What dose of paracetamol for older people?

Paracetamol, on its own or in combination with other analgesics, is widely used to treat pain associated with acute and chronic conditions. It is considered safe enough to have a general sales licence (GSL) for use by "adults, elderly and children over 16 years" and has few listed cautions or contraindications.[1,2] However, recently the effectiveness and safety of paracetamol for some conditions have been challenged,[3,4] and there are published case reports of liver failure associated with therapeutic doses.[5–9] Here, we review the use of paracetamol, its pharmacokinetics, the mechanisms by which it can cause liver damage and consider whether frail older people are at greater risk of adverse effects. We also discuss if dose reduction should be considered in some circumstances.

Paracetamol and its use

Paracetamol is a non-opioid analgesic recommended for the first-line management of mild to moderate pain and pyrexia.[1,10] According to the British National Formulary (BNF), it has similar analgesic efficacy to aspirin but without anti-inflammatory activity.[1] It is less of an irritant to the gastrointestinal tract than aspirin and, for this reason, is preferred, particularly for older people, for whom the use of NSAIDs and opioids may be inappropriate. The only listed contraindication to paracetamol is hypersensitivity to the active ingredient or excipients.[2] The warnings and precautions documented in the summary of product characteristics (SPC) include non-cirrhotic alcoholic liver disease and severe renal or hepatic impairment.

The evidence for paracetamol's effectiveness, particularly for low back pain and osteoarthritis, has been questioned.[3,4,11,12] Nevertheless, it is included as a first-line analgesic in guidelines for many types of painful conditions, with a recommendation to increase to the maximum dose of 1g four times a day before switching to (or combining with) another analgesic.[10,13,14]

We are not aware of any large-scale clinical trials that have assessed efficacy and safety of paracetamol, specifically in older people. Although some clinical trials for analgesics have included patients aged over 65 years, most trials exclude frail older people with multimorbidity.[15] Frail patients may have significant changes in body composition that alter pharmacodynamics and pharmacokinetics of medicines, so the clinical outcomes from studies that exclude frail older people cannot be extrapolated with confidence.

Dosing

The usual adult dose for oral paracetamol is 0.5 to 1g every 4–6 hours up to a maximum of 4g in 24 hours with no dose reduction advised for older people.[1,2] Adverse effects with standard doses are rare.[2] However, as liver damage and, less frequently, renal damage can occur following overdose, warnings not to exceed 4g in 24 hours are prominent in the patient information leaflet and on package labels.

The SPC for intravenous paracetamol has more detailed dosing instructions based on weight (see Table 1), with a recommendation that the dose should be reduced in patients who weigh 50kg or less and in those with risk factors for hepatotoxicity.[1,16,17] The Medicines and Healthcare products Regulatory Agency (MHRA) emphasised the importance of the dosing instructions for the intravenous product following case reports of accidental overdose where there had been confusion between the prescription of intravenous paracetamol in milligrams and administration in millilitres.[18]

Table 1: Dose recommendations for intravenous paracetamol[2]

Patient weight	Single dose	Maximum in 24 hours
>33kg to ≤50kg	15mg/kg	60mg/kg
>50kg and additional risk factors for hepatotoxicity	1g	3g
>50kg and no additional risk factors for hepatotoxicity	1g	4g

The BNF includes a warning that some patients "may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body-weight under 50kg and those with risk factors for hepatotoxicity".[1] The BNF recommends that clinical judgement should be used to adjust the dose of oral and intravenous paracetamol in such patients. However, the National Institute for Health and Care Excellence's Clinical Knowledge Summary could find no clinical guidance or evidence that low body-weight alone, in the absence of other risk factors, causes hepatotoxicity.[10]

Metabolism and pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal (GI) tract with peak plasma concentrations occurring 30 to 60 minutes after oral doses.[2] Following oral administration, its systemic bioavailability is dose-dependent and ranges from 70–90%.[19] It is distributed into most body tissue and metabolised by the liver.[2] The metabolites are excreted in the urine and the half-life varies from 1 to 4 hours. Paracetamol is metabolised by glucuronidation and sulfation, but a small amount is metabolised via cytochrome P450 isoenzymes (CYP2E1, 1A2 and 3A4) to a hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).[16,17,20,21] At therapeutic doses, NAPQI is conjugated with glutathione and inactivated. 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.

The effect of age on pharmacokinetics

The effect of older age on some parameters of paracetamol pharmacokinetics has been studied. Research into single doses of oral paracetamol compared the plasma levels achieved in a group of 16 young people in good health (mean age 28 years; range 22–39 years), with 12 older people (mean age 71 years; range 61–78 years).[22] Three of the older group had stable, controlled cardiovascular disease but all were fit and active. Absorption was not significantly reduced in the older cohort.

In an observational cohort study, the effects of ageing and frailty on serum paracetamol concentrations were assessed in hospital in-patients.[23] Younger patients aged 18-55 years (n=19) were compared with fit (n=24) and frail (n=28) older patients aged over 70 years. Medical and surgical patients who had not taken paracetamol during the 7 days before admission were included in the study and given regular paracetamol (3–4g/day with a maximum of 3g/day in older patients). A serum paracetamol concentration was measured at day 5 and found to be highest in older frail participants ($p<0.005$). Both groups of older patients had higher average plasma concentrations despite receiving lower daily doses of paracetamol. Alanine aminotransferase (ALT) was also measured on admission and after 5 days in all groups plus matched controls who had not received paracetamol. Small increases in ALT were observed and the researchers concluded that the higher paracetamol plasma concentrations in the older patients were not associated with hepatotoxicity. However, the study was of short duration and not powered to detect any significant differences in liver enzymes between the younger and older patients and the control group.

Other studies have reported an association between reduced clearance of paracetamol and increasing age and frailty.[24,25] In a group of patients in good general health undergoing orthopaedic surgery, those aged 80–90 years had higher plasma concentrations 8 hours after a paracetamol infusion (1g) than younger adults.[24] The 80–90 year old cohort included more women, weighed less and were shorter compared with the younger age groups, which could account for some of the decrease in clearance (3.3mL/min/kg in those aged 70–80 years and 80–90 years and 4.6mL/min/kg in the cohort aged 20–40 years). The volume of distribution adjusted per kg of body weight was also lower in the older patients. The authors calculated that if the dose had been adjusted for body weight, the older patients would still have had 40% higher exposure to paracetamol.

In another study, paracetamol clearance values were adjusted for body weight with liver volume (assessed by scan) and frailty considered as factors.[25] Eight frail hospital in-patients aged over 60 years (mean age 82 years) with a variety of chronic conditions (e.g. cerebrovascular and musculoskeletal disease) were compared with 20 healthy older patients (mean age 73 years) and 19 healthy younger patients (mean age 25 years). The average liver volume was 1,124mL in the young group, 1,091 mL in the fit older group and 843mL in the frail older group. When paracetamol clearance was calculated with respect to liver volume, it was markedly lower in frail older patients (157mL/min/L liver) compared with younger patients (251mL/min/L liver) and fit older people (234mL/min/L liver).

Paracetamol and the liver

Liver damage caused by paracetamol overdose is well documented and can occur with ingestion of 5g of paracetamol (see Box 1).[2]

Box 1: Risk factors for liver damage with paracetamol overdose[2]

Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors, which include the following:

- long-term use of carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes;
- regular consumption of ethanol in excess of recommended amounts; or
- glutathione depletion (e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia).

Although conditions that deplete intrahepatic glutathione concentrations have been proposed as a risk factor for paracetamol-induced hepatotoxicity, there is no simple measure for glutathione stores to assess risk.[20,26]

An evidence review that assessed paracetamol use in liver impairment (including alcoholic liver disease, non-alcoholic fatty liver and chronic hepatitis C) identified risk factors that must be considered and advised dose reduction in severe decompensated liver disease and in patients who are malnourished or weigh less than 50kg.[27]

There have been reports of liver damage occurring at normal therapeutic doses.[6–9] A variety of risk factors have been proposed for these cases, including old age, low body weight, cardiac, pulmonary and renal insufficiency in conjunction with old age, co-administration of medicines that induce liver enzymes, hepatitis and chronic alcohol consumption. Case reports of liver failure have been described in two older women with no other known risk factors for hepatotoxicity who received therapeutic doses of paracetamol.[6] An 83-year-old who was prescribed paracetamol 4g per day on admission to hospital for diverticulitis experienced a rise in liver function tests after 4 days and an elevated trough paracetamol level on day 6 (54mg/L). A 91-year-old woman received paracetamol 4g daily for 3 weeks. Her trough paracetamol level was elevated (31mg/L). Neither case reported the time of the last dose of paracetamol. Treatment with N-acetylcysteine (NAC) is recommended if a 12-hour trough level is above 25mg/L[1], and both women received treatment with NAC.

The incidence of acute liver injury (ALI) was estimated from a retrospective study of cases that presented at 12 hospitals in Spain over a 6-year period.[28] After establishing a likely causal link with paracetamol, the researchers estimated the incidence of ALI following use of paracetamol at therapeutic doses to be 10 per million paracetamol users per year (95% CI 4.3 to 19.4). However, there were limitations to the methods used to establish causality and estimate the number of paracetamol users.

Other safety concerns

The general safety of paracetamol has been questioned.[3,5] The authors of a systematic review of observational studies suggested that paracetamol was associated with an increased risk of cardiovascular (CV) and renal adverse events and

gastrointestinal (GI) bleeding.[6] Regular, full dose, long-term paracetamol use was associated with the highest relative risk (RR) for CV events (RR 1.68, 95% CI 1.10 to 2.57), renal events (RR 2.19, 95% CI 1.4 to 3.43) and GI events (RR 1.49, 95% CI 1.34 to 1.66). However, the absolute risks were not reported and some of the studies were of poor quality. In addition, observational studies of this nature are often subject to channelling bias and may not adjust for all potential confounders.[29,30] For example, paracetamol may have been prescribed in preference to a NSAID to patients who had already experienced a GI bleed or cardiovascular event.

What do guidelines say about paracetamol doses in older people?

Neither the National Institute for Health and Care Excellence's (NICE) guideline on the management of osteoarthritis nor its Clinical Knowledge Summary on mild to moderate pain make specific dosing recommendations on the use of paracetamol in older people.[10,13] In 2014, based on its assessment of the evidence of benefits and harms, NICE had questioned the place of paracetamol in the management of osteoarthritis.[13] A full review of evidence on the pharmacological management of osteoarthritis was due to begin once the results of an MHRA assessment of the safety of over-the-counter analgesics had been completed. NICE has not published any further details on its website.

The British Geriatric Society guidelines for the management of pain in older people suggest that paracetamol is safe with a low incidence of adverse events.[14] Although the guidance cautions use in people weighing less than 50kg and in patients who may be malnourished, no specific dosing advice is given.

The association of Anaesthetists of Great Britain and Ireland recommend paracetamol as the safest first-line analgesic option in its guideline on peri-operative care of older people.[31]

Practical considerations

Reports of liver failure with therapeutic doses of paracetamol are very rare and widespread use of low doses of paracetamol may result in poorly managed pain and inappropriate escalation to use of NSAID or opioids.[2,15]

Old age is not a risk factor in itself and older people who are in good health and weigh over 50kg are unlikely to need a dose reduction.[2,20] However, age may be accompanied by frailty, low weight and renal or hepatic impairment. For some high-risk individuals, a lower starting dose and/or reduced frequency of dosing may be appropriate. Weight is an important consideration, and in an audit of patients prescribed paracetamol in care homes in south Manchester, 20% of residents weighed less than 50kg and 6% weighed less than 40kg.[32]

Hepatotoxicity can occur after taking more than 150mg/kg paracetamol within 24 hours, and the threshold dose of paracetamol that is thought to carry a small risk of liver toxicity is 75mg/kg within 24 hours.[1] For very frail patients (or patients weighing less than 50kg) in whom paracetamol clearance may be significantly reduced, lower doses and/or reduced frequency of administration may be appropriate. A maximum dose of 60mg/kg/day for those weighing 45–50kg equates to a total daily dose of 2,700–3,000g and, therefore, for some patients, a dose of 500mg four times per day or 1g three times per day may be appropriate. As there is a widely held belief that 1g four times a day is the standard safe dose for all adults, individual patient counselling will be important for patients and carers when lower doses are being used. It is also important that patients are encouraged to discuss the effectiveness of their analgesia on a regular basis.

Conclusion

Paracetamol has a long history of use as a first-line analgesic for mild to moderate pain. Although the evidence of its analgesic effectiveness for some conditions has been questioned, it remains in widespread use, either on its own or in combination with other analgesics. It is often used to avoid or reduce the need for NSAIDs or opioids.

The summary of product characteristics (SPC) for oral formulations of paracetamol recommend a dose for adults of 0.5 to 1g every 4–6 hours up to a maximum of 4g in 24 hours with no dose reduction advised for older people. Although the SPC for the intravenous formulation of paracetamol also specifies a maximum dose of 4g in 24 hours, it has more detailed dosing instructions based on weight and recommends a lower maximum daily dose for people with low bodyweight and/or risk factors for liver disease.

The risk of liver problems associated with paracetamol overdose is well established, but liver damage from standard doses of paracetamol in healthy people is rare. However, the pharmacokinetics of paracetamol may change with age and studies have shown a reduction in clearance of paracetamol associated with age and frailty. In addition, older people may have one or more risk factors, making them more prone to adverse effects of paracetamol, including liver damage. Risk factors for hepatotoxicity from paracetamol include low body weight, cardiac, pulmonary or renal insufficiency, co-administration of medicines that induce liver enzymes, hepatitis and chronic alcohol consumption. It is, therefore, prudent to consider whether a lower dose and/or reduced frequency of administration of paracetamol might be appropriate for frail people with low body weight and other risk factors for hepatotoxicity. In such cases, patients must be counselled to ensure they know why they are being prescribed a lower dose and pharmacists must be alert when supplying paracetamol to frail older patients and advise them accordingly. As with all analgesics, there should be a regular clinical review of their effectiveness and assessment of adverse effects.

[R=randomised controlled trial; M=meta-analysis]

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