



# Nomogram Line Crossing in Acetaminophen Combination Product Overdose

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## Background

The Rumack-Matthew nomogram (RMN) predicts the risk of hepatotoxicity after acute acetaminophen (APAP) overdose based on a level obtained  $\geq 4$  hours after ingestion. Xenobiotics that slow gastrointestinal motility can delay APAP absorption (1, 2) and complicate use of the RMN. Patients with opioid or antimuscarinic coingestants may become "line-crossers" with a non-toxic 4 hour APAP followed by a subsequent level that is above the RMN treatment line (3). The aim of this study was to determine the incidence of line-crossing after acute overdose of APAP combination product (ACP) containing an opioid or diphenhydramine (DPH).

## Methods

This was a review of data collected prospectively at a single regional poison center (RPC). Entry criteria included: 1) acute overdose of ACP, 2) presentation to a health care facility (HCF) within 4 hours of ingestion, and 3) age  $> 12$  years. Standard RPC recommendations to HCFs after ACP overdose included obtaining a 7-8 hour APAP level if the 4 hour level was detectable but below the RMN treatment line. N-acetylcysteine (NAC) treatment was then recommended if the 7-8 hour level was above the treatment line. If the 7-8 hour level was greater than the 4 hour level but below the treatment line, a third level was recommended. RPC records were reviewed for 4 and 7-8 hour APAP levels, initial and repeat aminotransferases, and NAC treatment.

Case	APAP Combination Product	Other Co-ingestants by History	Initial APAP (mcg/mL) / Post-ingestion time	2 <sup>nd</sup> APAP / Post-ingestion time	Comments
1	APAP-DPH	Ethanol	88 at 4.5 hours	78 at 8.5 hours	Drowsy with urinary retention
2	APAP-hydrocodone	Ibuprofen, aspirin	145 at 4 hours	99 at 7 hours	Somnolent
3	APAP-oxycodone	Oxycodone	118 at 4 hours	101 at 7.5 hours	Alert
4	APAP-hydrocodone		131 at 4 hours	126 at 6.5 hours	Asymptomatic
5	APAP-oxycodone	Unknown cold-cough pill	47 at 4 hours	67 at 8 hours	Tachycardic, hypertensive
6	APAP-DPH		64 at 5 hours	69 at 7 hours	Tachycardic

**Table.** Line-crossers (cases 1-4): Initial APAP level below and repeat level above RMN treatment line  
Near-line crossers (cases 5-6): Second  $>$  first APAP level with both below RMN treatment line

## Results

Between 1/22/11 and 7/7/14, 75 patients met entry criteria. 54 (72%) were female. Mean age was  $29.2 \pm 14.5$  years (SD), and median age was 24 years. 28 patients (37.3%) received at least an initial dose of NAC. 4/75 patients (5.3%, 95% confidence interval 1.5 to 13.1) were line crossers with nontoxic APAP levels at 4-4.5 hours of 88-131 mcg/mL. Their repeat levels obtained at 6.5-8.5 hours were above the RMN treatment line (see Table). ACPs in these cases contained DPH, hydrocodone, and oxycodone. All 4 patients were treated with NAC, their APAP cleared, and none developed liver injury. Two were described as asymptomatic and 2 had symptoms attributable to ACP components.

An additional 2 'near-line-crosser' patients had 7 or 8 hour APAP levels greater than their 4 hour levels, but still below the RMN treatment line. Their APAP levels subsequently declined and neither developed liver injury.

Two non-line crossers had initial ALT  $> 100$  but  $< 200$  U/L that subsequently improved, suggesting inaccurate/incomplete histories or a non-APAP-related cause. Both were treated with NAC.

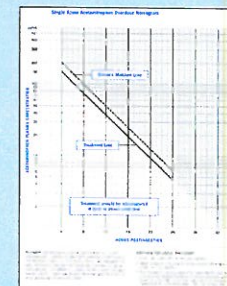
## Conclusions

After acute overdose of APAP combination products containing opioids or DPH, a 4 hour APAP level below the RMN treatment line should be followed by a 7-8 hour level. Patients with APAP levels crossing the treatment line may not manifest signs/symptoms of the opioid or antimuscarinic coingestant.

Repeat APAP determination might be unnecessary if the 4 hour level is sufficiently below the treatment line, but larger studies would be needed to determine such a threshold.

## References

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Rumack-Matthew nomogram  
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