The standard treatment protocol is inadequate following overdose of extended release paracetamol – A pharmacokinetic and clinical analysis of 53 cases.

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Overdose with extended release paracetamol poses challenges beyond those with immediate release.

**Case report:** Dose 66.5 g extended release. Peak s-paracetamol 19 hours post-ingestion, high levels up to 40 hours. Liver impairment (max ALT 6660 U/L at 77 hours) despite timely NAC and restart after 24 hours.
Formulation of extended release paracetamol in Sweden

Bilayer tablet with 665 mg paracetamol
- 31% immediate release
- 69% extended release

"Contains a *HPMC-polymer which hydrates, forming a gel layer around the matrix. Paracetamol is released by a combination of diffusion from and erosion of the gel layer".

*hydroxypropyl methylcellulose
Increasing sales number related to consultations to Swedish Poisons Information Centre
Methods

• Retrospective study 2009-2015

• Hospital case records including laboratory analyses, identified by consultations to Swedish Poisons Information Centre.
  - Study cases: Acute overdoses of extended release paracetamol ($n=53$)
  - Reference cases: Acute overdose of immediate release paracetamol ($n=22$)
Methods

- **Inclusion criteria**
  - A reported toxic dose of \( \geq 10 \text{ g} / 140 \text{ mg/kg} \)
  - S-paracetamol and standard liver tests documented in case record
  - A stated time interval between ingestion to measured s-paracetamol

- **Analysis of data**
  - Graphical analysis and descriptive statistics (R 3.1.3 and Excel)
  - Population pharmacokinetic modelling (NONMEM 7)
Gender, age and dose range in study cases

- In total 53 cases were included:
  - Female: 40 (75%)
  - Male: 13 (25%)
- Age range: 13-68 years (mean 30.5)
- Reported dose range: 10-166 g (mean 38.8)
Observed s-paracetamol vs time in 36 cases with dose interval 10-50 g
Observed s-paracetamol vs time in all 53 cases, dose interval 10-166 g

S-paracetamol per individual: range 1-10 (mean: 3.4)
Differences in exposure profile between extended and immediate release paracetamol formulations

Treatment nomogram
Possible explanation of the delayed absorption

30 tablets of extended release (665 mg) paracetamol in simulated gastric juice after 8 hours forming a “gel-aggregate”

(In vitro study in manuscript, to be published)
Liver impairment despite timely *N*-Acetylcysteine (NAC)

- In total 43 patients out of 53 were treated with NAC, 34 of them within 8 hours
- Liver impairment developed in 11 patients, 7 of them despite timely NAC
### Conclusion

**Overdose of extended release paracetamol**

- Highly unpredictable exposure profile and clinical course.
- Prolonged absorption with delayed peak(s) of s-paracetamol, correlating to increasing dose.
- The standard treatment protocol based on immediate release paracetamol is inadequate.
Conclusion
Overdose of extended release paracetamol

- Hence, after ingestion of a toxic dose:
  - Serial measurements of s-paracetamol are recommended, even if NAC is ongoing.
  - A prolonged period with higher infusion rate of NAC may be warranted in cases with persistently high serum levels.

- Further studies are ongoing to better determine the optimal treatment.
Thanks for your attention!
Current management in Sweden after overdose of extended release paracetamol

• Serial measurements of s-paracetamol to at least 18 hours after ingestion, even if NAC is ongoing

• Treatment nomogram for “risk patients” used as cut-off levels for NAC treatment

• Bolus dose of NAC followed by the second dose level (12.5 mg/kg/h) used as maintenance dose until s-paracetamol is undetectable.
Differences in exposure profile between extended and immediate release paracetamol formulations.