

# ALTERNATIVE VIEWPOINTS

## Drug Induced Hepatotoxicity in a 9-Year Old Boy: Possible Cause is Cotrimoxazole, Acetaminophen or Both Medicines

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Sulfonamides<sup>1</sup> and acetaminophen at therapeutic doses,<sup>2</sup> either alone or in an association with other hepatotoxic medicines, have been incriminated in hepatic damage in children and adults. The proposed mechanism is either idiosyncrasy or intrinsic toxicity. Both sulfonamide and acetaminophen are metabolized in the liver by glucuronide conjugation and have the potential to induce hepatotoxicity.<sup>1, 2</sup> Therefore, the title “Trimethoprim-sulfamethoxazole-induced hepatotoxicity in a pediatric patient” of the case report by Dr. Bell and her colleagues<sup>3</sup> may be inappropriate.

Considering the several cases reported of acetaminophen-induced hepatotoxicity at therapeutic dose,<sup>4, 5</sup> acetaminophen could also be responsible for the hepatotoxicity in the patient. Unfortunately, his clinical history was inadequate and the authors did not provide a balanced evidence to exonerate acetaminophen as a suspect medicine. We will therefore like to comment on the deficiencies in the history and provide an alternative explanation to the authors' views.

The patient developed fever, headache and neck pain on the 11<sup>th</sup> day of cotrimoxazole therapy. Fever, headache and neck pain may constitute the early symptoms of a multi-systemic adverse drug reaction (ADR) as multi-systemic ADRs often mimic other illnesses<sup>6</sup> such as the presumptively diagnosed viral infection. Ingenuity was therefore required for the authors to suspect an ADR at the initial presentation of the patient.

Fever was the only indication for prescribing the patient acetaminophen. Although acetaminophen was to be used when necessary, the normal therapeutic serum concentration (14.9 µg/ml) and persistent fever (102.8°F) reported in the patient may suggest that acetaminophen was frequently used. Significantly, elevated serum transaminases following therapeutic dose of acetaminophen in healthy adults<sup>4</sup> and those who developed acute hepatotoxicity while concomitantly using other hepatotoxic medicines<sup>5</sup> have been documented. Early onset (2 days) of acetaminophen-induced acute hepatotoxicity had been reported.<sup>7</sup> Therefore, exonerating acetaminophen as a culprit medicine based on normal therapeutic serum concentration is rather ill-advised. The standard practice is to stop all medicines in cases of suspected ADRs and gradually re-introduce them upon recovery of the patient.<sup>6</sup> We therefore assume that both acetaminophen and cotrimoxazole were discontinued in the patient. However, such vital information about acetaminophen discontinuation was missing in the case report by Dr. Bell and her colleagues. It is strongly believed that acetaminophen, either

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alone or in an association with cotrimoxazole, may be responsible for the hepatotoxicity experienced by Dr. Bell's patient.

An ADR in a patient on multiple medicine therapies would require a causality assessment for each of the medicines, using a standard causality assessment tool such as the Naranjo probability scale.<sup>8</sup> But surprisingly, causality assessment was made for only co-trimoxazole with an overestimated score of 5. Given the available information in the case report and using the Naranjo probability scale, we found a possible association of hepatotoxicity with cotrimoxazole (Naranjo score = 3) and acetaminophen (Naranjo score = 2) used by the patient (Table 1).

Cotrimoxazole was used for 14 days before the patient commenced acetaminophen. Exposure of the patient to these potentially hepatotoxic medicines may likely have induced chemical-chemical interaction causing cotrimoxazole to potentiate the hepatotoxic action of acetaminophen. Two types of chemical-chemical interactions, toxicokinetic (altered disposition of the chemical) and toxicodynamic (altered tissue response to chemical or the resulting injury), may be involved in hepatotoxicity.<sup>9</sup> While toxicokinetic interactions act primarily by inhibiting or enhancing the metabolizing enzymes, toxicodynamic interactions act by inducing or depleting tissue factors, altered inflammatory response, tissue repair mechanisms, or the hemodynamics of the

chemical. The case report of Dr. Bell and her colleagues may therefore represent a predominantly toxicokinetic chemical interaction with a toxicodynamic component.

It is possible that cotrimoxazole had initiated the hepatic damage as indicated by the clinical symptoms of the patient at initial presentation. The progressive worsening of his clinical symptoms after commencing acetaminophen may suggest that acetaminophen was partly or wholly responsible for the acute hepatotoxicity.

Acetaminophen was administered concomitantly with cotrimoxazole for 3 days. Since both medicines are metabolised primarily by glucuronidation, it is possible that cotrimoxazole had depleted the glucuronic acid level of the patient which may result in increased alternate metabolic pathway such as the glutathione conjugation of acetaminophen. Pharmacokinetic studies of acetaminophen in humans have indicated gradual decline of glutathione levels at doses as low as 0.5–3 g.<sup>10</sup> Thus a critically low level of glutathione may have been reached in the patient, which was not sufficient to effectively inactivate *N*-acetyl-benzoquinone imine (NAPQI).<sup>11</sup> NAPQI is a toxic metabolite which when not inactivated due to reduced glutathione, would result into hepatic damage.

Amidst the limitations of this case report, physicians should be aware that acute hepatotoxicity in children may occur at therapeutic doses of cotrimoxazole, acetaminophen or following co-administration of both

Table 1. Naranjo probability score for hepatotoxicity causality with cotrimoxazole or acetaminophen.

| Scoring parameters   | Medicine      |               |
|--|---------------|---------------|
|  | Cotrimoxazole | Acetaminophen |
| Are there previous conclusive reports of this reaction?  | +1            | +1            |
| Did the adverse event occur after the suspected drug was given?                                      | +2            | +2            |
| Did the reaction improve when the drug was stopped?  | +1            | 0             |
| Did the adverse reaction reappear when the drug was given again?                                     | 0             | 0             |
| Are there alternative cases that, on their own, could have caused the reaction?                      | -1            | -1            |
| Did the reaction reappear after placebo was given?   | 0             | 0             |
| Was the blood level detected known to be toxic?  | 0             | 0             |
| Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | 0             | 0             |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure?       | 0             | 0             |
| Was the adverse event confirmed by any objective evidence?   | 0             | 0             |
| Total score  | 3             | 2             |

N.B. Interpretation of the total result

≥ 9 means ADR is definite or highly probable

5-8 means ADR is probable

1-4 means ADR is possible

≤ 0 means ADR is doubtful

medicines. It is to be hoped that our comment would stimulate interest on more work that will appropriately explain the mechanistic action of acute hepatotoxicity in association with cotrimoxazole and acetaminophen co-administration.

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## Authors' Reply

We appreciate the additional comments of Oshikoya and his colleagues in regard to our case-report on trimethoprim-sulfamethoxazole (TMP-SMX) induced hepatotoxicity in a pediatric patient and wish to provide additional insight into the case as well as commentary to their points. While we cannot completely eliminate that co-administration of acetaminophen may have contributed to the patient's hepatotoxicity through a toxicokinetic interaction resulting in a toxicodynamic response; the medical team along with my colleagues reviewing the case believe that a preponderance of the evidence implicates TMP-SMX as the primary culprit in his hepatotoxicity, and acetaminophen was not a major contributor.

To further clarify the patient's acetaminophen use, the patient only received a total of four doses upon re-evaluation of the patient's medical records and our notes from interviews with the parents. The patient, who presented with symptoms of fever, headache and neck pain, had not received any doses of acetaminophen prior to his first emergency room (ER) visit, but did receive one dose of acetaminophen while there. As Dr. Oshikoya and his colleagues stated, the patient could have been experiencing early symptoms of a multisystemic adverse drug reaction (ADR), however, at this initial ER visit, his only medication was TMP-SMX. Unfortunately, liver function tests were not taken at this particular visit. Subsequently, at his second ER visit, per his mother, he received 2 doses of acetaminophen prior to his presentation and only one dose was given prior to his symptoms of abdominal pain. At this second visit to the ER, an acetaminophen blood concentration was obtained eight hours after the patient received a 500 mg dose in the ER and was 14.9 µg/ml. Utilizing the Rumack-Matthew nomogram for acute ingestion of acetaminophen, the patient is not likely at risk for hepatotoxicity from acetaminophen (Figure 1).<sup>1</sup> Acetaminophen was not continued when the patient was admitted to the hospital. Additionally, references provided by Oshikoya et al do not seem to correlate well with our pediatric patient, as the patients in their references were primarily adult patients who received maximum daily doses of acetaminophen (4 grams) in combination with other medications or also consumed alcohol.<sup>2,3</sup>

Utilizing the Naranjo scoring system, our total score was a 5 for TMP-SMX and we disagree with Oshikoya and his colleagues' score of 3 (Table 1).<sup>4</sup> A point was given for the adverse event being confirmed by objective evidence, as he had a leukopenia with a secondary bone marrow response causing a bandemia which could be explained by a TMP-SMX reaction.<sup>5</sup> We gave an additional point for answering no, in terms of did the reaction appear when a placebo was given. We were unable to find any pediatric case reports of patients with normal acetaminophen concentrations experiencing hepatotoxicity in addition to leukopenia. Retrospectively, we could have included a Naranjo score for acetaminophen (Table 1) which would have strengthened our case for TMP-SMX causing the hepatotoxicity, however when calculating the score it did not seem that acetaminophen was responsible for the reaction. We do however agree further research is

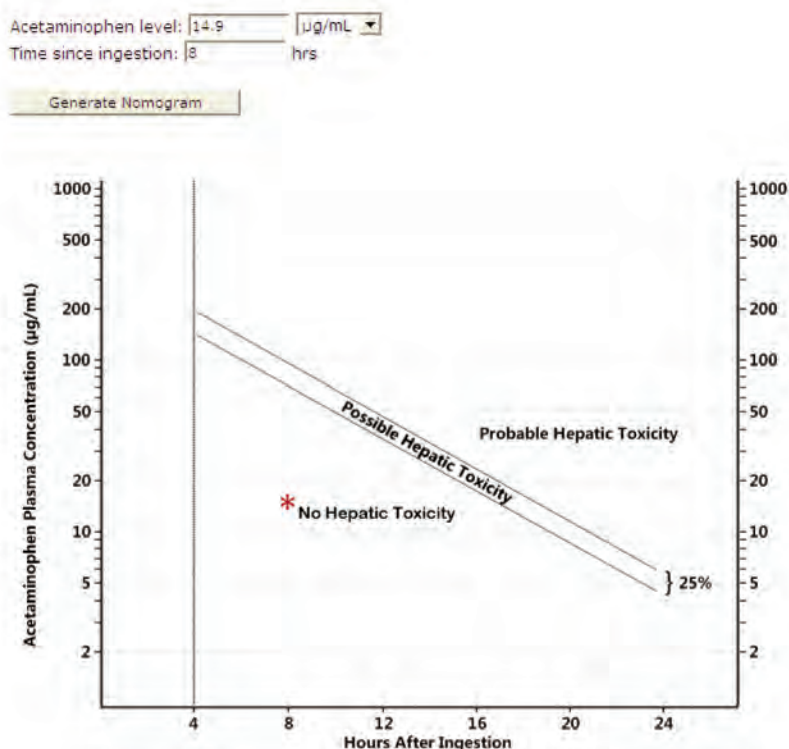


Figure 1. Rumack-Matthew nomogram for acute ingestion of acetaminophen.

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| Did the adverse event occur after the suspected drug was given?                                      | +2            | +2            |
| Did the reaction improve when the drug was stopped?  | +1            | 0             |
| Did the adverse reaction reappear when the drug was given again?                                     | 0             | 0             |
| Are there alternative cases that, on their own, could have caused the reaction?                      | 1             | -1            |
| Did the reaction appear when a placebo was given? (No=1 pt)  | 1             | 1             |
| Was the blood level detected known to be toxic?  | 0             | 0             |
| Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | 0             | 0             |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure?       | 0             | 0             |
| Was the adverse event confirmed by any objective evidence?   | 1             | 0             |
| <b>Total score</b>   | <b>5</b>      | <b>3</b>      |

N.B. Interpretation of the total result  
 ≥ 9 means ADR is definite or highly probable  
 5-8 means ADR is probable  
 1-4 means ADR is possible  
 0 means ADR is doubtful

needed to define and understand if a relationship exists with hepatotoxicity and coadministration of TMP/SMX and acetaminophen.

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