

**ປຶ້ມ**

# **A Systematic review of Effectiveness of Ibuprofen versus Acetaminophen in Reducing pediatric fever**

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- Objective** : To summarize previous studies of the effectiveness of single-dose acetaminophen (10-20 mg/kg) comparing with ibuprofen (5-10 mg/kg) for reducing pediatric fever at 4<sup>th</sup> hour after administration.
- Methods** : Reports were gathered by searching from electronic databases (from Jan 1990 to Aug 2008), hand-searching, reference lists and Identification of unpublished studies by consulting expert.
- Result** : Three double blinded randomized control trials with children under 12 years old receiving either medication (ibuprofen or acetaminophen) to reduce fever were selected. Outcomes were measured in differences in mean of body temperature before and after receiving medication. Heterogeneity was addressed,  $I^2$  test = 0.84. Qualitative data was presented. Two studies revealed that there was no statistical difference between ibuprofen and acetaminophen, while the other one statistically preferred ibuprofen.
- Conclusions**: Due to high heterogeneity, our study can not draw any conclusion about the effectiveness of antipyretic between ibuprofen and acetaminophen. In addition, more studies will be required.

Fever is an increase in body temperature, resulting from the resetting of temperature regulatory set point in higher than normal value for an individual.

Fever is defined as a rectal temperature above 38°C (100.4°F), oral temperature above 37.8°C (100°F), axillary temperature above 37.5°C (99°F) or tympanic membrane temperature above 38.0°C (100.4°F). There are many causes of fever (such as infection, inflammation, exogenous toxin) that stimulate the production of endogenous pyrogens (including IL-1, IL-6, TNF-alpha, IFN-beta, IFN-gamma)<sup>1</sup>. After that, endogenous pyrogenic cytokines directly stimulate hypothalamus to produce PGE<sub>2</sub>, which then resets the thermostat<sup>1</sup>.

Fever in children is one of the most important problems that parents are concerned about and why they bring their children to the hospital<sup>2-4</sup>. Fever in children can cause many sequelae such as exacerbate cardiac insufficiency in patients with heart disease or chronic anemia, pulmonary insufficiency in those with chronic lung disease, metabolic instability in children with DM or inborn error of metabolism and children between the ages of 6 mo and 5 yr are at increased risk of benign febrile seizure<sup>1</sup>. distress, anxiety and---in some parents---"fever phobia"<sup>2, 3, 5-7</sup>.

Antipyretic agents have been used to reduce febrile body temperature. The pharmacological options are acetaminophen and ibuprofen<sup>6,8</sup>. Both drugs inhibit hypothalamic cyclooxygenase, thus inhibiting PGE<sub>2</sub> synthesis<sup>9</sup>. But there are differences in pharmacological properties (acetaminophen; peak Cp = 30-60 min, half-life= 2 hr, Ibuprofen; peak Cp = 15-30 min, half-life= 2-4 hr)<sup>9</sup>. Some physicians choose ibuprofen

because they think that ibuprofen has high efficacy to reduce fever<sup>9</sup>, although it may cause gastrointestinal bleeding (5-15%), nephrotoxicity or other rare serious side effects<sup>9</sup>. Because they carefully use it in some patients' setting such as dengue hemorrhagic fever or renal impairment. On the other hand, some physicians use acetaminophen due to the safety in its therapeutic dose (10-15 mg/kg/d)<sup>1,10</sup>.

As a result from systematic review 2004 which suggested that ibuprofen (5-10 mg/kg) was more effective in antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, 6 hour, but in general practice there is still controversy and there might be more updating information during the recent 4 years, which may draw a conclusion of effectiveness between both medications. So, we investigated by way of Systematic review to assess the effectiveness of ibuprofen compared with acetaminophen for reducing fever among children less than 12 years.

## METHODS

### Eligibility criteria

The database used in this study are the electronic databases, the method of hand-searching, reference lists and identification of unpublished studies (consulting expert). Then we included the studies which have the following eligibility criteria: 1) Participants, included in this review, were under 12 years and got acute fever that was diagnosed by physicians, but some patients were excluded due to underlying diseases (such as bleeding tendency, liver disease, renal disease, asthma etc.). 2) Partial interventions such as NSAIDs, narcotics were excluded; however co-intervention can be acceptable if that interven-

tion does not effect pyretic. 3) The study design is a randomized control trial with double blind intervention.

When all the above criteria were met, the participants were divided into 2 groups; one group received ibuprofen (dose range from 5 to 10 mg/kg in oral form), the other group receive acetaminophen (dose range from 10 to 20 mg/kg in oral form). If any interventions (e.g. antibiotics) were assigned, they had to be applied in both groups.

For our review, we are concerned about 1) the body temperature reduction at the 4<sup>th</sup> hour after first dose administration. 2) body temperature must be recorded by nurse or person who was well-trained in method of measurement among OPD cases and 3) body temperature can be assessed by any routes (e.g. oral, rectal, axillary, tympanic membrane) but the assessment both before and after receiving medication must be the same method.

### **Data sources**

We searched the electronic databases (from January, 1990 to August, 2008) to identify the studies which were relevant about the effectiveness of Ibuprofen and acetaminophen in reducing pediatric fever; by using combinations of "Paracetamol[MeSH]", "Ibuprofen[MeSH]" "Fever" "Children OR Preschool OR Infant" "RCT" as search terms in Cochrane library, OVID, SCOPUS, and Pubmed databases

Moreover, we included hand searching studies from the Thailand pediatric infectious society (PDST) library, the Thai society of pediatrician journal. By method of systematic reviews in 2001 and 2004, reference lists were also searched to find relevant studies. Besides,

we consulted experts in The Department of Pediatrics, Thailand for unpublished studies.

### **Outcome definition**

The primary outcome is difference in mean body temperature and reduction in body temperature at the 4th hour after drug administration. Of each finally selected studies, the fixed effect model was used for analyzing the data collected from cluster randomized trials. The outcomes were analyzed by the review manager version 5.0.16 program (meta-analysis analyzed program) from Cochrane library.

### **Data collection and analysis**

#### **I. Selection of studies**

We undertook two steps in selecting the studies. Firstly, colleagues were divided into two groups. They then independently selected the studies which met eligibility criteria by reading through their title and abstract. Duplicate studies were removed by intense examination; collecting all data and alphabetically rearranged by spreadsheet software, the manual reviewing to exclude the duplicated study, double checking, if any uncertainty occurred, full text would be required. We used Kappa statistics to estimate reliability between the studies selection of each two groups. Disagreement of selection was solved by consensus.

Then, the full paper was required to assessing the article in detail to select the papers which finally met eligibility criteria by two groups of colleague also. Kappa statistics was used to measure reliability in this secondary selection for the final studies.

## II. Data extraction and Data management

All data were independently extract to data collection forms which were designed to record characteristics of the corresponding studies.

The characteristics are included (as following): the title of the review, author's name and year of publication, characteristics of the study subjects which consisted of sample size, age, and sex, missing participants, exposure and measurement of outcome, assessment of eligibility of the study, key pieces of information and its site in report (differences of body temperature before and after receiving medication represented in the form of differences in mean and SD), confounding factors and biases.

## III. Risk bias assessment

The characteristic of all included study is a RCT and intervention given in double-blind trials. All eligible studies were evaluated in our quality assessment method for reducing bias by using point scoring criteria distributed in 4 categories (i.e. selection bias, performance bias, attribution bias and detection bias) total score is 12 points.

## RESULTS

### Study inclusion and selection

Electronic searches of public databases, hand searching, reference lists from the systematic review 2001 and 2004, and contacting experts for unpublished journals of selected bibliographies yielded 726, 5, 2, 2 citations orderly. Totally the number of potential articles were 735 studies. Primary screening of titles and abstracts, Kappa statistics = 0.992, were done to identify 29 relevant articles. There were 6 articles that we were not allowed to access the full text, we solve this problem by consulting the authors via calling and

e-mailing. We also asked the international journal clubs to help us search and we contacted the WHO via the Chulalongkorn Librarian.

The methods section of the remaining 23 articles were analyzed for compliance with the systematic review protocol. 20 studies were excluded (Kappa statistic= 0.909):

1. Two studies, the participants' age group did not meet criteria for inclusion.

2. One study, all of the participants have underlying diseases; asthma.

3. One study, the participants received some antipyretics before the study start.

4. Three studies were not randomized control trial studies.

5. Two studies represent outcomes that are not our primary outcome.

6. Four studies represent outcomes in the area under the curve pattern. We contacted the authors to ask for more information. Finally, all of these studies were excluded because raw data cannot be accessed. Thus, this was unable to converse the outcome of these studies into differences in mean, which met our eligibility criteria.

7. Two studies did not be evaluated the outcome by hours.

8. One study has a co-intervention; L-arginine combined with ibuprofen.

9. One study, the amount-based dosage of ibuprofen does not meet the criteria for inclusion.

10. In three studies, their method does not meet criteria for inclusion. Two studies compared Ibuprofen with placebo, another one trial compared combination of ibuprofen and acetaminophen with ibuprofen.

Three reports fulfilled criteria for inclusion. *Table 1* summarizes the characteristics of the included studies.

All studies were typically single-dose, randomized, double-blinded trials of 5-10 mg/kg of ibuprofen, 10-20 mg/kg of paracetamol. All dosages for each drug fell within the recommended range for clinical practice.

All three eligible studies were also reported the side effect of both medications along the trials, for example; seizure, gastrointestinal bleeding, exanthemas, insomnia and hypothermia. But no serious side effect; which could exclude the participants, occurs in all the studies.

### Quality of studies

The quality of the three studies included in this systematic review is shown in *table 2*.

The study by Anthony Wong, MD had co-intervention (antibiotics). At the end of the study, 11% of patients who entered the trial were lost by the time off follow-up. The data was analyzed by per protocol principle. The outcomes were not measured by one person. The trial did not show that there was no contamination and the care giver was blinded.

The study by Adrianus Van Esch, MD had co-intervention (antibiotics). At the end of the study, there were 11.42% of patients who entered the trial who were lost before follow-up; intention to treat analysis. Although the outcomes were not measured by one person, the temperatures were measured by well-trained parents.

The study by Carabano et al., there were 23% of patients---who entered the trial---had lost the follow-up. The intention to treat was used to analyze. The outcomes were not measured by one person.

### Heterogeneity analysis

The heterogeneity was measured by  $I^2$  test. The result reveal 0.84 (*table 3*) which strongly suggest heterogeneity. Therefore, meta-analysis is not recommended for our study. To explore heterogeneity, subgroup analysis should be done. Due to our limitation, we did not set hypothesis for subgroup analysis before analyzed the data. As reviewing the literature, there is no external evidence support the hypothesized subgroup difference. Thus, we conclude and demonstrate the data in qualitative form.

Table 1. Characteristics of included studies.

Study	Patient characteristics					Max. days of symptoms before enrollment	Intervention		
	Total patients, N	Male, n	Female, N	Mean age, year	Age range, year		Ibuprofen, dose/kg	Acetaminophen, dose/kg	Additional therapy
Anthony W, 2001	419	228	191	2.5	6 mo - 6 yr	NS	BT $\geq$ 39.2°C; 10 mg/kg BT<39.2°C; 5 mg/kg	12 mg/kg	antibiotic when indicated
Carabaño A, 2005	129	54	75	4.1	6 mo- 12 yr	NS	7 mg/kg	15 mg/kg	-
Adrianus V, 1995	70	43	27	2.1	10 mo - 4 yr	NS	5 mg/kg/dose	10 mg/kg/dose	-

**Effects of interventions**

Adrianus Van Esch<sup>1</sup> shows ibuprofen reduced fever 0.5 degree more than acetaminophen did at 4 hours after the first dose (95% confidence interval [CI, -0.98 to -0.02]. Mean difference = 0.36 [0.26, 0.46]. The participants involved in this study has febrile seizure at a temperature of 38.5°C or higher. Rectal temperature was recorded for collecting the mean of differences of reducing temperature.

Anthony Wong<sup>12</sup> reveals no statistical difference in mean of reducing body temperature at 4 hour between ibuprofen and acetaminophen, mean difference = -0.03 [-0.22, 0.16]. Children who having a history of febrile seizure within 6 months prior to the study were excluded. And this study

perform measurement of temperature by tympanic membrane route.

Carabano et al.<sup>13</sup> shows effectiveness of ibuprofen and acetaminophen was similar, mean difference = 0.21 [-0.19, 0.61]. Only children who had fever caused by respiratory tract infection enrolled in this study. Axillary temperature measurement was recorded.

In summary, two studies relevantly reveal that there is no statistical difference between ibuprofen and acetaminophen. While one study prefer ibuprofen rather than acetaminophen. Obvious heterogeneity may be effected by differences between Adrianus Van Esch<sup>11</sup> and Anthony Wong<sup>12</sup>. In aspect of population and method of fever measurement discussed above.

Table 2. Quality of each study.

Study	Selection bias	Performance bias	Attribution bias	Detection bias	Total (12)
Anthony W, 2001	3	0	2	3	8
Carabaño A, 2005	3	2	1	2	8
Adrianus V, 1995	3	2	2	3	10

Table 3. Outcome of the study.

Study	Outcomes						Weight	Mean Difference IV, Random, 95% CI
	Ibuprofen			Acetaminophen				
	Total patients, n/N	Mean BT reduction, °C	SD	Total patients, n/N	Mean BT reduction, °C	SD		
Anthony W, 2001	185/209	1.44	0.98	191/210	1.47	0.91	35.9%	-0.03 [-0.22, 0.16]
Carabaño A, 2005	65/129	1.60	1.31	64/129	1.39	0.98	23.7%	0.21 [-0.19, 0.61]
Adrianus V, 1995	31/34	1.64	0.18	31/36	1.28	0.23	40.4%	0.36 [0.26, 0.46]
Total (95% CI)	281/372			286/375			100%	0.18 [-0.11, 0.48]

Heterogeneity: Tau<sup>2</sup> = 0.05; Chi<sup>2</sup> = 12.48, df=2 (p = 0.002); I<sup>2</sup> = 84% Test for overall effect: Z = 1.24 (p = 0.22)

### Limitations

We included only published reports because our literature search can not locate all unpublished study.

As acknowledged---the method section---electronic databases, we excluded a few studies because we could not extract some data such as area under the curve. Therefore we contacted the authors for access to the full text and ask for primary data but some of them could not provide data for us because it was not convenient for them to access their primary data and some databases could be used by trial registries only..

During the hand searching step we also found some studies without the full text and some were not met the eligibility criteria. From the reasons mentioned above, our review may have some publication bias

### DISCUSSION

In all three studies that met the eligibility criteria, a comparison between the effectiveness of acetaminophen (10-20 mg/kg) and that of ibuprofen (5-10 mg/kg) in reducing febrile temperature at the 4th hour after intervention among children under 12 years of age was analyzed.

The only three included studies from 735 studies might resulted from our rigorously eligibility criteria eg. fever must be diagnosed by physicians, the participant must have no underlying diseases, others interventions assigned must not effect on patient's fever and must undertaken by both groups of participants. The review limited the range of administration dosage (ibuprofen 5 to 10 mg/kg and acetaminophen 10 to 20 mg/kg), also the outcome must be measured

only by nurse or well-trained persons.

Due to these strong eligibility criteria, we include few studies, thus, small size of sample may lead a high heterogeneity. For further, we need more randomized control trial to clarify this clinical problem more obviously.

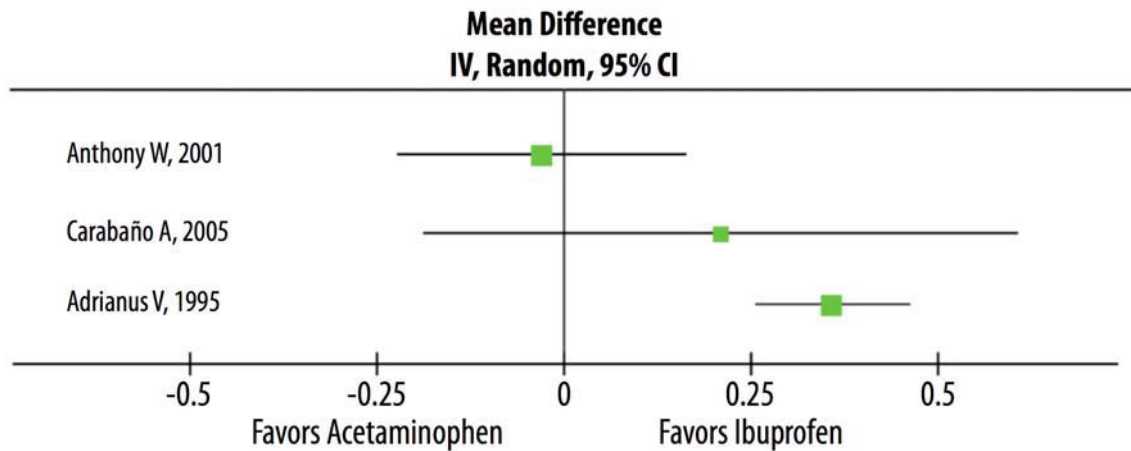
In protocol; systematic reviews 2004, 17 studies met the inclusion criteria, providing 3 data sets for pain relief, fever reduction and safety analysis. For our review, 3 studies met the inclusion criteria and analyzed only fever reduction. According to protocol, there is one new study.

Both review and protocol were typically single-dose, randomized trials and compared ibuprofen (5-10 mg/kg) and acetaminophen in oral form. Dosage of acetaminophen in protocol is 10-15 mg/kg while in our review is 10 - 20 mg/kg.

Protocol reported efficacy in reducing fever in terms of the mean between drug difference in temperature at 2, 4, and 6 hours after treatment, whereas our review studies were conducted at the 4th hour only.

Besides, in protocol, all point-estimates of the mean weighted-effect sizes for comparisons between ibuprofen and acetaminophen were positive. In our review, due to high degree of heterogeneity, thus, there is no obvious conclusion. While in the protocol can draw conclusion about better efficacy of ibuprofen in reducing pediatric fever in statistical significant.

Figure 1. Forrest plot shown outcome of the study.



**AUTHORS' CONCLUSIONS**

**Conclusion and implications for practice**

The most common antipyretic drugs for pediatrics in the hospitals of Thailand are acetaminophen and ibuprofen. Today there is no consensus in the medical literature of the relative efficacy between these drugs. This is the reason why we chose this topic.

Implications for practice in Thailand, most hospitals usually measure the body temperature every 4 hours. When pediatric patients have fever and physicians want to reduce their body temperature. Physicians can prescribe either acetaminophen or ibuprofen, because our study results are not able to draw any conclusion about the antipyretic effect between these drugs to reduce the body temperature depend on patient's condition and physician experience.

Further issues may include more update researches or hand searching in order to compare the effectiveness of ibuprofen and acetaminophen. Moreover, we may study about antipyretic medication compare with other pyretic-reducing methods---e.g. tepid sponging---or compare the side effects of the antipyretic agents.

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### ความคิดเห็นจากอาจารย์ที่ปรึกษา

งานวิจัยชิ้นนี้เป็นผลงานที่นิสิตแพทย์ชั้นปีที่ 5 ปีการศึกษา 2551 ศูนย์แพทยศาสตรศึกษาชั้นคลินิก โรงพยาบาลพระปกเกล้า ได้รับมอบหมายในช่วงที่ศึกษารายวิชามูลฐานการวิเคราะห์ทางเวชศาสตร์ (Evidence-based medicine) ซึ่งเป็นหลักสูตรของคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และได้จัดการเรียนผ่านสื่อทางไกล โดยคณาจารย์คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย รูปแบบงานวิจัยนี้เป็นการทบทวนอย่างเป็นระบบ (Systematic review) ซึ่งหมายถึงการทบทวนวรรณกรรมต้นฉบับ (Original articles) หลายฉบับที่เกี่ยวข้องกับคำถามการวิจัยที่ตั้งไว้ ภายใต้ระเบียบวิธีวิจัยที่กำหนดไว้ก่อนอย่างชัดเจน ทั้งการสืบค้นวรรณกรรม การคัดเลือก การประเมินคุณภาพวรรณกรรมต้นฉบับ การรวบรวมข้อมูล วิเคราะห์และสรุปผล สำหรับการวิจัยของนิสิตแพทย์ครั้งนี้ นิสิตได้ฝึกตั้งคำถามการวิจัยและปฏิบัติตามระเบียบวิธีวิจัยชนิดทบทวนอย่างเป็นระบบทุกขั้นตอน เพียงแต่มีข้อจำกัดด้านการสืบค้นวรรณกรรม ทั้งข้อจำกัดการเข้าถึงฐานข้อมูลทางอิเล็กทรอนิกส์บางฐาน การสืบค้นวรรณกรรมที่ไม่อยู่ในฐานข้อมูลทางอิเล็กทรอนิกส์ ข้อจำกัดด้านภาษาที่ใช้ในการตีพิมพ์ และข้อจำกัดด้านเวลา อย่างไรก็ตามงานวิจัยชิ้นนี้ได้แสดงให้เห็นศักยภาพของนิสิตแพทย์ในยุคที่ใช้ความรู้จากห้องเรียนสู่การปฏิบัติตามที่ได้รับมอบหมายจากอาจารย์

พญ.อุไร ภูนากุล

## เวชกรรมบันทึก

# ภาวะแทรกซ้อนจากการได้รับยาพาราเซตามอล เกินขนาดเฉียบพลัน

สมบัติ พนธารา พ.บ.\*

**Abstract**      **Complication of acute paracetamol overdose****Sombat Panathara M.D.\***

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Liver toxicity is a common complication of paracetamol overdose. This case reports describe a patient, who ingests overdose of paracetamol for suicide. This report is composed of liver toxicity and complications of paracetamol overdose, and proper guideline for management of paracetamol overdose. The case report was observed at 1 month follow up.

## บทนำ

Paracetamol หรือ Acetaminophen เป็นยาแก้ปวดและลดไข้ที่ได้รับการยอมรับและใช้กันอย่างแพร่หลาย ปัจจุบันเป็นยาแก้ปวดที่ใช้กันบ่อยมากเป็นอันดับหนึ่ง เนื่องจากเป็นยาที่แพทย์จ่ายให้ผู้ป่วยบ่อยที่สุด รวมถึงเป็นยาสามัญประจำบ้าน ที่ซื้อหาได้ง่ายในร้านขายยาหรือร้านค้าชุมชน ไม่มีการควบคุมจำกัดปริมาณการซื้อขาย จึงเป็นสาเหตุสำคัญในผู้ป่วยที่ตั้งใจรับประทานยาเกินขนาด โดยไม่รู้ถึงผลข้างเคียงที่อาจเกิดขึ้น (จากสถิติการเกิดภาวะพิษในคนที่ครบถ้วนและทันสมัยที่สุดในประเทศไทย ปัจจุบันยาพาราเซตามอลเป็นยาที่มีรายงานการเกิดภาวะพิษมากที่สุด) นอกจากนี้แพทย์โดยทั่วไป

อาจจะยังให้การรักษาภาวะเกินขนาดจากยานี้ไม่เหมาะสม หรือให้ยาต้านพิษช้าเกินไป ถ้าแพทย์เข้าใจถึงปริมาณที่ทำให้เกิดพิษ กลไกการเกิดพิษ และให้การรักษาได้ทันท่วงที่จะสามารถป้องกันและลดความรุนแรงของอาการตับอักเสบจนถึงตับวายและเสียชีวิตได้

ผู้ป่วยหญิงอายุ 25 ปี สุขภาพแข็งแรง ไม่มีโรคประจำตัว ปฏิเสธการแพ้ยา ญาตินำส่งโรงพยาบาลด้วยเรื่องพบว่าผู้ป่วยซึม การตอบสนองลดลง หลังจากรับประทานยาพาราเซตามอลเกินขนาด เนื่องจากมีภาวะเครียดจากปัญหาทะเลาะกับบิดามารดาบุณธรรม

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