Single intramuscular injection of diclofenac sodium in febrile pediatric patients

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ABSTRACT

Objectives: There are few reports on the effectiveness and safety of intramuscular (IM) antipyretic injections in pediatric patients. This study reports the efficacy and adverse effects of a single IM injection of diclofenac sodium in pediatric patients.

Materials and Methods: This was an observational study in which records of febrile pediatric patients presenting to the emergency department were analyzed. Subjects included pediatric patients presenting to the emergency department with a temperature of 38°C or higher. Infants under 12 months of age were excluded. Patients were excluded if they received antipyretics within 4 h prior to presenting to the emergency department. Body temperature was measured at 30–60 min intervals following diclofenac sodium injections. Fever alleviation was defined as the temperature decline to 1°C below the temperature at presentation. Patients who received diclofenac sodium twice or more on different days were observed for side effects such as allergic reaction. Records from the emergency department and outpatient clinics were analyzed.

Results: The dose of diclofenac sodium injected was approximately 2 mg/kg. The average time elapsed until antipyresis was 69.1 ± 23.8 min. The average temperature reduction after 1 h was 1.1 ± 0.6°C. The average proportion of temperature change after 1 h was 40.6 ± 22.2%. During the period at the emergency department, there were no reported serious side effects.

Conclusions: A single dose of diclofenac sodium provided effective antipyresis in pediatric patients. Serious side effects were not observed.

KEY WORDS: Antipyretics, diclofenac sodium, intramuscular, pediatric, side effects

Introduction

Fever is the most common symptom resulting in pediatric emergency visits. In many adult patients, fever is not treated with antipyretics for various reasons, such as observation of fever patterns. It has been reported that fever is integral to fighting infection. There is no evidence that fever causes serious complications like brain damage, so antipyretics are not always indicated in children. However, many parents insist on administering antipyretics, and present to the emergency department solely for this purpose. Many clinicians aggressively treat fever in children. Fever in children is more likely to result in poor oral intake and dehydration, and antipyretics alleviate these symptoms. Antipyretics such as acetaminophen and ibuprofen are widely used, but many pediatric patients present with fever uncontrolled by these oral and rectal medications. Alternative methods for fever control include fluid administration and intramuscular (IM) or intravenous (IV) injection of antipyretics. As it may be difficult secure an IV route of administration in pediatric patients, IV administration of fluids and antipyretics is difficult in an emergency setting. A single IM antipyretic injection is used widely. There are few reports on the effectiveness and safety of IM antipyretic injections in pediatric patients. This study reports the efficacy and adverse effects of a single IM injection of diclofenac sodium in pediatric patients and reviews several related reports.

Materials and Methods

This was a retrospective study in which records of febrile pediatric patients presenting to the emergency department, and outpatient clinics were analyzed. The hospital uses ibuprofen and acetaminophen as oral antipyretics, and a single dose of
injectable diclofenac sodium. This study was approved by the Kangwon National University Hospital Institutional Review Board (IRB) on March 21, 2014. (IRB No: KNUH-2014-03-006)

**Patients**

Subjects included pediatric patients presenting to university hospitals in areas with a population of ~300,000 with a temperature of 38°C or higher. Infants under 12 months of age were excluded.

We analyzed records from the emergency department and outpatient clinics from December 2012 to September 2013. Medical records of patients who received diclofenac sodium twice or more on different days were analyzed for side effects like allergic reaction. Patients were excluded if they received antipyretics within 4 h prior to presenting to the emergency department, or if records of temperature measurements were incomplete.

**Body Temperature Measurement**

Body temperature was measured from the eardrum using an Infrared Thermometer IRT 4520 (Key Tronic Corp., Mexico) at 30–60 min intervals following diclofenac sodium injections.

**Data Analysis**

Time at Onset of antipyresis was defined as the temperature decline to 1°C below the temperature at presentation. Temperature change (Δtemp) was defined as the change in temperature 1 h following injection of diclofenac sodium. The percentage temperature change (%Δtemp) after 1 h was defined as (baseline temperature−temperature at 1 h)/(baseline temperature−36.5°C) × 100.

For analysis, the IBM SPSS statistics 20.0 was used. To compare antipyretic effects by age, the subjects were divided into two groups: Less than 24 and >60 months of age. A multiple linear regression analysis was performed to identify factors affecting the antipyretic effects. The Mann–Whitney U test was performed to compare antipyretic effects by age. The level of significance was considered a $P < 0.05$.

**Results**

The number of pediatric patients who received diclofenac sodium was 982 during the study period.

By inclusion criteria, a total of 300 subjects [Table 1] were included: 165 males and 135 females (average age 38 ± 27 months, average weight 15.3 ± 6.6 kg). The average dose of diclofenac sodium injected was 28 ± 12 mg. The average temperature on presentation to the emergency department was 38.8 ± 0.5°C. Diagnoses included: Respiratory infection (94), fever (69), pharyngitis (56), acute tonsillitis (33), gastroenteritis (11), etc., [Table 2].

We could identify accurate medical records of antipyresis in 116 patients and accurate medical records of 89 patients with change in temperature 1 h following injection.

The dose of diclofenac sodium injected was approximately 2 mg/kg [Table 3].

**Diclofenac Sodium Side Effects**

One patient developed hypothermia 4 h following injection of diclofenac sodium. The temperature decreased to 36.0°C. The prevalence of hypothermia was 0.3% (95% confidence interval: 0.1–1.9%).

A total of 37 patients had a history of asthma or asthmatic bronchitis, but no asthmatic attacks occurred in the emergency room during the observation period. Two patients with a history of asthmatic bronchitis had wheezing, but a direct relationship to the injection could not be proven since one patient visited the pediatric outpatient clinic after 1-day and the other after 2 days.

During the period at the emergency department, there were no reported allergic reactions. One patient presented to the emergency department the following day, but as cephalosporin antibiotics were co-administered, the causal relationship between diclofenac sodium and allergic symptoms was unclear.

**Table 1:** Subject demographics and clinical data of patients

| Characteristics          | n=300 |
|--------------------------|-------|
| Male n (%)              | 165 (55) |
| Female n (%)            | 135 (45) |
| Age (months, mean±SD)   | 38±27 |
| Weight (kg, mean±SD)    | 15.3±6.6 |
| Dose of diclofenac sodium (mg, mean±SD) | 28±12 |
| Baseline temperature (°C, mean±SD) | 38.8±0.5 |

**Table 2:** Diagnoses associated with fever in the study population

| Diagnosis                        | n=300 |
|----------------------------------|-------|
| Upper respiratory infection      | 94    |
| Fever                            | 69    |
| Acute pharyngitis                | 56    |
| Acute tonsillitis                | 33    |
| Influenza                        | 9     |
| Gastroenteritis                  | 11    |
| Acute otitis media               | 6     |
| Pneumonia                        | 6     |
| Herpangina                       | 5     |
| Febrile convulsion               | 4     |
| Hand-foot-mouth disease          | 2     |
| Chickenpox                       | 1     |
| Croup                            | 1     |
| Scarlet fever                    | 1     |
| Sinusitis                        | 1     |
| Viral exanthem                   | 1     |

**Table 3:** Administered dose of diclofenac sodium in pediatric patients with fever

| Weight (kg) | Dose (mg) |
|-------------|-----------|
| 6-10        | 15        |
| 11-14       | 22.5      |
| 15-17       | 30        |
| 18-21       | 37.5      |
| 22-25       | 45        |
| 26-28       | 52.5      |
| 29-32       | 60        |
| 33-35       | 67.5      |
| >36         | 75        |
The number of patients included was 116 with an average age of 41 ± 27 months and an average body weight of 15.7 ± 6.3 kg. The average injected dose of diclofenac sodium was 29 ± 12 mg. The average time elapsed until antipyresis was 69.1 ± 23.8 min.

Changes in Body Temperature 1 h Following Injection [Table 4]

The number of patients included was 89 with an average age of 41 ± 27 months and an average body weight of 15.5 ± 5.7 kg. The average temperature on presentation to the emergency department was 39.1 ± 0.6°C. The average proportion of temperature change after 1 h was 1.1 ± 0.6°C. The average proportion of temperature change after 1 h was 40.6 ± 22.2%.

Factors Affecting Antipyresis [Tables 5 and 6]
The baseline temperature (correlation coefficient = −0.291, r² = 0.083, P = 0.001) and patient age (correlation coefficient = 0.221, r² = 0.046, P = 0.013) influenced time of antipyresis. Only baseline temperature affected change in temperature 1 h following injection (correlation coefficient = 0.476, r² = 0.227, P < 0.001).

Comparison between Two Age Groups [Tables 7 and 8]
Children <24 months of age were compared with those >60 months of age; a significant difference in time of antipyresis was identified (P = 0.012). There was no difference in change in temperature 1 h following injection between the two groups (P = 0.484 and P = 0.185, respectively).

Discussion
Diclofenac sodium is a derivative of phenylacetic acid and is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects.[3] When administered orally, rectally, or intramuscularly, it is absorbed rapidly and reaches peak plasma concentrations in 10–30 min.[14,15] The principal metabolite is 4'-hydroxydiclofenac and is eliminated through urinary and biliary excretion.[6,7] Like other NSAIDs, it is a potent inhibitor of prostaglandin synthesis.[3]

Diclofenac sodium is used to treat inflammatory diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gout. It is also used for controlling pain associated with dysmenorrheal, as well as renal and biliary colic.[8-13] In children, diclofenac sodium is used for conditions such as rheumatoid arthritis and postoperative pain relief.[14,15] Gastrointestinal symptoms such as nausea, vomiting, and gastric upset are the most frequent side effects. Allergic reactions resulting in symptoms such as rash or dizziness may occur.[16]

### Table 4:
Onset of antipyresis and change in temperature 1h following injection of diclofenac sodium

| Characteristics | Mean±SD |
|-----------------|---------|
| Onset of antipyresis (n=116) | 41±27 |
| Age (months) | 41±27 |
| Weight (kg) | 15.7±6.3 |
| Dose of diclofenac sodium (mg) | 29±12 |
| Temperature on presentation (°C) | 39.1±0.6 |
| Time for antipyresis (min) | 69.1±23.8 |
| Change in temperature 1 h following injection of diclofenac sodium (n=89) | |
| Age (months) | 41±27 |
| Weight (kg) | 15.5±5.7 |
| Dose of diclofenac sodium (mg) | 29±12 |
| Temperature on presentation (°C) | 39.1±0.6 |
| ΔTemp1h (°C) | 1.1±0.6 |
| %ΔTemp1h | 40.6±22.2 |

### Table 5:
Association of antipyresis with variables analyzed by univariate linear regression

| Variables | Regression coefficient (β) | SE | P |
|-----------|---------------------------|----|---|
| Time at onset of antipyresis | | | |
| Age (month) | 0.186 | 0.079 | 0.020 |
| Baseline temperature (°C) | −12.356 | 3.859 | 0.002 |
| Dose of diclofenac sodium (mg) | 0.220 | 0.190 | 0.248 |
| Ratio of dose (mg) to weight (kg) | −3.848 | 9.850 | 0.697 |
| Change in temperature 1 h following injection | | | |
| Age (month) | −0.001 | 0.002 | 0.541 |
| Baseline temperature (°C) | 0.486 | 0.096 | <0.001 |
| Dose of diclofenac sodium (mg) | 0.002 | 0.005 | 0.753 |
| Ratio of dose (mg) to weight (kg) | −0.062 | 0.261 | 0.813 |

### Table 6:
Association of onset of antipyresis with variables analyzed by multiple linear regression analyses

| Variables | Regression coefficient (β) | SE | Partial R² | P |
|-----------|----------------------------|----|------------|---|
| Age (month) | 0.190 | 0.076 | 0.046 | 0.013 |
| Baseline temperature (°C) | −12.531 | 3.772 | 0.083 | 0.001 |

### Table 7:
Comparison of patients ≤24 and ≥60 months of age for antipyretic effect of a single injection of diclofenac sodium

| Variables | ≤24 months (n=38) | ≥60 months (n=27) | P |
|-----------|------------------|------------------|---|
| Temperature on presentation (°C, mean±SD) | | | |
| Onset of antipyresis after injection (min, mean±SD) | | | |
| Change in body temperature after 1 h | | | |
| Temperature on presentation (°C, mean±SD) | | | |
| ΔTemp1h (°C, mean±SD) | | | |
| %ΔTemp1h | | | |

NS = Not significant, SD = Standard deviation
Diclofenac sodium is an effective antipyretic agent. Studies have documented antipyresis after oral or rectal administration in children, and an approximately 1.5°C temperature reduction was observed within 2 h of injection of a 0.25 or 0.5 mg/kg dose.[17]

The recommended dosage of diclofenac sodium in children differs among countries. The British National Formulary 2009 recommends oral administration of 3–5 mg/kg daily divided among two to four doses for patients 6 months to 18 years of age.[2]

An accurate antipyretic dose was not established for pediatric patients. There are no reports on the antipyretic effects after IM injection in children. In the current study, approximately 2 mg/kg diclofenac sodium was administered in a single IM injection. Most pediatric patients were observed for 1–2 h and left the hospital when the temperature was reduced by 1–1.5°C. Therefore, it was impossible to observe the antipyretic effects for an extended time. Accordingly, the antipyretic effects during the 1st h following injection and the time at which the temperature was reduced by 1°C were analyzed. Adverse effects for an extended time were not observed. However, as more than one antipyretic is generally given, considering the dosage and avoiding the use of concurrent antipyretics may reduce the risk of hypothermia.

In conclusion, a single dose of diclofenac sodium provided effective antipyresis in pediatric patients. Antipyresis occurred more rapidly in younger patients. Serious side effects were not observed. The risk of hypothermia can be reduced by decreasing the dosage or avoiding concurrent antipyretic use.

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Table 8:

Comparison of patients ≤24, 25-59 months and ≥60 months of age for antipyretic effect of a single injection of diclofenac sodium

| Onset of antipyresis | ≤24 months (n=38) | 25-59 months (n=51) | ≥60 months (n=27) | P |
|----------------------|------------------|-------------------|-----------------|---|
| Temperature on presentation (°C, mean±SD) | 39±0.6 | 39±0.6 | 39±0.5 | 0.233 |
| Onset of antipyresis after injection (min, mean±SD) | 64.5±23.9 | 65.2±21.5 | 80.4±25.1 | 0.018 |
| T° | a | a | b |
| Change in body after 1h | ≤24 months (n=29) | 25-59 months (n=39) | ≥60 months (n=21) | P |
| Temperature on presentation (°C, mean±SD) | 39±0.5 | 39±0.6 | 39±0.6 | 0.677 |
| ΔTemp_onset | 1.1±0.6 | 1.1±0.5 | 0.97±0.7 | 0.756 |
| (%ΔTemp_onset) | 42.9±22.8 | 40.8±19.2 | 36.9±26.9 | 0.644 |

*The same letters indicate nonsignificant difference between groups based on Scheffe multiple comparison test. SD = Standard deviation.
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