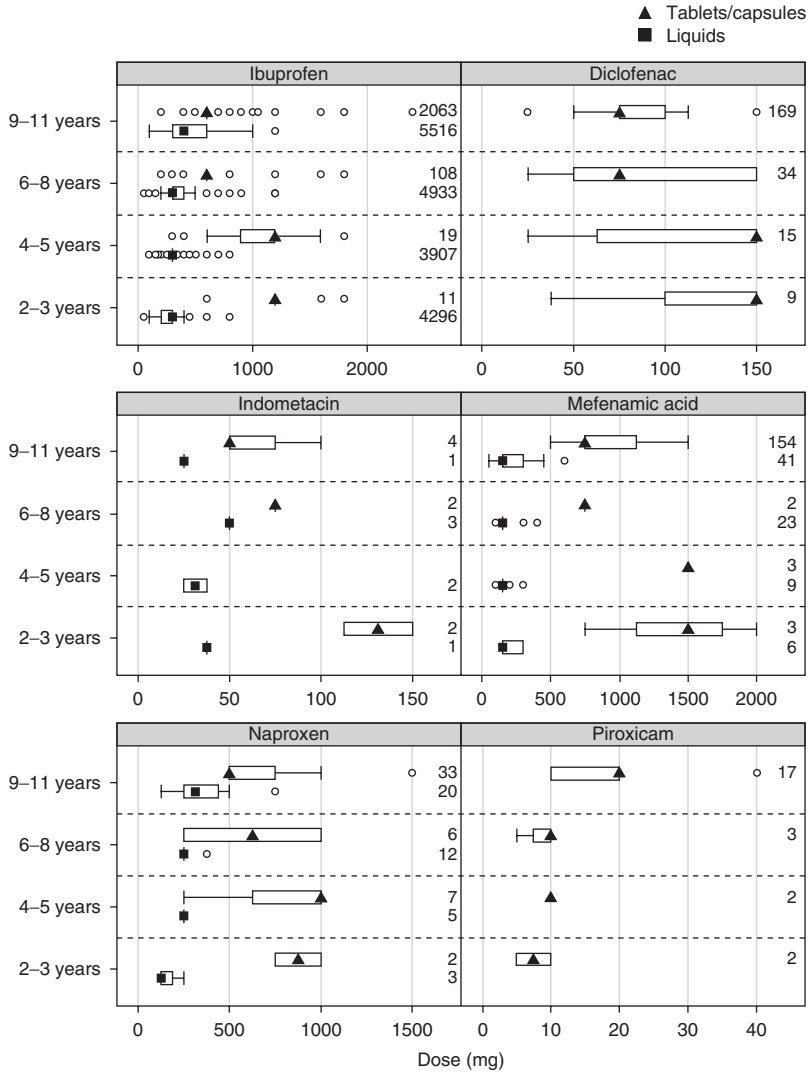

Fig. 3. Prescribed daily doses (milligrams) by NSAID substance, age group and dose formulation. Upper and lower box limits denote third and first quartiles (Q3 and Q1, respectively); upper and lower whiskers denote the highest observation still within 1.5 times the interquartile range from Q3 and the lowest observation still within 1.5 times the interquartile range from Q1, respectively. Outliers are denoted by unfilled circles. Numbers to the right indicate the number of prescriptions for the respective groups. Note that prescriptions of granules and suppositories are not included.

The consistent pattern of higher PDDs for tablets/capsules than for liquids in all age groups and for all substances where a comparison could be made is intriguing. We can only speculate about the reasons for these higher rPDDs of tablet/capsule prescriptions. A possible explanation was that tablets were chosen because a high dose was needed for children with diagnoses such as juvenile idiopathic arthritis, and were found to be easier to administer. However, prescriptions indicated for rheumatic disease were not associated with a higher rPDD in this study. The influence of dosage form on the prescribed dose seen in this study could be a sign of difficulties that GPs

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experience when prescribing suitable doses for children. In a study on attitudes among GPs in the UK, they considered clear dose information and the development of appropriate child formulations as the most important factors to reduce off-label prescribing.[25]

What are the reasons behind prescribing tablets in the first place for young children, as seen in this data? For some of the NSAIDs the choice of dosage form was limited, as for piroxicam where tablet formulation was the only choice, and for diclofenac where the only other alternative was suppositories. The tablet formulation might have been preferred by the parent and therefore requested. In a study on postoperative pain treatment with ketoprofen tablets, the majority of children between 1 and 9 years of age tolerated taking tablets fairly well, although swallowing difficulties were more common in children below 4 years of age.[26] Another explanation for choosing tablet formulation could be because some of them came as dispersible tablets. With this study we can only hypothesize around the observed prescribing patterns. In addition it could not be confirmed whether the prescription was dispensed or if the child actually took the tablet.

Our study has demonstrated that a range of NSAIDs were prescribed for children. Naproxen was prescribed with the highest rPDD and these higher naproxen doses could not be explained by age, indication, time of prescription or dosage form. However, except for one outlier, the PDDs for naproxen were never higher than the maximum recommended dose, as stated for pain and inflammation in rheumatic disease in the BNFC.[13] There are only small differences in the anti-inflammatory activity for the various NSAIDs but the patient response and tolerance can differ.[13] There is a lack of published research for these variations in patient response and tolerance, particularly among children,[27] to serve as a guide when switching or choosing between NSAID products in an attempt to optimize treatment for the child.

The median rPDD for liquid prescriptions was almost the same for the young age groups as for the older children included in this study, both in the ibuprofen and NSAID groups. According to the BNFC,[13] the recommended daily dose for 1- to 4-year-olds with mild to moderate pain or fever is ibuprofen 300 mg, while ibuprofen 900 mg daily is stated for 10- to 12-year-olds. In this study, the median PDD for ibuprofen liquid prescriptions for ages 1–8 years was 300 mg, and 400 mg for ages 9–11 years. Prescribed low doses for children are not an isolated phenomenon in this study alone; they have been noted earlier in studies on children classified as off-label prescriptions.[5-7] There are three possible reasons for prescribing NSAIDs at a low daily dose:

1. The NSAIDs may be effective for the purposes prescribed with lower than recommended PDDs, e.g. they are only needed at a certain time of day, resulting in a low PDD.
2. The lower doses prescribed might suggest uncertainty by the prescriber about what dose to prescribe.
3. The prescriber is cautious of potential adverse effects that could occur from higher doses of NSAIDs.

A major limitation in this study was that the PDDs could not be related to optimal doses for the specific individuals included. The main reason was that weight and height were rarely recorded with certainty at the time of prescription. Comparison across substances was enabled by relating PDDs to the daily assumed average maintenance dose for a substance used for its main adult indication. However, in view of the above limitations, it is not possible to infer, based on the rPDD, for an individual child, whether the dose was too low or too high. Rather, the rPDDs should be seen as a means to studying general patterns in prescribed doses, for example across various age groups.

In only 60% of the recorded NSAID prescriptions in this study, the PDDs could be determined, which in part could be explained by NSAIDs often being prescribed 'as needed'. This great proportion of unspecified PDDs is important as a patient safety matter since the prescriptions were imprecise in the direction for use.

A limitation of this study is that several of the NSAIDs can be bought over the counter, making the generalizability of this study less certain, since the population might not represent all the

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children taking NSAIDs in the UK, particularly as children seeking a prescription are presumably more ill than children receiving drugs bought over the counter. Another study limitation is that prescribed NSAID doses rather than administered doses were studied; we do not know what dosage the child in fact received. The findings in this study on rPDDs are, however, important since studies focusing on doses or dosage forms among children are sparse.[28]

As for any observational dataset, errors in data can occur; however, data inaccuracies in the UK IMS Disease Analyzer are kept to an absolute minimum by extensive ongoing quality assurance work; one example of this work is outlined by De Lusignan et al.[21] Any inaccuracy of records has not been possible to verify due to the anonymity of the patient data. The high number of NSAID prescriptions, especially for ibuprofen, and the account of a 'real-life' child situation regarding prescribed dosages make this study a valuable contribution to the characteristics of prescriptions for children.

Conclusions

This study is, to our knowledge, the first to show a correlation between higher prescribed NSAID doses and tablet/capsule dose formulation. Further analyses of the findings in this study on NSAIDs are needed to determine if this problem is applicable to other substances as well. Prescribers should carefully consider using age-appropriate dose formulations for young children, and regulatory authorities and pharmaceutical manufacturers should be encouraged to work towards providing suitable drug dose formulations to paediatric patients, enhancing the chance of correct dosing.

Acknowledgements

No funding was provided for this study. The authors have no conflicts of interest relevant to this study. We thank IMS Health for allowing us to use the UK IMS Disease Analyzer data for the purposes of this study. Many thanks to the Research Department at the Uppsala Monitoring Centre for their help and constructive ideas, enhancing the progress of this paper. Andrew Bate is now a full-time employee of Pfizer; however, his major contribution to this manuscript was provided while he was employed at the Uppsala Monitoring Centre.

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