

Comparison the Antipyretic Effect of Paracetamol, Metamizole Sodium and Diclofenac Potassium in Breaking down Fever in Children

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Abstract: The objective is to study the antipyretic effect of three different drugs used to treat fever in children paracetamol (Cetal[®] syrup), metamizole sodium (Novalgin[®] syrup) and diclofenac potassium (Catafly[®] syrup). Fever is a common symptom, the most frequent causes of fever are infections. Although it is necessary to treat the cause of fever, fever management is also important, we wanted to study the patients' discomfort accompanying fever and the beneficial effects of the fever management. The fever discomfort can be an important reason for the antipyretic treatment. Three antipyretics were tested in three groups of patients, The study included 60 patients with axillary temperature at least 37.6^oC, patients were divided into three equal groups each group of 20 patients, group A received paracetamol at dose of 15mg/kg\4hrs, group B received metamizole sodium at dose of 15mg/kg\6hrs, and group C received diclofenac potassium at dose of 1mg/kg\8hrs, we asked the first 30 study subjects to fill in a questionnaire concerning their opinions about fever, fever-associated discomfort, and relief upon antipyretic therapy. All study medications had a significant antipyretic effect. Diclofenac potassium at the dose 1 mg/kg was considered as the most effective as that of metamizole sodium which is more effective than paracetamol. All tested antipyretics significantly improved comfort in fevered children.

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1. Introduction

Fever is defined as temperature above the normal range, rectal temperature above 38.8^oC, oral temperature above 37.8^oC and an axillary temperature above 37.2^oC all are considered abnormal.

Fever in children is one of the most common clinical symptoms managed by pediatricians and other health care providers, Fever is not the primary illness but is a physiologic mechanism that has beneficial effects in fighting infection [1], Many parents administer antipyretics even when there is minimal or no fever because they concern that the child must maintain a normal temperature.

Elevation in the body temperature occur when concentrations of prostaglandin E₂ (PGE₂) increase with certain area of the brain, Fever benefits nonspecific immune response to invading microorganisms, it is also source of discomfort and commonly suppressed with antipyretic mediation. Most antipyretics work by inhibiting the enzyme cyclooxygenase and reducing the level of PGE within the hypothalamus[2, 3] and they are able to reduce pro-inflammatory mediators boost antipyretic message within the brain[3]. High temperature (high fever) induce mild dehydration, discomfort, febrile delirium and uncomplicated seizures, more serious is circulatory failure(heat stroke) which occurs often in

dehydrated children, mental disabilities may occur and epilepsy may manifest during febrile episodes, Although antipyretic drugs are the main form of treatment, this report considers the part that physical treatments might play arole in reducing the temperature of febrile children. Such treatments include tepid sponging, removing clothing, and cooling the environment of these treatments, tepid sponging has been studied most extensively, as an addition to paracetamol [4].

Body temperature measurement is most commonly taken to confirm the presence or absence of fever, many decisions concerning the treatment of children based on the result of temperature measurement, the axillary, rectal and oral sites are the most commonly used to record body temperature[5].

Paracetamol is the most commonly used antipyretic for children and the drug of first choice for reducing fever, paracetamol is effective when there is combination between pain and fever, It is not effective for prevention febrile convulsion[6], The recommended dose of paracetamol for children is 10-15 mg/kg\4-6 hrs.[7].

Diclofenac potassium (Catafly syrup) is a non-steroidal anti-inflammatory drug (NSAID), it is rapidly and well absorbed at low dose and are consistent with rapid onset of action of the drug [8],

the recommended dose of diclofenac potassium for children is 1 mg/kg/8 hrs.[9].

Metamizole sodium (Novalgin syrup) is a non-steroidal anti-inflammatory drug (NSAID), commonly used in many countries as a powerful painkiller and fever reducer, it is used with caution particularly over long periods and in large doses due to the probability of incidence of aplastic anemia and agranulocytosis [10], the recommended dose of metamizole sodium for children is 10-15 mg/kg/6-8 hrs. [11].

2. Patients and methods:

Patients:

Local hospital research ethical committee approval was obtained for the study. Patients were collected in this study from Pediatric department at Beni-suef University hospital with fever. All parents of infants were informed of the purpose of the study, expected procedures and potential risks and benefits of the study, patients with reported episodes of high fever from pediatric clinic at Beni-suef University hospital were recruited.

Children with any of the following criteria were excluded: antipyretic treatment within the last four hours, history of allergy to any of the study medications, severely ill children, history of seizures, frequent vomiting within the previous two hours, history of liver, renal or hematological disease, immune suppression, or severe malnutrition [12].

Methods:

Patients were divided into three equal groups A, B and C each of 20 patients, group A received paracetamol syrup (Cetal[®] syrup 120 mg/5 ml) at dose of 15 mg/kg/4hrs[7], group B received metamizole

sodium (Novalgin[®] syrup 250 mg/5ml) at dose of 15 mg/kg/6hrs[11] and group C received diclofenac potassium (Catafly[®] syrup 2 mg/1 ml) at dose of 1 mg/kg/8 hrs.[9], OTC treatment duration of 3 days for fever is recommended[13].

At 15, 20, 30, 40, 45 min and 1, 1.15, 1.5, 2, 3, 4, 5, and 6 hrs. after drug administration body temperature is measured, all temperature measurements were axillary and were acquired using a glass-mercury thermometer held in place for 5 minutes.

Statistical methods:

The collected data results were subjected to the following statistical tests:

- **Descriptive analysis** of the results in the form of percentage distribution for qualitative data (minimum, maximum, mean and standard deviation) calculation for quantitative data.

- **F- Test (One way ANOVA):** a test statistics calculated for comparison between means of the three groups.

- **Kruskal-Wallis test for several independent samples**

The Kruskal–Wallis test is a nonparametric test that is used with an independent groups design comprising of more than two groups.

- **P:** The probability/significance value

- **P value > 0.05** (NS) Not significant

- **P value < 0.05 *** Significant at 0.05 level

- **P value < 0.01 **** Significant at 0.01 Level

For statistical analysis, Statistical package for social science (SPSS) software version 17 was used.

3. Results:

Table (1): Descriptive analyses of age, weight, temp., does, onset and duration in Paracetemole syrup (120 mg/5ml) group

	N	Minimum	Maximum	Mean	SD
Age/year	20	0.75	9	3.8	2.2
Weight/kg	20	8	25.5	16.0	5.0
Temp	20	37.6	39.5	38.0	0.5
Dose/mg	20	5	15	9.5	3.0
Onset/min	18	45	85	65.3	11.0
Duration/hrs	18	3.45	7	4.0	0.9

-Paracetamol syrup has no antipyretic effect for children who have temperature above 39°C.

Table (2): Descriptive analyses of age, weight, temp., does, onset and duration in Metamizole sodium (250mg/5ml) group

	N	Minimum	Maximum	Mean	±SD
Age/year	20	0.66	8	3.6	1.9
Weight/kg	20	7.5	28	15.9	5.4
Temp	20	38	40	38.9	0.5
Dose/mg	20	2	7	4.3	1.3
Onset/min	20	40	65	50.3	7.5
Duration/hrs	20	4.5	6.5	5.6	0.5

Table (3): Descriptive analyses of age, weight, temp., does, onset and duration in Diclofenac potassium 2mg/ml (Cataflya syrup) group

	N	Minimum	Maximum	Mean	±SD
Age/year	20	0.83	9	4.3	2.4
Weight/kg	20	9	30	17.8	6.0
Temp	20	37.8	40	38.7	0.6
Dose/mg	20	3	9	5.3	1.8
Onset/min	20	30	65	45.3	9.0
Duration/hrs	20	5.5	8	6.8	0.7

Table (4): Comparison between all groups according to age, weight, temp., does, onset and duration

	Paracetemole syrup (120 mg/5ml) Mean±SD	Metamizole sodium (250mg/5ml) Mean±SD	Diclofenac potassium 2mg/ml (cataflya syrup) Mean±SD	p-value	Sig.
Age/year	3.8±2.2	3.6±1.9	4.3±2.4	0.610	NS
Weight/kg	16.0±5.0	15.9±5.4	17.8±6.0	0.495	NS
Temp	38.0±0.5	38.9±0.5	38.7±0.6	0.001	HS
Dose/mg	9.5±3.0	4.3±1.3	5.3±1.8	0.001	HS
Onset/min	65.3±11.0	50.3±7.5	45.3±9.0	0.001	HS
Duration/hrs	4.0±0.9	5.6±0.5	6.8±0.7	0.001	HS

-There was high significant difference between temperature, Dose/mg, Onset/min and Duration/hrs of group A, B and C, this mean that the three drugs have different antipyretic effects.

- Diclofenac potassium administrated as single dose of 3 mg/kg/day in divided doses significantly

reduce fever in patient with acute sore throat, bronchitis, cold and flu, gum inflammation and gastroenteritis, the overall efficacy of these doses was significantly higher than that of paracetamol at dose of 15 mg/kg/4-6 hrs[14-16] and higher than that of metamizole sodium at dose of 15 mg/kg/hrs[16].

Table (5): Multiple comparisons between all groups according to age, weight, temp., does, onset and duration

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	±Std. Error	Sig.
Age/year	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	0.19	0.70	0.783
		Diclofenac potassium 2mg / ml (cataflya syrup)	-0.48	0.70	0.492
		Metamizole sodium (250mg / 5ml)	-0.68	0.70	0.336
Weight/kg	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	0.07	1.73	0.966
		Diclofenac potassium 2mg / ml (cataflya syrup)	-1.75	1.73	0.316
		Metamizole sodium (250mg / 5ml)	-1.83	1.73	0.296
Temp	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	-0.83	0.17	0.001
		Diclofenac potassium 2mg / ml (cataflya syrup)	-0.61	0.17	0.001
		Metamizole sodium (250mg / 5ml)	0.23	0.17	0.191
Dose/mg	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	5.25	0.68	0.001
		Diclofenac potassium 2mg / ml (cataflya syrup)	4.25	0.68	0.001
		Metamizole sodium (250mg / 5ml)	-1.00	0.68	0.146
Onset/min	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	15.03	2.99	0.001
		Diclofenac potassium 2mg / ml (cataflya syrup)	20.03	2.99	0.001
		Metamizole sodium (250mg / 5ml)	5.00	2.91	0.042
Duration/hrs	Paracetemole syrup (120 mg / 5 ml)	Metamizole sodium (250mg / 5ml)	-1.55	0.23	0.001
		Diclofenac potassium 2mg / ml (cataflya syrup)	-2.8	0.23	0.001
		Metamizole sodium (250mg / 5ml)	-1.26	0.22	0.001

There was high significant difference between onset of action of group A,B and A,C and B,C .this mean that diclofenac potassium has shortest onset of action(gives faster antipyretic effect) than that of metamizole sodium which gives faster antipyretic effect than paracetamol.

-There was high significant difference between duration of action of group A,B and A,C and B,C. this mean that diclofenac potassium has longer duration of

action(gives longer antipyretic effect) than that of metamizole sodium which gives longer antipyretic effect than paracetamol.

Diclofenac potassium was detected in plasma within 15 min after oral administration and the maximum plasma drug concentration is reached 30 min after administration and mean terminal half life is 1-2 hrs allowing a 4-6 hrs of activity[13].

Table (6): Comparison between all groups according to side effects

Side effects	Paracetemole syrup (120 mg/5ml) No.(%)	Metamizole sodium (250mg/5ml) No.(%)	Diclofenac potassium 2mg/ml (cataflya syrup) No.(%)	p-value	Sig.
No	20(100)	20(100)	20(100)	1	NS
Yes	0(0)	0(0)	0(0)		

Since the drugs used for short time there was no observed side effects

4. Discussion:

Although some authors argued that fever might be beneficial [4, 17], it is generally accept that the fever lowering –therapy does not seem to prolong the illness or to affect its course negatively[3, 18], The appropriate management of the primary illness must play the central role[1, 19],patient has made the usage of antipyretic very common[20].

According to the result of our questionnaire; 60% of patients considered fever as harmful, 89% of them declared the symptomatic management of fever as useful, and 87% of patient felt relief of adverse symptoms accompanying fever after the administration of antipyretics.

Our study found significant differences between the three drugs, Diclofenac and metamizol were evaluated as comparably effective in one pediatric trial[21], but another pediatric study evaluated diclofenac as more potent[13-16] It should be noted that diclofenac can diminish fever even at a considerably lower single dose, The antipyretic effect of metamizole sodium is higher than that of paracetamol[14, 22].

No differences among the treatment groups were observed in the improvement of symptoms accompanying fever. At least 87% of patients reported improvement and 27% of them found it as a considerable.

Administration of any tested drug may lead to potentially severe complications [23].This is necessary to keep in mind. The most serious side effect of metamizole is agranulocytosis[10, 24, 25], Diclofenac most frequently causes gastrointestinal side effects, among which bleeding seems to be the most serious. Of concern could be its interaction with the pharmacokinetics of cyclosporin A and methotrexate, and worsening of renal function[26,

27], Liver failure is a well-recognized consequence of paracetamol overdose in our present study[28-30], we did not follow patients regularly after the administration of antipyretics. Since the time of this study, however, we have been adopting the policy of fever management into our routine daily practice and we have not observed serious adverse event potentially linked to the antipyretics.

Conclusions:

The antipyretic effect of diclofenac potassium is higher than that of metamizole sodium and higher than that of paracetamol.

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