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**Transient major hypothermia associated with acetaminophen: a pediatric case report
and literature review**

Short title: Transient major hypothermia associated with acetaminophen

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Abstract

We report the case of a 4-month-old baby boy who presented hypothermia (rectal temperature 36°C) after acetaminophen intake for post-vaccination fever. A recurrence of the hypothermia was observed after acetaminophen rechallenge for fever. We reviewed 14 other pediatric cases of hypothermia secondary to therapeutic doses of acetaminophen. Hypothermia after a therapeutic dose is a very rare side effect of acetaminophen. Several hypotheses have been made but the exact mechanism remains unknown.

Key words: acetaminophen, hypothermia, pediatrics

Conflicts of interest: none

1. Introduction

We describe here a pediatric case of hypothermia after the use of acetaminophen. To explain the occurrence of this rare adverse effect, we review all other similar cases reported to French Regional Pharmacovigilance Centers as well as all cases published to date.

2. Observation

A 4-month-old baby boy, 7.82 kg, born at term with no known medical history, was vaccinated with Infanrix hexa® and Prevenar 13® in March 2018. A 39°C fever occurred 4–5 days after the vaccination for which the mother gave 15 mg/kg of acetaminophen syrup. One to 2 h after the intake, the baby was reactionless, hypotonic, absent and had a 36°C rectal temperature. The baby was taken to the hospital emergency unit. The clinical examination was normal and the progression was favorable within a few hours after external heating. Acetaminophen was stopped.

A few days later, a second fever episode at 39°C occurred. Once again, the mother gave 15 mg/kg of acetaminophen syrup and 1–2 h after, a relapse was observed with major hypothermia (rectal temperature at 34.8°C). Once more, the clinical examination was normal and the outcome was favorable after the external heating at the emergency unit.

3. Review of other cases reported to the French Regional Pharmacovigilance Centers

Cases of hypothermia were identified from the French Pharmacovigilance Database (FPVD), which includes all adverse drug reactions (ADRs) reported to the 31 French Regional Pharmacovigilance Centers since 1985 [1]. For the present study, we collected all cases of hypothermia in children (0–15 years), recorded from 1985 to September 15, 2018, in which acetaminophen was involved. Hypothermia was defined by the preferred term "hypothermia"

according to the Medical Dictionary for Regulatory Activities 11.0. The causal relationship between hypothermia and acetaminophen was evaluated by applying the French drug reaction assessment method [2]. Nine pediatric cases of hypothermia secondary to acetaminophen were selected and analyzed. For each case, drugs associated with hypothermia were classified as suspect (drug with the highest chronological and semiological score) or other (drug with the lowest chronological and semiological score) to retain only cases of hypothermia for which acetaminophen was solely involved. These nine children were 3 months to 13 years old (median, 19.5 months; IQR 11.25–32.5 months) and six were girls. When data were available ($n=5$), the hypothermia occurred 1–4 h after acetaminophen intake for post-vaccination fever in three cases and for nasopharyngitis with fever in two cases, at a median dose of 80 mg (80; 300 mg). In five cases for which a rechallenge of acetaminophen was performed, it led to a relapse of hypothermia.

4. Discussion

In the case reported herein, the temporal relationship after the administration of acetaminophen and the occurrence of hypothermia, the quick decline of the hypothermia after external heating and the recurrence after the rechallenge were very suggestive of the role of acetaminophen. Furthermore, no other causes of hypothermia were found in the emergency unit for two episodes. Then, using the French drug reaction assessment method, the imputability of this case was considered as “plausible.”

Since 1985, only nine pediatric cases of hypothermia secondary to acetaminophen have been reported to the Regional French Pharmacovigilance Centers. However, as cases of hypothermia are generally of low or moderate severity, it is likely that it is undernotified by practitioners. Five other pediatric cases of hypothermia secondary to therapeutic doses of acetaminophen intake were also published concerning children aged 3 months to 4.5 years

(Table 1) [3,4]. As for our case, some episodes occurred after the intake of acetaminophen for a post-vaccination fever or for post-vaccination fever prevention, which ruled out hypothermia of infectious origin. Furthermore, some cases have also been published in healthy and sick adults. Four cases have been reported in patients with AIDS occurring 6 h after the administration of acetaminophen, which were well tolerated and regressed spontaneously [5]. In a trial including nine healthy males [6], acetaminophen-induced hypothermia was exacerbated during cold stress.

To date, the antipyretic and hypothermic actions of acetaminophen are not well understood. In mice, a high dose of acetaminophen induces central hypothermia, due to the acetaminophen itself and not to its toxic reactive metabolite [7]. Moreover, there is a reduction of mice brain PGE₂ levels when acetaminophen induces hypothermia at therapeutic doses [8]. Therefore, acetaminophen produces hypothermia independent of opioid, cannabinoid CB₁, or NOP receptor activation, which induces its antinociceptive effects [9]. Unlike nonsteroidal anti-inflammatory drugs, acetaminophen does not significantly bind to the cyclooxygenase (COX) isozymes at analgesic doses, but it acts as an antipyretic by blocking the increase of the concentrations of PGE₂ induced by pyrogens in cerebrospinal fluid [10,11]. The results of an experimental study [12] suggested that the hypothermic activity of acetaminophen may be mediated by its effect at GABA_A benzodiazepine receptor. But TRPV1 (transient receptor potential vanilloid 1) activity in vivo regulates body temperature, and recent studies have demonstrated that activation of TRPA1 (transient receptor potential ankyrin 1) in sensory neurons mediates the hypothermic effect of acetaminophen in mice, since the response was abolished by chemical ablation of TRPV1 containing sensory neurons [13].

Due to the complex nature of the central regulation of body temperature, we are unable to explain the exact mechanism by which acetaminophen can cause hypothermia at a therapeutic dose, but it seems likely that TRPA1 mediates the hypothermic action of acetaminophen

5. Conclusion

Acetaminophen is an effective antipyretic agent, which produces pronounced hypothermia when administered to rodents and a small hypothermic effect in humans.

Therefore, therapeutic doses of acetaminophen can exceptionally cause hypothermia in febrile children. Physicians should be aware of this possible, very rare side effect in children receiving acetaminophen, in particular after vaccination, where hypothermia could be erroneously attributed to the vaccine, while it is secondary to acetaminophen.

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Table 1. Characteristics of reported and published cases of hypothermia in children

Reference	Age	Gender	Dose	Route	Indication	Minimum temperature	Time before occurrence	Recurrence after rechallenge
1	35 months	F	Unknown	Unknown	Fever	34.3°C	2 hours	Positive
2	3 years	F	300 mg	Oral	Nasopharyngeal infection without fever	35°C	1 hour	Unknown
3	3 months	F	50 mg	Oral	Post-vaccination fever	36°C	4 hours	Unknown
4	21 months	F	80 mg	Rectal	Post-vaccination fever prevention	36°C	1 hour	Positive
5	3 months	M	80 mg	Rectal	Post-vaccination fever prevention	Unknown	Unknown	Unknown
6	11 months	M	60 mg/kg	Oral	Nasopharyngitis with fever	34.3°C	1 hour	Positive
7	1 year	F	Unknown	Oral	Unknown	Unknown	Unknown	Positive
8	18 months	F	Unknown	Unknown	Unknown	35.7°C	Unknown	Unknown
9	13 years	M	Unknown	Unknown	Unknown	Unknown	Unknown	Positive
[2]	15 months	F	15 mg/kg	Unknown	Fever	33.6°C	Unknown	Unknown
[3]	4.5 years	F	250 mg	Rectal	Fever	35°C	2 hours	Unknown
[3]	21 months	M	125 mg	Rectal	Fever	35°C	3 hours	Unknown
[3]	4 months	F	125 mg	Rectal	Post-vaccination fever	35°C	3 hours	Unknown
[3]	3 months	M	35 mg	Rectal	Nasopharyngitis with fever	35°C	Unknown	Unknown