

## **Paracetamol half-life declines over time following an acute overdose.**

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**Background.** Paracetamol (acetaminophen) is one of the most used drugs in the world and the most common drug-induced poisoning. A paracetamol overdose is associated with hepatotoxicity and treated with N-acetylcysteine. Until now, prolonged paracetamol half-life (>4 hours) is considered the best predictor for hepatotoxicity and might prompt longer N-acetylcysteine treatment. Based on clinical experience, this half-life seems to decline over the course of the treatment. This might have implications for duration of N-acetylcysteine treatment, as the toxicity might be less severe than initially suspected. This study aims to investigate the change in paracetamol half-life during a paracetamol overdose.

**Methods.** The lab information system GLIMS was used to select patients with  $\geq 3$  paracetamol plasma levels during a single overdose between 1 April 2016 and 1 March 2024. One academic and one teaching hospital in the Netherlands were included. Patients with a first sample <75 mg/L were excluded. Half-life was calculated between the first and second sample and second and third sample. Samples below the LLOQ (5.0 mg/L) were replaced by 2.5 mg/L. Medians were compared using the Wilcoxon Signed Rank test, correlations analyzed using the Pearson correlation.

**Results.** Data from 113 paracetamol overdoses from 88 patients were analyzed. Median (IQR) age was 25 (18-42) years and 81% were female. The median (IQR) half-life changed from 4.7 (3.3-8.3) hours between samples 1 and 2, and 3.5 (2.5-4.8) hours between samples 2 and 3 ( $p < 0.001$ ). This effect was more pronounced in patients with a prolonged half-life (>4 hours). In this subgroup ( $N=73$ ), the half-life almost halved from 7.2 (4.9-11.2) hours to 3.9 (3.0-5.4) hours ( $p < 0.001$ ). No correlation was detected between the first sample and half-life for both the total population ( $p=0.614$ ) and the patients with a prolonged half-life ( $p=0.944$ ).

**Conclusions.** Paracetamol half-life exhibited a reduction during the course of a paracetamol overdose in patients with a prolonged half-life. These findings underscore the importance of conducting tertiary serum sample analysis in cases where the first, prolonged half-life of paracetamol implies longer NAC treatment.

**Key words.** paracetamol, N-acetylcysteine, toxicity, half-life.