Position Statement March 2022

Prescribing weight-adjusted oral paracetamol in adults

Recommended dosing:

Dosing guide for patients with risk factors for hepatotoxicity with paracetamol. Clinical judgement must always be used.

	Weight * ≤ 40kg	Weight * 41kg to 49kg	Weight * > 50kg
Oral dosing (PO)	500mg Four times daily	500mg - 1g Three times daily	500mg - 1g four times daily
Maximum daily dose	2 g	3 g	4 g
*Dry weight should be used If over 50kg (dry weight), 1g QDS PO is safe for short periods (≤ 7 days) If needed regularly long-term (> 7 days), reduce dose Irrespective of weight where the patients eGFR is less than 30ml/min/1.73m2, the interval between dosing must be a minimum of 6 hours			

Risk Factors for hepatotoxicity with paracetamol[1, 2]:

- Dry body weight under 50kg
- Elderly/frail
- Renal insufficiency
- Decompensated liver disease
- Chronic malnutrition
- Chronic dehydration
- Cachexia
- Chronic alcohol consumption or regular consumption of alcohol in excess of recommended amounts
- Long-term treatment with liver enzyme-inducing drugs e.g. carbamazepine, phenytoin, primidone, rifampicin, phenobarbital, St John's Wort or other drugs that induce liver enzymes

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Background:

Paracetamol is metabolised mainly in the liver by glucuronic acid conjugation and sulphuric acid conjugation with a small fraction metabolised by cytochrome P450 to a hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI)[1]. At therapeutic doses, NAPQI is conjugated with glutathione and inactivated and eliminated in the urine. In overdose, the glucuronidation and sulfation pathways become saturated and more paracetamol is metabolised via CYP450 to form NAPQI. When glutathione stores are exhausted, NAPQI accumulates and exerts a direct hepatotoxic effect.

There is information to suggest that pharmacokinetics of paracetamol is altered in severe liver disease[3]. There are case reports of malnourished patients, frail elderly patients, and patients with a history of liver disease developing acute liver failure following administration of oral paracetamol at a dose of 4g daily (1g four times a day)[3].

A reduction of the maximum dose of oral paracetamol to 3g in 24 hours (1g three times a day) should be considered for patients with risk factors for hepatoxcitiy with paracetamol, as highlighted above regardless of weight. This reduction should also be considered for patients with decompensated cirrhosis, particularly with long term use. This is the current practice of the several liver units around the United Kingdom based on case studies and expert consensus.

Although there is insufficient evidence to suggest that low body weight is an independent risk factor for developing acute liver failure from oral paracetamol, low body weight may be a symptom of an underlying condition, which would be an indication for reducing oral paracetamol doses. If a patient has a low body weight, increased age and/or frailty, the risks and benefits of oral paracetamol should be regularly reviewed. If patients are prescribed a lower dose they should be informed of the reasons why and advised accordingly, including purchase of paracetamol containing OTC medicines.

Note that the above guidance is for oral paracetamol only - guidance on the dosing of IV paracetamol for patients under 50kg is available in the BNF and product literature, and should be followed.

References:

1. Aurobindo Pharma – Milpharm Ltd UK, 2021, SPC Summary of Product Characteristics: Paracetamol Tablets 500mg. https://www.medicines.org.uk/emc/product/10817/smpc Accessed February 2022
2. BNF Online, February 2022. PARACETAMOL | Drug | BNF content published by NICE
3. What dose of paracetamol for older people? *Drug and Therapeutics Bulletin* 2018;**56:**69-72.
4. BASL Clinical Guideline: Symptom control and end of life care in adults with advanced liver disease. Symptom control in adults with advanced liver disease - BASL Final.pdf

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