

High fatality in low weight children related to suprathreshold doses of paracetamol in countries with unrestricted access to medication

Mohamad Haidar^{1,2}, Kensute Takahashi¹, Nicoletta Belio³, Jean-Claude Alvarez⁴, Robin E Ferner⁵, Luke Bawo⁶, Klaudia Proten¹, Frederic J Baud^{2,3}

¹Epicentre, Paris, France, ²UMR 8257, Paris Descartes University, ³Medecins sans Frontieres, ⁴Paris France, ⁵AP-HP; University VSQ, Paris, France, ⁶City Hospital, Birmingham, UK, ⁶Ministry of Health and Social Welfare, Monrovia, Liberia

Background

MSF medical personal had faced syndromes of liver insufficiency among children in the different pediatrics hospitals. Investigating attributed causality (ischemic, viral, or toxic) was generally not possible due to the limited resources within these contexts.^{1,2}

In July 2015, increased admissions with similar syndrome were noted in Barnesville Junction Hospital (BJH) in Monrovia, Liberia.

Children were reported to have consumed unprescribed conventional medications including paracetamol, antimalarials, and antibiotics, in addition to traditional treatments prior to hospitalization.

Lacking an infectious etiology, we hypothesized a toxic origin. We adopted a toxidrome-based approach,³ hypothesizing that the syndrome was associated with treatments consumed prior to hospitalization.

Methods

Case-series

Children over one month old admitted to BJH between July and December 2015 presenting at least two organ-specific symptoms with suspicion of toxicity were included.

29 plasma samples were transported to Laboratoire de Toxicologie, Hôpital Raymond Poincaré, France and tested for 1389 compounds and acetaminophen quantification.



Matched Case-control

To reach power of 80%, 30 cases and 60 controls were required. Therefore, the aim was to match the 30 cases with 60 hospital based- and 60 community based-controls.



The definition of cases used was:

Definition

Respiratory distress Bradypnea, Tachypnea, nasal flaring, inter- or sub costal retractions, grunting
Normal SpO2 in ambient air SpO2 > 94% while breathing ambient air

In addition to one of the following symptoms

Absence of fever <38.0°C axillary temperature
Hepatomegaly ≥2 cm palpable below the right costal margin
Low blood glucose level ≤60 mg/dl

The controls had to have at least one episode of non-trauma illness and were matched with the cases according to the following criteria:

Matching Variables	Hospital Controls	Community Controls
Age Group	✓	✓
Sex	✓	✓
Same Month of admission	✓	✓
Same Triage Results	✓	✓
Same Month of Illness	✓	✓
Residence in Proximity of the Case	✓	✓

Results

From July to December 2015, 77 children admitted to BJH with suspected intoxication were enrolled in the case-series study; 68/77(88%) were two years of age and younger and 35/77(46%) died during hospitalization (Figure 1). The syndrome was characterized by liver necrosis with severe lactic acidosis (Table 1), meeting acetaminophen intoxication criteria.^{3,4}

Figure 1. Number of suspected cases of intoxication by outcome and week number in the case-series

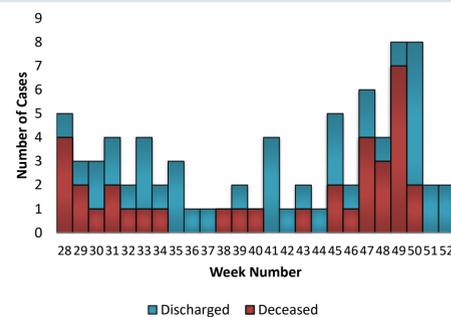


Table 1. Clinical and toxicological characteristics of the syndrome among children included in the case-series.

Parameter	n/N(%)
Aspartate Transaminase > 2 times	64/69(93)
Alanine Transaminase > 2 times the	58/69 (84)
Altered consciousness	56/77(73)
Hypoglycaemia	43/77(57)
Blood Lactate (N=26)	
Median [IQR]	7.1[2.0-20.4]

Measured plasma acetaminophen concentration lined with the clinical diagnosis highlighting acetaminophen at toxic levels among majority of patients with crude values upon admission or after pharmacokinetic calculations (Table 2).

	N	Median (IQR)	SD	None Detected		
				<10 µg/mL	>10 µg/mL	
Blood plasma concentration upon admission	13	16.6 (11.1-53.0)	32.2	0	3(23.1)	10(76.9)
Total after Pharmacokinetic calculations	29			4(13.8)	5(17.2)	20(69.0)

Thirty percent (9/30) of the cases and 9.4% (5/53) of the controls enrolled in the case-control study died during hospitalization. Suprathreshold doses of acetaminophen were higher among the cases than both hospital and community control groups, in contrast to the other potential hepatotoxic substances which were found to be similar across groups. Multivariable analysis revealed statistically significant higher odds of acetaminophen suprathreshold doses and the toxic syndrome (Table 3).

Table 3. Adjusted Odds ratio (aOR) of the toxic syndrome for different potential hepatotoxins based on cases, hospital and community controls for patients enrolled in the case-controls study.

	Cases (n=30)	Hospital Controls (n=53)	p-value	Community Controls (n=48)		p-value
	n(%)	n(%)		aOR(95%CI)*	aOR(95%CI)*	
Acetaminophen (total)	26(86.7)	28(52.8)		46(95.8)		
Acetaminophen suprathreshold dose	9(30.0)	5(9.4)	4.3 (1.1-17.0)	0.039	2(4.2) (1.8-296.9)	0.016

*The multivariate models were adjusted for all hepatotoxic drugs reported including medications with adverse effects on the liver (cotrimoxazole, erythromycin, amodiaquine, artesunate, all traditional treatments)

Discussion

Clinical plausibility, toxicology screening and statistical association, identified acetaminophen suprathreshold doses as the main toxicant.

Acetaminophen toxidrome has been rarely reported in children aged two years and younger, yet they remain the most susceptible due to their body weight of 10 kgs and less.^{4,5,6} While the toxicity of high single-dose of acetaminophen is well understood, the time-course of toxic effects induced by suprathreshold staggered doses is not fully characterized, especially in low-weight children.

A definitive diagnosis of a toxic cause requires the exclusion of non-toxic diagnoses. All these conditions were ruled out either by time-course effects or through comparison with hospital controls. There were no signs such as icterus and meningism, suggestive of hemolytic-uremic syndrome or leptospirosis.

The study highlights a public health problem that has been underdiagnosed not just in Liberia, but possibly in all countries with unrestricted access to medications.

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Acknowledgments

This research was funded by Médecins sans Frontières (MSF). We would like to thank MSF field team in Monrovia for supporting to conduct this study.

