ORIGINAL RESEARCH

A Report on the Use and Safety of Nonsteroidal Anti-inflammatory Drugs among 22,553 Children from Sample Hospitals in Shanghai

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ABSTRACT

Context • The safety of medication for pediatric patients has always been a concern, and non steroidal anti-inflammatory drugs (NSAIDs) are one of the essential and commonly used drugs in children. Therefore, it is necessary to conduct a study on the efficacy and safety of NSAIDs in pediatric patients.

Objective • To study the use and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) among 22 553 pediatric patients from 14 hospitals in Shanghai.

Methods • We collected the clinical data of 22 553 pediatric patients who received NSAIDs during their stay in 14 hospitals in Shanghai from January 2005 to May 2011, which were then retrospectively analyzed. The use of nimesulide, paracetamol, and ibuprofen was observed among these children. The age and gender distribution, discharge status, length of hospital stay, and types of diseases treated with NSAIDs were analyzed. The relationship between death and length of hospital stay was assessed. The safety of NSAIDs in these children was discussed.

Results • The response rate of nimesulide and ibuprofen was 71.23% and 73.12%, respectively. There was no significant difference in response rate between the two drugs ($P > .05$). The response rate of paracetamol was the lowest among the three drugs (59.67%, $P < .05$). The average length of hospital stay was significantly longer in children receiving paracetamol than in those receiving nimesulide. The average length of hospital stay was significantly longer in children receiving nimesulide than in those receiving ibuprofen ($P < .05$). The diseases treated with nimesulide were less diverse than those treated with ibuprofen and paracetamol. To be specific, bronchopneumonia was predominant among all the diseases treated with nimesulide. Although bronchopneumonia was also the most common among all the diseases treated with ibuprofen and paracetamol, the diseases treated with these two drugs were more diverse. The incidence of abnormal liver function among children receiving nimesulide was significantly lower than in those receiving ibuprofen and paracetamol ($P < .05$). There was no significant difference in the incidence of abnormal liver function caused by paracetamol and ibuprofen ($P > .05$).

Conclusion • Nimesulide and ibuprofen achieved a generally higher response rate than paracetamol among the surveyed children from Shanghai. Although bronchopneumonia was the most common diagnosis among all children treated with NSAIDs, the diagnoses were less diverse in those treated with nimesulide. The length of hospital stay was the shortest among children receiving ibuprofen, while the response rate of paracetamol was the lowest. The incidence of abnormal liver function was the lowest in children receiving nimesulide. All of the three NSAIDs might induce liver function impairment, but the risk was not significantly different between them. This study also has some limitations, such as limited drug types and regional limitations. In summary, Nimesulide is a highly effective and safe non steroidal anti-inflammatory drug that can meet the clinical medication needs of pediatric patients. Future research is contemplating the clinical benefits of Nimesulide in treating more diagnostic types besides pediatric bronchopneumonia, in order to investigate its greater medicinal value. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) include aspirin, paracetamol, indometacin, naproxen, nambumetone, diclofenac, ibuprofen, nimesulide, rofecoxib, and celecoxib. NSAIDs are commonly used for anti-inflammatory, anti-rheumatic, analgesic, antipyretic, and anti-coagulant effects due to their ability to inhibit cyclooxygenase II. Clinically, Thereby reducing the synthesis and release of inflammatory factors such as prostaglandins and leukotrienes, exerting antipyretic and analgesic effects NSAIDs have been widely used to relieve a variety of symptoms, including osteoarthritis, rheumatoid arthritis, and fever and pain associated with many conditions.[1,2] At present, NSAIDs are the most common drugs worldwide.[3] About 30 million people take NSAIDs every day throughout the world.[4] Along with the increasing use of NSAIDs, the safety problems of these drugs have been a priority among clinicians, pharmacists, patients, governments, and some other sections of society. Medication safety in children has become another hot topic.[5,6] NSAIDs have been on the market for many years and are consumed in large quantities. Therefore, large amounts of clinical data are available for retrospective analyses.[7,8] It is important that the clinical data are collected and properly utilized to assess the safety of NSAIDs in children through a retrospective study design. Three common NSAIDs were chosen for study, namely, nimesulide, paracetamol, and ibuprofen. The use of the three drugs and the incidence of associated adverse

reactions were discussed retrospectively in children. Building upon this foundation, we conducted a review and assessment of the safety of these three nonsteroidal anti-inflammatory drugs in children. Our aim is to provide a more comprehensive understanding and offer substantive information and guidance for pediatric clinical practice. Research endpoint estimation: Nimesulide is a non steroidal anti-inflammatory drug with better efficacy and higher safety among three drugs used in pediatric patients.

MATERIALS AND METHODS

General information

A retrospective analysis was conducted on the clinical data of 22 553 children who received NSAIDs during their stay at 14 hospitals in Shanghai from January 2005 to May 2011. The purpose was to observe the use and safety of the three NSAIDs in children. Inclusion criteria: (1) Aged 0 to 12 years old; (2) having taken one of the three NSAIDs, namely, nimesulide, paracetamol, and ibuprofen. Exclusion criteria: (1) Having contraindications for NSAIDs; (2) having discontinued the use of NSAIDs due to drug-related discomfort; (3) incomplete clinical data; (4) participating in other studies during the same period.

Methods

(1) **Dosage of nimesulide:** Conventional dose was prescribed: 5 mg per kg of body weight per day, split into 2-3 doses.

(2) **Dosage of paracetamol:** A single dose of 125 mg for children aged 1-3 years old and weighing 10-15 kg; a single dose of 125 mg-250 mg for children aged 4-9 and weighing 16-21 kg; a single dose of 250 mg-375 mg for children aged 10-12 and weighing 28-32 kg;

(3) Dosage of ibuprofen: The recommended dose for fever was a single dose of 20 mg/kg of body weight three times a day; the recommended dose for analgesia was a single dose of 30mg/kg of body weight three times a day. The dosage should comply with the instructions, for example, the dosage of Nimesulide for children is 5mg/ (kg. d) divided into 2-3 doses. Experimental drugs included Nimesulide Granules (Honz Pharmaceutical Co., Ltd., H20020137) and Nimesulide Dispersibe Tablets (Honz Pharmaceutical Co., Ltd., H20052324).

Observation indicators

Children's age, discharge status, length of hospital stay, and diagnoses were collected. The relationship between death and length of hospital stay was analyzed, and the incidence of liver function impairment was estimated to assess the safety of NSAIDs. The specific evaluation indexes of liver function injury include transaminase index, bilirubin index, serum protein index, and alkaline phosphatase index.

Discharge status was divided into different types, namely, cured, improved, not cured, dead, and other. Being cured referred to the complete disappearance of symptoms after treatment, with all indicators returning to normal; "improved" referred to a significant improvement of various clinical symptoms and indicators after treatment; "not cured" referred to the situation where the clinical symptoms and indicators didn't change dramatically or even deteriorated after treatment; "dead" referred to death that occurred during a hospital stay. Others referred to transfer to other hospitals during the treatment period.[9]

Table 1. Discharge status of children receiving NSAIDs [n=16709, n (%)]

Discharge status	Nimesulide	Paracetamol	Ibuprofen	Total
Cured	1099 (27.14)	1674 (37.38)	3169 (38.74)	5942
Improved	1786 (44.10)	998 (22.29)	2813 (34.38)	5597
Responsive (improved+cured)	2885 (71.23)	2672 (59.67)	5982 (73.12)	11539
Not cured	119 (2.94)	107 (2.39)	238 (2.91)	464
Other	990 (24.44)	275 (6.14)	1367 (16.71)	2632
Death	50 (1.23)	86 (1.92)	96 (1.17)	214
Missing	6 (0.15)	1338 (29.88)	498 (6.09)	1860
Total	4050	4478	8181	16709
χ^2	2979.487			
P value	<.001			

Statistical analysis

Statistic Package for Social Science (SPSS) 18.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as $\bar{x} \pm s$, and compared by *t* test. Enumeration data were expressed in percentages and compared by χ^2 test. Multiple group comparisons were conducted using analysis of variance. F-tests were performed to compare group means. A *P*-value less than .05 was considered to be statistically significant.

RESULTS

Basic information about the collected cases

A total of 22 553 children receiving NSAIDs were collected, and these children were aged 0 to 12 years old. There were 4745 children receiving nimesulide, 6265 children receiving paracetamol, and 11 543 children receiving ibuprofen. Among all children aged 1 to 12 years old, there were 4050 children receiving nimesulide, 4478 children receiving paracetamol, and 8181 children receiving ibuprofen. There were 16709 children aged 1 to 12 years old. The present study was primarily conducted in this age group.

Discharge status of children receiving NSAIDs

There was no significant difference in response rate between nimesulide and ibuprofen ($P > .05$). However, the response rate was the lowest for paracetamol, and the difference was statistically significant compared with the other two drugs ($P < .05$). As shown in Table 1.

Length of hospital stay in children receiving NSAIDs

The average length of hospital stay was significantly longer in children receiving acetaminophen than in those receiving nimesulide. The average length of hospital stay was significantly longer in children receiving nimesulide than in those receiving ibuprofen ($P < .05$). As shown in Table 2.

Top 20 most common diagnoses among children receiving NSAIDs

The diseases treated with nimesulide were less diverse than those treated with ibuprofen and acetaminophen. That is,

Table 2. Length of hospital stay in children receiving NSAIDs (n=16709, d)

Length of hospital stay	Nimesulide	Paracetamol	Ibuprofen	Total
Mean±standard deviation	14.53±15.2	15.61±14.7	12.64±12.5	13.75±13.8
Median	10.00	11.00	9.00	10.00
Minimum; Maximum	0.00; 494.00	1.00; 218.00	0.00; 494.00	0.00; 494.00
Missing	6	1298	53	1357
Total	4050	4478	8181	16709
F	62.41			
P value	<.001			

Table 3. Top 20 most common diagnoses among children receiving NSAIDs (%)

Disease diagnosed	Percentage of children treated with nimesulide for a specific disease among all children treated with nimesulide	Percentage of children treated with paracetamol for a specific disease among all children treated with paracetamol	Percentage of children treated with ibuprofen for a specific disease among all children treated with ibuprofen
1. Bronchopneumonia	34.06	15.89	19.09
2. Acute bronchitis	7.84	13.02	9.89
3. Bronchitis	13.65	3.53	8.1
4. Pneumonia	9.7	4.53	7.55
5. Acute tonsillitis	7.91	8.39	6.66
6. Exudative tonsillitis	0.62	0.55	3.73
7. Acute purulent tonsillitis	2.79	2.32	1.32
8. Bronchopneumonia (lobular pneumonia)	0.23	6.62	0.64
9. Acute pharyngitis	1.78	2.76	0.85
10. Bronchial asthma	0.62	0.88	2.21
11. Asthmatic bronchitis	0.62	0.66	1.99
12. Acute upper respiratory tract infection	1.4	2.65	0.76
13. Tonsillitis	0.16	2.32	1.1
14. Mycoplasma pneumonia	2.02	1.99	0.08
15. Bronchopneumonia (wheezing type)	0	0.11	1.53
16. Herpes angina	0	0.88	1.15
17. Lobar pneumonia (right lower lobe)	0	0.33	1.27
18. Hand-foot-and-mouth disease	0.23	1.32	0.76
19. Acute purulent tonsillitis	0	0.11	1.32
20. Acute gastritis	0.47	1.99	0.25

Table 4. Incidence of liver function impairment in children receiving NSAIDs

Drug	Total (cases)	No changes in liver functions after taking NSAIDs	Abnormal liver functions after taking NSAIDs	Incidence of abnormal liver functions (%)
Nimesulide	1101	900	201	18.3
Paracetamol	1065	807	258	24.2
Ibuprofen	359	261	98	27.3
χ^2_1	11.55			
P_1	<.01			
χ^2_2	13.59			
P_2	<.01			
χ^2_3	1.35			
P_3	>.05			

Note: P_1 represents the comparison between nimesulide and paracetamol; P_2 represents the comparison between nimesulide and ibuprofen; P_3 represents the comparison between paracetamol and ibuprofen.

bronchopneumonia was predominant among all the diseases treated with nimesulide. Although bronchopneumonia was also the most common among all the diseases treated with ibuprofen and acetaminophen, the diseases treated with these two drugs were more diverse compared with the situation with nimesulide (As shown in Table 3).

Incidence of liver function impairment in children receiving NSAIDs

The results showed that the incidence of abnormal liver function among children receiving nimesulide was significantly lower than in those receiving ibuprofen and acetaminophen ($P < .05$). There was no significant difference in the incidence of abnormal liver function caused by acetaminophen and ibuprofen ($P > .05$). As shown in Table 4.

DISCUSSION

Children are particularly susceptible to drug-related adverse reactions, as their organ functions are not fully developed yet. As children grow up and develop, their body proportions and composition change dramatically, and such a dynamic maturation process is what distinguishes children from adults.[10,11] Physical and physiological changes lead to pharmacological changes, which further gives rise to discrepancies between children and adults in drug efficacy, toxicity, and dosing regimen.[12,13] There is an urgent need to reduce drug-related serious adverse reactions based on evidence-based therapeutics. A retrospective analysis of the use and safety of NSAIDs in children is one pathway to reach this goal.[14,15]

NSAIDs are widely used in children. Nimesulide is a common NSAID that selectively inhibits cyclooxygenase II. And the other two are non selective cyclooxygenase mixed enzyme inhibitor. While nimesulide specifically inhibits inflammatory prostaglandins, it does not inhibit physiological prostaglandins.[16,17] Nimesulide significantly relieves pain, fever, and inflammation within 15 minutes after taking the drug. Moreover, nimesulide is found to be more effective than ibuprofen and paracetamol and has been reported to cause fewer NSAIDs-related gastrointestinal adverse effects compared to ibuprofen and paracetamol.[18,19]

In the present study, 22 553 children from sample hospitals in Shanghai were chosen for the study, including 16,709 children aged 1-12 years old. Analysis of the discharge status showed that the response rate was not significantly different between nimesulide and ibuprofen ($P > .05$). Both drugs were more effective than paracetamol, and the response rate was significantly different ($P < .05$). The comparison of the average length of hospital stay showed that the hospital stay was the shortest among children receiving ibuprofen and the longest among those receiving paracetamol. But considering the relationship between the type of primary disease and length of hospital stay, we cannot jump to a hasty conclusion that ibuprofen was more effective than the other two NSAIDs. As for the types of diseases treated with different NSAIDs, bronchopneumonia was the most common among all children receiving whatever treatment. This indicated the narrow spectrum of indications for the three NSAIDs. Compared with nimesulide, the diagnoses were more diverse, apart from bronchopneumonia, in children receiving paracetamol and ibuprofen. The above results demonstrated the narrow spectrum of all the NSAIDS and the higher specificity of indications for nimesulide in comparison with the other two NSAIDs. As for the incidence of abnormal liver functions, we found that it was much lower in children receiving nimesulide than in those receiving the other two NSAIDs. This is probably because nimesulide is metabolized by the liver to produce hydroxyl derivatives, which are almost all excreted in the urine, causing a lesser

burden on the liver.[20] It is recommended that when children use nonsteroidal anti-inflammatory drugs, the interaction between drugs should be fully evaluated to reduce the probability of adverse reactions. There were also some limitations in this study, such as few drug types and regional limitations. Future studies may consider increasing the types of NSAIDS and expanding the scope of research.

In conclusion, all of the three NSAIDs had a narrow spectrum of indications. The length of hospital stay was the shortest in children receiving ibuprofen. The response rate was the lowest with paracetamol. The three drugs differed little in hepatotoxicity and shared comparable safety profiles. Besides, the incidence of abnormal liver functions was the lowest with nimesulide. It was generally safe to use nimesulide in children under proper guidance. This will provide a basis for clinical doctors to make choices when using nonsteroidal anti-inflammatory drugs for pediatric patients.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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AUTHOR CONTRIBUTIONS

LW and WD designed the study and performed the experiments, LW and RM collected the data, WD and RM analyzed the data, LW and WD prepared the manuscript. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Nanjing Medical University School of Pharmacy.

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