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## Running Title:

Prolonged paracetamol use


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## Conflict of Interest

No conflict of interest has been declared by the author(s).

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# Prolonged use of paracetamol and the prescribing patterns on rehabilitation facilities

## ABSTRACT

**AIM:** The study investigated: (a)the usage patterns of paracetamol, and (b)the association between paracetamol use and patient outcomes such as liver and kidney functions among older people.

**BACKGROUND:** Paracetamol is a well-known analgesic and antipyretic drug, with an excellent safety profile when used within its recommended dose. It is a commonly used drug by people aged over 65 years to treat chronic pain. Prolonged use of paracetamol in the elderly is poorly understood. As such, there is a genuine risk among older people of unintentional overdose.

**METHODS:** A retrospective analysis of medical records in rehabilitation wards was undertaken from July 1, 2016, to June 30, 2017. Patients' paracetamol use, prescribing patterns, and biochemical results were analysed to assess for differences in admission and discharge biochemistry results. The TREND Statement was utilised to guide study reporting (Enhancing the QUAlity and Transparency Of health Research, 2021).

**RESULTS:** A total of 1119 patients were admitted for seven or more days in a metropolitan tertiary hospital in Melbourne. Almost three-quarters (74%) of patients were administered paracetamol; 76.1% received 'Immediate Release Paracetamol' (IRP), and 23.9% were given "Sustained Released Paracetamol" (SRP). A proportion (4.5%) of patients in both the IRP and SRP groups received more than the daily recommended dose. There were limited statistically significant differences between patients' admission and discharge biochemistry results; group or time differences were observed, which were indicative of improvements within the paracetamol group.

**CONCLUSION:** Paracetamol was a commonly used medication among long-stay elderly patients. Precaution to ensure paracetamol use does not exceed recommended daily doses is required. This study suggests that paracetamol used at a therapeutic level in older patients had limited, negative associations with liver and kidney function.

**RELEVANCE TO CLINICAL PRACTICE**: The clinical practice regarding prolonged use of paracetamol is ambitious. The increased risk of paracetamol toxicity among the frail elderly is a concern. Optimising the dose adjustment in the elderly is important to avoid adverse outcomes.

**KEYWORDS**

Paracetamol
Long-term
Elderly
Overdose
Toxicity
Adverse outcomes

# INTRODUCTION

Pain in many older adults is often overlooked and dismissed as a part of the aging process (Noroozian, et al., 2018). Untreated pain can become chronic pain and affect older people's quality of life (Schug et al., 2015). According to Pain Australia (2019), one in three people aged 65 and above suffer chronic pain. Among those who live in nursing homes, 92% of residents are dependent on at least one pain medication. Paracetamol is an effective medication for pain relief and is considered safe at therapeutic doses. It is widely used as a first-line treatment for pain amongst older adults (Freo et al., 2021). The daily recommended oral dosage of paracetamol in adults is 500 milligrams (mg) to one gram every four to six hours, or 665 mg to 1330 mg of sustained released paracetamol (SRP) every six to eight hours, with a maximum dosage of four grams per day (Therapeutic Good Administration [TGA], 2019). However, the effectiveness and safety of paracetamol at therapeutic levels has been questioned by recent studies (Caparrotta, et al., 2018; Mowry et al., 2016; Sarges et al., 2016). The narrow safety margin of paracetamol is a growing concern for the community, particularly for older people (Caparrotta et al., 2018)

# BACKGROUND

Paracetamol is often used to relieve pain and fever. Worldwide, it is the most common over the counter analgesia available as single formula or in combination with other medications (Tittarelli et al., 2017). Moreover, paracetamol toxicity is the second most cause of liver transplant (Wong & Graudins, 2017). The annual report between 2007-08 and 2016-17 related to paracetamol overdose hospitalisation and deaths has increased in Australia, and greater numbers are associated with liver injury (Cairns et al., 2019). Additionally, a statistic comparing paracetamol related hospital admissions and deaths in Australia shows an increased yearly rate of 3.8% and an average of 43 deaths between 2004 and 2017. Large relative increases were also seen in older age group, with a 160% increase in people aged 65-74 years, and a 253% increase in patients aged 85 years and older

(Cairns et al., 2019). In the United States, unintentional and intentional paracetamol exposures is a significant cause of morbidity and mortality (Rotundo & Pyrsopoulos, 2020). In 2016, a report from the American Association of Poison Control Centers' National Poison Data System found 49,417 paracetamol-related cases, of which 680 were life-threatening and 82 fatal cases. Furthermore, 21,676 cases involving paracetamol in combination with another drug, of which 446 were life-threatening and 42 were fatal cases (Gummin et al., 2017). Similarly, in the UK paracetamol is the most common cause of unintentional overdose, accounting for approximately 50000 emergency presentations per year (Dear et al., 2018).

In the last decade, the use of pain medication in the community had increased (Sarganas et al., 2015). Several studies have suggested an increased risk of adverse events, particularly among the elderly on regular doses of paracetamol for pain management (Caparrotta et al., 2018; Mowry et al., 2016; Sarges et al., 2016). A population-based study reported more than three-quarters of adults aged 62- to 86-years had prescriptions for analgesia in 2012, of which 41% had been for paracetamol, excluding over the counter (OTC) paracetamol. This suggests that the actual incidence of paracetamol use in elderly patients may be higher than reported (Marttinen et al., 2021). Many medications contain paracetamol as an active ingredient, which increases the risk of exceeding the daily paracetamol dose of 4 grams amongst older people who take multiple medications (Mitchell et al., 2020). The most common risk of paracetamol toxicity is an alteration to liver function (Roberts et al., 2015), though the level of risk varies among individuals. The risk of paracetamol toxicity increases with factors including older age, genetics, malnutrition (fasting/starvation), alcohol consumption, concomitant use of drugs, long term use and underlying comorbidities (Australian Commission on Safety and Quality in Health Care [ACSQHC], 2016; TGA, 2019)

Moreover, pain is the most common presentation to emergency departments (ED), and paracetamol is the second most common simple analgesic administered in the ED (Sarganas et al., 2015). In Australia, a quality key performance indicator (KPI) for EDs is time to analgesia, which is currently set at 30 minutes (Van Woerden et al., 2016). Nurse-initiated analgesia protocols are often introduced by healthcare organisations to improve pain management practices. Patients presenting to triage in pain are offered paracetamol by the triage nurse to meet this KPI (Varndell et al., 2018). However, the increasing presentations and ED overcrowding exceeds the ability to provide quality care within a reasonable time frame (Morley et al., 2018). Patients waiting time in the ED waiting room has significantly increased. Consequently, triage nurse to patient ratio and risk factors associated with frequency of medication errors in acute setting is concerning (Morley et al., 2018). Compared to the general population, hospitalised patients may be more vulnerable exceeding the daily 4 grams of paracetamol (Civan et al., 2014). Therefore, continuous knowledge for nurses is essential to improve clinical practice (Cabilan et al., 2016).

A gap of consumer knowledge related to paracetamol containing medications, dosing and toxicity has been recognised (Roberts et al., 2015), increasing concern regarding unintentional

overdose of paracetamol (Wróblewski et al., 2015). This combined with the amount of paracetamol administered in the hospital setting is of concern (Sarganas et al., 2015). Accordingly, there is a need to improve prescribing methods, especially among the elderly. Evidence regarding prolonged use of paracetamol is ambiguous, and primarily focusses on the detrimental effects of acute ingestion of paracetamol (Shaheed et al., 2021). Paracetamol related hospital admissions and deaths in Australia has been steadily increasing with large increases in the older age group being reported (Mowry et al., 2016; Sarges et al., 2016). This study aimed to investigate: (1) the usage patterns of paracetamol and (2) associations between paracetamol use and patient outcomes such as liver and kidney functions.

# METHOD

## STUDY DESIGN AND SAMPLE

A retrospective audit was conducted to obtain information about paracetamol use in four rehabilitation wards of a large metropolitan hospital in Melbourne, Australia. The inclusion criteria of this study were (a) participants aged 50 years and older and (b) an admission period in rehabilitation for more than seven days. Patients with less than seven days admission were excluded as it could not be established that the patient had received long term paracetamol treatment. Patients who had received paracetamol-containing combination analgesics such as paracetamol-codeine, paracetamol 500mg + codeine phosphate 30mg or paracetamol 500mg + codeine phosphate 8mg were excluded from the study. Furthermore, missing data that prevented comparison of data from admission and discharged for either estimated Glomerular Filtration Rate (eGFR), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) were excluded.

## DATA COLLECTION

Data was sourced from four rehabilitation wards drawing upon all admissions between July 1, 2016, to June 30, 2017. De-identified medical records of inpatient admissions were extracted by the Business Intelligent Unit (BIU) of the hospital. Data included patients' demographic information, biochemistry results, paracetamol administration records, and duration of the patients stay. The data was provided electronically in an Excel CSV file (Microsoft, Version 16.34) and specifically included paracetamol use in oral tablet, liquid and soluble tablet with the dosage in milligram (mg). The Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) Statement was utilised to guide study reporting (Enhancing the QUAlity and Transparency Of health Research, 2021) (Supplementary File 1).

There were 1931 patient admissions to the four wards during the study period. Patients who stayed less than seven days (n=420) or who had received paracetamol-containing combination analgesics (n=124) or patients aged under 50 years (n=4) were also excluded from this study. Furthermore, the sample size decreased if there were missing admission results and/or discharge results for either eGFR, ALT or ALP, leaving 1119 participants for analysis.

# ETHICS

Ethical approval for this study was received from the Hospital's Human Research Ethics Committee (Riskman Q Number 27692) and La Trobe University Ethics Office (EC00204).

**DATA ANALYSIS**

Data were provided by the BIU in a Microsoft Excel spreadsheet and was imported into IBM SPSS Statistics (IBM, Version 24) for analysis. This data was sorted into groups based on patients who were administered paracetamol (Group 1) and patients who were not administered paracetamol (Group 2). Group 1 was further divided into two groups: patients receiving Immediate Released Paracetamol — IRP (Group 1.1), and patients receiving Sustained Released Paracetamol — SRP (Group 1.2). Both groups that received paracetamol had a daily dosage calculated using the patients' total amount of paracetamol administered in milligram (mg) divided by their total length of stay (LOS). Based on the data available, this was determined to be the most accessible and accurate means to represent the patient's daily dose. According to the daily dose administered, both groups (Group 1.1 and Group 1.2) were further subdivided into their likely administration regimen. A complete list of groups and subgroups is provided in Table 1 (TGA, 2019).

Frequencies and descriptive statistics were used to describe practices in paracetamol use in the rehabilitation wards among older patients. Differences between paracetamol and no paracetamol use for health outcomes such as liver and kidney function over time were examined using a mixed between-within analysis of variance (ANOVA). The chi-square test was used for categorical data. Demographic data were compared using t-test for continuous data and chi-square for categorical data. Significant associations between variables were assessed using a $p < 0.05$.

Biochemistry results (eGFR, ALT and ALP) were extracted for Paracetamol (Group 1) and No — Paracetamol (Group 2) to investigate if any differences in patients' liver and/or kidney functions during the inpatient stay, and if differences in biochemistry results were apparent between subgroups of patients' paracetamol use. Estimated glomerular filtration rate (eGFR), Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were included in this study to investigate the potential damage to kidney and liver function. Table 2, 3 and 4 described the eGFR, ALT and ALP range, respectively.

# RESULTS

Of the 1119 participants included in the study, three-quarters of the participants were given paracetamol during their period of care (74.8%; n=837), while one-quarter received no paracetamol (25.2%; n=282). The age of the participants ranged from 50 to 104 years of age, with an average age of 82.79 (SD+/-8.78) (Table 5). An independent sample t-test was conducted to compare the age of the participants in the paracetamol group (M=83.22, SD+/-8.45) and the no paracetamol group (M=81.52, SD+/-9.61); a difference that was statistically significant [t(436.3)=2.651, p=0.008]. Fifty-

four per cent of participants were female (n=605), and 46% were males (n=511). There was a significantly higher proportion of females in the group that received paracetamol (58%, n=485) compared to the no paracetamol group (42.9%, n=120) [$\chi 2$ (1) =19.413, p<0.001]. The average length of stay (LOS) was 25.43 days (SD+/-20.23). The average LOS for the paracetamol group was 26.14 days (SD+/-20.49) compared to 23.3 days (SD+/-19.32) for the no paracetamol group; again, a difference that was statistically significant [t (1117) = 2.040, p=0.042] (Table 5).

## DESCRIBING DOSE AND FREQUENCY FOR THE PARACETAMOL GROUP

Of the 837 patients who received paracetamol, immediate-release paracetamol (IRP) was given to 76.1% (n=637) of participants and sustained released paracetamol (SRP) was given to 23.9% (n=200) of participants (Table 6). Overall, the pattern of prescribing paracetamol was evenly distributed between percentage as required (PRN) (20.4%), twice a day (BD) (25.1%), three times a day (TDS) (20.7%) and four times a day (QID) (29.0%). The prescribing pattern for paracetamol varied between the IRP and SRP. While there was no QID option for SRP, there was a tendency for twice-daily paracetamol (69.5%) for patients receiving SRP. In the IRP group, prescriptions tended to be more equally distributed across four times daily (38.1%), three times daily (22.8%), and as required (23.1%). Patients in IRP (38.1%) received a maximum daily dose four times a day (QID), whereas 20.7% in SRP received a maximum daily dose, three times a day (TDS). There were 38 instances (4.5%) where paracetamol was prescribed, and the patient received above the maximum daily dose of paracetamol (an overdose), the rate of which was comparable between the IRP group and the SRP groups.

## ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)

The results for eGFR are presented in Table 7 for admission and Table 8 for discharge. No evidence of an interaction between time and paracetamol use was detected [F(1, 1117)=.213, p=.645], nor was the main effect for paracetamol observed [F(1, 1117)=2.950, p=.086]. A significant increase and improvement in eGFR over time was found [F(1, 1117)=.985, p<.001] although the partial eta squared result (.015) would suggest the effect size remained small.

Participants in both groups (paracetamol and no paracetamol) were clustered according to their stage of kidney function as indicated by their eGFR scores. At baseline, most participants were classified as being at stage 2 (43.0%) or stage 3 (36.8%). There were only 7.7% of patients who were in stage 1 (normal function). A minority of patients (12.5%) were classified as having stage 4 and 5, indicating severe dysfunction. Chi-square tests showed that there was no statistically significant difference in the stage of participants, when the whole sample (paracetamol and no paracetamol group) at baseline [$\chi 2$ (3) =3.445, p=0.328], was compared with discharge [$\chi 2$ (3) =2.294, p=0.514]. Due to small cell sizes, a comparison between admission and discharge of the kidney stages associated with individual dosage groups was not conducted.

## ALANINE AMINOTRANSFERASE (ALT)

The results for ALT are presented in Table 9 for admission and Table 10 for discharge. Further tests were conducted to assess the effects of time and paracetamol use on ALT. No evidence of an interaction between time and paracetamol use was detected [F(1, 606)=.998, p=.284], nor was the main effect for a time observed [F(1, 606)=.471, p=.493]. However, a significant difference in ALT was found between the paracetamol and no paracetamol groups [F(1, 606)=7.504, p=.006] with patients who received paracetamol recording lower average ALT scores at both admission and discharge, suggesting more 'normal' ALT status. The partial eta squared result (.012) would suggest the effect size remained small.

At the time of admission, most of the participants had an ALT result that was in the normal range for both the paracetamol group (88.8%) and the no paracetamol group (76.3%). Only a minority of participants (1.6%) were in mildly elevated range (paracetamol 1.7%, n=8; no paracetamol 1.5%, n=2). Chi-square tests found the classifications of ALT function differed significantly between the paracetamol and no paracetamol groups at baseline [$\chi 2$ (2)=14.348, p <0.001] and discharge[$\chi 2$ (2)=9.158, p=0.010].

**ALKALINE PHOSPHATASE (ALP)**

The results for ALP are presented in Table 11 for admission and Table 12 for discharge. Regarding ALP for IRP, data for 366 patients who had admission and discharge results were available. There were missing data for the SRP group. No evidence of an interaction between time and paracetamol use was detected for ALP scores [F(1, 503)=.005, p=.943], nor was the main effect for paracetamol found [F(1, 503)=.498, p=.481]. A significant reduction and improvement in ALP over time was found [F(1, 503)=4.394, p=.037], although a small effect size is indicated (partial eta squared=.009).

At baseline, nearly three-quarters of participants were in the normal range of ALP (74.3%, n=375), and one quarter was classified in the abnormal range (25.7%, n=130). The majority of the participants who received paracetamol QID (four times a day) (81.8%, n=108) were classified in the normal range for ALP. The highest for the abnormal range was found to be those participants who received paracetamol TDS (three times a day) (29.8%, n=25). A chi-square test was conducted comparing the paracetamol group and no paracetamol group at baseline for their proportions of participants in the normal and abnormal ranges; the difference was not found to be statistically significant [$\chi 2$ (1)=0.085, p=0.770].

# DISCUSSION

This study aimed to examine the prolonged ingestion of paracetamol and its effect on biochemistry results amongst people aged 50 years old and above. Biochemistry results included an estimated Glomerular Filtration Rate (eGFR) for the patient's kidney function, and Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) for the patient's liver function. A

retrospective audit of patients admitted to rehabilitation wards was conducted, paracetamol use was described, and biochemistry results from admission were compared on discharge for both paracetamol and no paracetamol groups.

This study collected results for older patients who were admitted to rehabilitation wards for seven or more days. The average length of stay (LOS) for patients that received paracetamol was 26.2 days (SD+/-20.5), suggesting prolonged use of paracetamol during the patient's episode of care. Prolonged use of paracetamol to treat acute or chronic pain has been linked to an increased risk of toxicity (Roberts et al., 2016). A systematic review found a four-fold increased risk of abnormal liver function test results for individuals who take paracetamol regularly compared to non-regular paracetamol users (Shaheed et al., 2021). Paracetamol is one of the most commonly prescribed pain management medications for older adults who experience adverse health effects from prolonged pharmacological therapy (ACSQHC, 2016). This study did not appraise paracetamol use before or after the patient's acute episode, and as such, duration of use could be longer. Given the prolonged use of paracetamol in this study, the acute episode could be treated as an opportunity to review paracetamol use and educate patients regarding the safe use of this medication.

Approximately three-quarters of the elderly patients (74%) were administered paracetamol during their stay, making paracetamol a commonly used medication in this service. When paracetamol was used, IRP was more commonly utilised (74.8%) than SRP (25.2%). Although the frequency of SRP administration is less in this population compared to IRP, SRP may be a preferred option for the elderly to reduce the daily dosage whilst still providing continuous analgesia (Yue & Liu, 2018). Furthermore, the use of SRP can enhance compliance and improve pain management by preventing accidental overdose, as well as avoiding complications that may be caused by decreased clearance of the medication (Yue & Liu, 2018). A proportion of patients in both the IRP and SRP groups received more than the daily recommended dose (i.e., 4 grams); 4.5% in each group, respectively. A study reported similar finding that 2.6% of the hospitalised patient received paracetamol doses exceeding 4 grams on at least one hospital day (Civan et al., 2014). There is an increased risk of paracetamol toxicity with 5 grams in 24 hours (Mitchell et al., 2020). Likewise, increasing the dose to 7.5 grams in 24 hours may lead to Acute Liver Failure (ALF), the most common cause of paracetamol toxicity (Caparrotta et al., 2018; Sarges et al., 2016). Furthermore, nearly two-thirds of individuals diagnosed with ALF are likely to develop Acute Kidney Injury (AKI) (Appenrodt & Lammert. 2018). In addition to the risk of toxicity, an adverse event can result following prolonged hospital stays (Dear et al., 2018). Although overdose was detected for a minority of patients, given the known effects of paracetamol overdose, mechanisms to avoid any incidence of an overdose within the acute setting are required.

Kidney function is represented by glomerular filtration rate (GFR), a biochemistry result that is estimated from blood creatinine levels and is also known as estimated glomerular filtration rate (eGFR) (Solomon & Goldstein, 2017). Kidney function is commonly represented by five different

stages that are based on the filtration rate. There were no differences in either the average scores or proportions in each stage of kidney function found between the paracetamol and no paracetamol groups in this study. An effect for time was found, which suggested that eGFR improved over time. These findings are inconsistent with prior studies that report that prolong use of paracetamol is associated with an increased risk of developing AKI (Kanchanasurakit et al., 2020). Some studies have also reported the risk of developing AKI in the absence of liver toxicity (Chen et al., 2015). Previous researchers found that taking paracetamol regularly for prolonged periods significantly increased the risk for kidney dysfunction (Kanchanasurakit et al., 2020) the short duration of follow up in this study may account for the study data not reflecting these same results.

A marker of hepatocellular injury is increased serum aminotransferases (also known as transaminases). Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes are specific indicators of liver injury. The increased concentration of these enzymes is used to identify liver injury (Popiolek et al., 2021). In this study, no significant change over time was found; however, significant differences between the paracetamol and no paracetamol groups were detected, which indicate that the paracetamol group achieved better ALT status. This could be attributed to prescribers avoiding prescribing paracetamol in patients with worse ALT, due to the known risk of paracetamol use in liver impairment.

There was missing data for SRP; hence the analysis of ALP was based on the IRP and no paracetamol group. Approximately three-quarters of the participants in both paracetamol and no paracetamol groups were within the normal range at baseline. No significant differences were detected between paracetamol use and no paracetamol use. However, an effect for time was found, suggesting that ALP scores improved during the acute care episode for study participants.

There is a large body of literature linking the use of paracetamol and liver toxicity (Mowry et al., 2016; Sarges et al., 2016; Roberts et al., 2016). Liver toxicity is the most common outcome of paracetamol toxicity, which can occur when paracetamol is consumed over the daily recommended dose (Mowry et al., 2016; Sarges et al., 2016); or when taken for several days to treat acute or chronic pain (Roberts et al., 2016). Furthermore, the prevalence of acute liver failure (ALF) is mainly caused by paracetamol overuse and drug-induced aetiology, with paracetamol toxicity an independent cause of ALF (Sarges et al., 2016). Several other studies reported paracetamol to be the most common cause of Drug-Induced Liver Injury (DILI) in the United Kingdom (Mowry et al., 2016), Canada and most European countries (Kaur et al., 2020). Although the average LOS in the current study was 25.43 days, the present study findings were inconsistent with the reported literature and do not suggest extensive liver function problems or associations between paracetamol use and liver function. Potentially the short duration of follow up and patient's use of paracetamol before the acute episode could mask the effects of paracetamol on liver function.

Several risk factors of ageing influence paracetamol pharmacokinetics such as absorption, distribution, metabolism, and elimination even at the daily recommended doses (Mian et al., 2018;

Yue & Liu, 2018). Decreased clearance of medications in older people has been reported in the literature, which may cause paracetamol toxicity at the daily recommended dose (Mian et al., 2018; Yue & Liu, 2018). Older age alone is not responsible for changes in paracetamol pharmacokinetics. The additional risk factors associated with ageing, such as multiple comorbidities, polypharmacy, and individual health conditions, can significantly affect the mechanism of paracetamol (Mian et al., 2018). Moreover, the number of other medications containing paracetamol (Mitchell et al., 2020) increases the risk of accidental overdosing for older individuals taking multiple medications without realising they have surpassed the daily recommended dose (Marttinen et al., 2021). This study did not examine the paracetamol use in conjunction with other medicines that may contain paracetamol. Further research investigating polypharmacy is recommended.

Limitations of this study include its use of a retrospective study design. The relevant details, such as the use of paracetamol before admission, the clinical indication for paracetamol, patient weight and pain assessment, were not included in this study. The age group of this study ranged from 50 years old or above; however, given that the average age was 80, it can be argued that this study included an older sample. Study data were collected from a single metropolitan hospital in Australia, limiting the study's external validity. Patient past medical histories that may alter the biochemistry results were not included. These data could have indicated if any of the patients had existing liver or kidney dysfunction. The method used to determine the dose was estimated based on the total amount of paracetamol administered throughout the patient length of stay (LOS). Furthermore, other biochemistry results such as creatinine, globulin level and albumin level were not included to measure the kidney function comprehensively. Additionally, patient's other regular medications and dosage were not included, which might have indicated drug to drug interaction and the possibility of alterations to biochemistry results.

Drug dosing is often challenging for elderly living with comorbidities. Despite several studies on paracetamol use among the elderly, many reported inconclusive outcomes. Most of the evidence is based on clinical experience, expert opinions and current policies related to younger populations. Even guidelines for paracetamol dosing among older people are not explicitly based on their age-related conditions. The comorbidities with advanced age and paracetamol dosage adjustment, incorporating metabolism, requires further research. There is a need for patient education to minimise the potential risk of unintentionally overdosing and increased vigilance among healthcare professionals to regularly review patient medications to prevent prolonged use.

Research is needed to identify safe and effective dosing guidelines for elderly patients with polypharmacy. A collaborative approach to patient education is necessary. Healthcare professionals, including nurses, pharmacists and doctors, can educate older patients regarding their medications and their potential side effects. Assessment before discharge regarding their prescribed medication and the provision of information regarding over the counter (OTC) medications, frequency, and dosage adjustment according to an individual health condition could prevent accidental overdosing. More

robust studies, including elderly participants, are required to examine this knowledge gap in prescribing patterns for older people.

## CONCLUSION

In conclusion, this study found that paracetamol was a regularly administered medication among older inpatients and was frequently used for a prolonged period during the sub-acute episode of care. Immediate released paracetamol (IRP) was most prescribed, with almost four in ten patients receiving the maximum daily dose and a minor percentage received excessive dosing of IRP and SRP. There were limited differences between the three biochemistry components considered in this study, and where group or time differences were observed, they were indicative of improvements over time or better health indication for the paracetamol group; the latter finding inconsistent with much of the published literature. This study suggests that paracetamol used at a therapeutic level in older patients had limited negative associations with liver and kidney function. Further research with older populations is encouraged to improve safeguards to prevent excessive dosing. Utilisation of an electronic system with automatic alerts regarding paracetamol containing medications and the daily cumulative dose is recommended. This study reported on biochemistry results for patients with an average length of stay of 25.43 days (SD+/-20.23). A prolonged hospitalised patients and patients discharge with a recommendation to take paracetamol for a period great than 6 months should have regular biochemistry monitoring performed.

## RELEVANCE TO CLINICAL PRACTICE

The prescription of paracetamol as the first-line analgesia is the most common approach to the treatment of pain. However, the recommended dosages should be adjusted according to physiological factors, clinical conditions, and concomitant drugs. This paper provides an overview of paracetamol use amongst the elderly in the sub-acute setting and indicates the need for safety protocols to be developed regarding timely review of paracetamol prescriptions amongst the elderly.

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## What does this paper contribute to the wider global clinical community?

- Age-related physiological changes can influence pharmacokinetics and delay the elimination of paracetamol. Prolonged use of paracetamol and safety in older people is an increasing concern.
- Older people with multiple comorbidities and concomitant medications in clinical trials are limited. Thus, dose adjustment is often inappropriate and based on expert opinions and clinical experience.
- The initiative towards bridging the knowledge gap of safety and appropriate paracetamol dosage in the elderly is necessary and requires further research.

**Table 1. Groups and sub-groups of the participants**

| |
|---|
| Group 1 – Paracetamol |

| Patient with Immediate Released Paracetamol – IRP (Group 1.1)(n=637) | Patient with Sustain Released Paracetamol – SRP (Group 1.2)(n=200) |
|---|---|
| Group 1.1.1 (PRN) (n=147) received either less than 1250 mg or once only during their length of stay. | Group 1.2.1 (PRN) (n=24) received 665 to 1330 mg or once only dose during their length of stay. |
| Group 1.1.2 (BD) (n=72) received 1251 to 2250 mg daily during their length of stay. | Group 1.2.2 (BD) (n=139) received 1331 to 2660 mg daily during their length of stay |
| Group 1.1.3 (TDS) (n=146) received 2251 to 3250 mg daily during their length of stay. | Group 1.2.3 (TDS) (n=28) received 2661 to 3990 mg daily during their length of stay. |
| Group 1.1.4 (QID) (n=243)received 3251 to 4250 mg daily during their length of stay. | - |
| Group 1.1.5 (OD) (n=29) received 4251 mg or more daily during their length of stay. | Group 1.2.4 (OD) (n=9) received more than 3990 mg daily during their length of stay. |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *OD = overdose; *PRN = percentage as required; *QID = four times a day; *SRP = Sustained Released Paracetamol; *TDS = three times a day

**Table 2. Glomerular Filtration Rate (eGFR) Stages**

| Stages | Filtration – millimetres per 1.73m2 |
|---|---|
| Stage 1 | A normal eGFR greater than or equal to 90 millilitres per 1.73m2 |
| Stage 2 | A slightly decreased eGFR between 60 and 89 millilitres per 1.73m2 |
| Stage 3a + 3b | A mild to moderate (3a) and moderate to severe (3b) decreased, between 30 to 59 millilitres per 1.73m2 |
| Stage 4 + 5 | A severe decrease (stage 4) and end-stage kidney disease (stage 5) less than or equal to 29 millilitres per 1.73m2 |

*eGFR = estimated Glomerular Filtration Rate

**Table 3. Alanine aminotransferase (ALT) range**

| | Males | Female |
|---|---|---|
| Normal range | 5 – 40 units per litre | 5 – 35 units per litre |
| Slight elevation | >40 – <120 units per litre | >40 – <120 units per litre |
| Mild elevation | =/>120 units per litre | =/>120 units per litre |

Note. Adjust the range for the difference by gender

**Table 4. Alkaline phosphatase (ALP) range**

| Range | |
|---|---|
| Normal range | 20 to 140 international units per litre (IU/L) |
| Abnormal range | >141 international units per litre (IU/L) |

**Table 5. Sample and episode characteristics (n=1119)**

| | | Paracetamol (n = 837; 74.8%) | No Paracetamol (n = 282; 25.2%) | Total (n = 1119) |
|---|---|---|---|---|
| Gender n (%) | Male | 351 (42%) | 160 (57%) | 511 (45.8%) |
| | Female | 485 (58%) | 120 (42.9%) | 605 (54.2%) |
| | Unknown | 1 (0.1%) | 2 (0.7%) | 3 (0.3%) |
| Age (years) | M (SD) | 83.22 (+/-8.45) | 81.52 (+/-9.61) | 82.79 (+/-8.78) |
| | Min.-Max. | 54 - 104 | 50 - 100 | 50 - 104 |

| | | | | |
|---|---|---|---|---|
| LOS (days) | M (SD) | 26.14 (+/-20.49) | 23.30 (+/-19.32) | 25.43 (+/-20.23) |
| | Min.-Max. | 7 - 257 | 7 - 182 | 7 - 257 |

*LOS = Length of stay; *M = Mean; *SD = Standard Deviation

**Table 6. Describing paracetamol dosage for the 'Immediate Release Paracetamol' (IRP) and Sustained Released Paracetamol" (SRP) group (n=837)**

| n (%) | Immediate-released paracetamol (IRP) n = 637 | Sustained-released paracetamol (SRP) n = 200 | Total n = 837 |
|---|---|---|---|
| PRN | 147 (23.1%) | 24 (12.0%) | 171 (20.4%) |
| BD | 72 (11.3%) | 139 (69.5%) | 211 (25.1%) |
| TDS | 146 (22.8%) | 28 (1.0%) | 174 (20.7%) |
| QID | 243 (38.1%) | - | 243 (29.0%) |
| OD | 29 (4.5%) | 9 (4.5%) | 38 (4.5%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *OD = overdose; *PRN = percentage as required; *QID = four times a day; *SRP = Sustained Released Paracetamol; TDS = three times a day

**Table 7. Glomerular Filtration Rate (eGFR) Admission**

| | IRP (n=639) | | | | | SRP (n=199) | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |
| n= | 147 | 72 | 145 | 243 | 29 | 24 | 138 | 28 | 9 | 835 | 280 | 1115 |
| M | 58.7 | 57.2 | 58.1 | 60.3 | 64.8 | 58.0 | 57.5 | 56.6 | 79.1 | 59.1 | 56.9 | 58.5 |
| (SD +/-) | (22.8) | (23.9) | (23.7) | (23.0) | (22.5) | (19.2) | (20.7) | (21.4) | (13.8) | (22.6) | (22.3) | (22.6) |
| Median (IQR) | 60 | 60.5 | 59 | 63 | 73 | 58 | 57 | 58.5 | 80 | 61 | 57 | 60 |
| | (37) | (38) | (42) | (39) | (45) | (26) | (33) | (40) | (14) | (38) | (36) | (37) |
| Min - Max | 8-91 | 7-91 | 8-91 | 3-91 | 25-91 | 14-91 | 8-91 | 25-91 | 46-91 | 3 - 91 | 5-91 | 3-91 |
| Stage of e-GFR function n= (%) | | | | | | | | | | | | |
| Stage 1 | 9 | 5 | 13 | 21 | 3 | 1 | 7 | 2 | 2 | 63 | 23 | 86 |
| | (6.1%) | (6.9%) | (9.0%) | (8.6%) | (10.3%) | (4.2%) | (5.1%) | (7.1%) | (22.2%) | (7.5%) | (8.2%) | (7.7%) |
| Stage 2 | 65 | 34 | 59 | 114 | 15 | 9 | 58 | 12 | 6 | 372 | 108 | 480 |
| | (44.2%) | (47.2%) | (40.7%) | (46.9%) | (51.7%) | (37.5%) | (42.0%) | (42.9%) | (66.7%) | (44.6%) | (38.6%) | (43.0%) |
| Stage 3a + 3b | 55 | 20 | 54 | 74 | 10 | 13 | 59 | 10 | 1 | 296 | 114 | 410 |
| | (37.4%) | (27.8%) | (37.2%) | (30.5%) | (34.5%) | (54.2%) | (42.8%) | (35.7%) | (11.1%) | (35.4%) | (40.7%) | (36.8%) |
| Stage 4 +5 | 18 | 13 | 19 | 34 | 1 | 1 | 14 | 4 | - | 104 | 35 | 139 |
| | (12.2%) | (18.1%) | (13.1%) | (14.0%) | (3.4%) | (4.2%) | (10.1%) | (14.3%) | | (12.5%) | (12.5%) | (12.5%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; TDS = three times a day

**Table 8. Glomerular Filtration Rate (eGFR) Discharge**

| | IRP | | | | | SRP | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |
| n= | 147 | 72 | 145 | 243 | 29 | 24 | 138 | 28 | 9 | 835 | 280 | 1115 |
| M(+/-SD) | 60.8 | 58.5 | 59.5 | 61.8 | 68.1 | 61.5 | 59.3 | 60.1 | 73.4 | 60.8 | 58.2 | 60.2 |
| | (22.2) | (24.5) | (23.7) | (23.0) | (20.6) | (19.9) | (20.1) | (19.6) | (29.3) | (22.5) | (22.6) | (22.5) |
| Median (IQR) | 63.0 | 60.5 | 61 | 66 | 73 | 65.5 | 58.5 | 65 | 87 | 63 | 59 | 62 |
| | (32) | (37) | (39) | (34) | (32) | (34) | (34) | (34) | (24) | (36) | (35) | (34) |
| Min - Max | 0-91 | 4-91 | 5-91 | 0-91 | 14-91 | 14-90 | 11-91 | 22-90 | 0-91 | 0-91 | 6-91 | 0-91 |
| Stage of e-GFR function n= (%) | | | | | | | | | | | | |
| Stage 1 | 13 | 7 | 16 | 23 | 5 | 1 | 7 | 1 | 3 | 76 | 23 | 99 |
| | (8.8%) | (9.7%) | (11.0%) | (9.5%) | (17.2%) | (4.2%) | (5.1%) | (3.6%) | (33.3%) | (9.1%) | (8.2%) | (8.9%) |
| Stage 2 | 67 | 31 | 58 | 121 | 15 | 13 | 59 | 16 | 5 | 385 | 117 | 502 |
| | (45.6%) | (43.1%) | (40.0%) | (49.8%) | (51.7%) | (54.2%) | (42.8%) | (57.1%) | (55.6%) | (46.1%) | (41.8%) | (45.0%) |
| Stage 3a + 3b | 50 | 23 | 51 | 73 | 7 | 9 | 63 | 9 | - | 285 | 107 | 392 |
| | (34.0%) | (31.9%) | (35.2%) | (30.0%) | (24.1%) | (37.5%) | (45.7%) | (32.1%) | | (34.1%) | (38.2%) | (35.2%) |
| Stage 4 +5 | 17 | 11 | 20 | 26 | 2 | 1 | 9 | 2 | 1 | 89 | 33 | 122 |
| | (11.6%) | (15.3%) | (13.8%) | (10.7%) | (6.9%) | (4.2%) | (6.5%) | (7.1%) | (11.1%) | (10.7%) | (11.8%) | (10.9%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; *TDS = three times a day

**Table 9. Alanine aminotransferase (ALT) Admission**

| | IRP | | | | | SRP | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |
| n | 96 | 48 | 86 | 133 | 20 | 13 | 60 | 11 | 6 | 473 | 135 | 608 |
| M | 36.3 | 30.9 | 22.9 | 22.0 | 21.0 | 27.0 | 19.7 | 28.5 | 12.4 | 25.9 | 32.2 | 27.3 |
| (+/-SD) | (55.4) | (33.2) | (15.6) | (13.1) | (11.9) | (18.4) | (12.7) | (15.7) | (11.3) | (30.0) | (30.2) | (30.1) |
| Median (IQR) | 23.5 | 20 | 18 | 19 | 17 | 24 | 17 | 26 | 18 | 19 | 25 | 21 |
| | (16) | (22) | (17) | (15) | (12) | (18) | (13) | (22) | (15) | (16) | (23) | (17) |
| Min - Max | 6-468 | 8-163 | 6-84 | 4-86 | 7-50 | 5-80 | 5-71 | 6-60 | 11-45 | 4-468 | 6-233 | 4-468 |
| Normal range | 81 | 40 | 76 | 121 | 19 | 12 | 57 | 9 | 5 | 420 | 103 | 523 |
| | (84.4%) | (83.3%) | (88.4%) | (91.0%) | (95.0%) | (92.3%) | (95.0%) | (81.8%) | (83.3%) | (88.8%) | (76.3%) | (86.0%) |
| Slightly elevation | 10 | 5 | 10 | 12 | 1 | 1 | 3 | 2 | 1 | 45 | 30 | 75 |
| | (10.4%) | (10.4%) | (11.6%) | (9.0%) | (5.0%) | (7.7%) | (5.0%) | (18.2%) | (16.7%) | (9.5%) | (22.2%) | (12.3%) |
| Mild elevation | 5 | 3 | - | - | - | - | - | - | | 8 | 2 | 10 |
| | (5.2%) | (6.3%) | | | | | | | | (1.7%) | (1.5%) | (1.6%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; *TDS = three times a day

**Table 10. Alanine aminotransferase (ALT) Discharge**

| | IRP | | | | | SRP | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | 96 | 48 | 86 | 133 | 20 | 13 | 60 | 11 | 6 | 473 | 135 | 608 |
| M | 35.3 | 26.0 | 20.2 | 20.3 | 25.4 | 17.5 | 18.9 | 20.6 | 17.8 | 23.8 | 32.7 | 25.8 |
| (+/-SD) | (42.3) | (25.3) | (13.6) | (13.9) | (31.9) | (7.2) | (11.1) | (8.1) | (8.6) | (24.7) | (49.1) | (31.9) |
| Median | 22.5 | 17 | 17 | 16 | 14.5 | 19 | 15 | 20 | 16 | 17 | 23 | 18 |
| (IQR) | (20) | (17) | (11) | (14) | (18) | (10) | (9) | (9) | (18) | (14) | (21) | (16) |
| Min - Max | 7 - 273 | 5 - 152 | 5 - 66 | 5 - 118 | 7 - 154 | 5-29 | 7-63 | 7 - 36 | 9 - 28 | 5 - 273 | 5 - 547 | 5 -547 |
| Normal range | 76 | 42 | 79 | 125 | 18 | 13 | 58 | 11 | 6 | 428 | 109 | 537 |
| | (79.2%) | (87.5%) | (91.9%) | (94.0%) | (90.0%) | (100.0%) | (96.7%) | (100.0%) | (100.0%) | (90.5%) | (80.7%) | (88.3%) |
| Slightly elevation | 16 | 5 | 7 | 8 | 1 | - | 2 | - | - | 39 | 24 | 63 |
| | (16.7%) | (10.4%) | (8.1%) | (6.0%) | (5.0%) | | (3.3%) | | | (8.2%) | (17.8%) | (10.4%) |
| Mild elevation | 4 | 1 | - | - | 1 | - | - | - | - | 6 | 2 | 8 |
| | (4.2%) | (2.1%) | | | (5.0%) | | | | | (1.3%) | (1.5%) | (1.3%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; *TDS = three times a day

**Table 11. Alkaline phosphatase (ALP) Admission**

| | IRP | | | | | SRP | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |
| n | 85 | 45 | 84 | 132 | 20 | - | | - | - | 366 | 139 | 505 |
| M | 129.7 | 164.0 | 138.7 | 107.2 | 130.9 | - | - | - | - | 127.9 | 121.5 | 126.2 |
| (+/-SD) | (92.9) | (164.0) | (132.2) | (47.5) | (68.1) | | | | | (102.9) | (93.2) | (100.3) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Median (IQR) | 101.0 (68) | 120 (83) | 100 (73) | 95.0 (54) | 104.5 (98) | - | - | - | - | 100 (68) | 97 (69) | 99 (66) |
| Min - Max | 40 – 547 | 56 – 1010 | 47 - 1091 | 32 - 277 | 60 – 285 | - | - | - | - | 32 - 1059 | 0-581 | 0 – 1091 |
| Normal range | 63 (74.1%) | 27 (60.0%) | 59 (70.2%) | 108 (81.8%) | 13 (65.0%) | - | - | - | - | 270 (73.8%) | 105 (75.5%) | 375 (74.3%) |
| Abnormal range | 22 (25.9%) | 18 (40.0%) | 25 (29.8%) | 24 (18.2%) | 7 (35.0%) | - | - | - | - | 96 (26.2%) | 34 (24.5%) | 130 (25.7%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; *TDS = three times a day

**Table 12. Alkaline phosphatase (ALP) Discharge**

| | IRP | | | | | SRP | | | | P Total | NP Total | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRN | BD | TDS | QID | OD | PRN | BD | TDS | OD | | | |
| n | 85 | 45 | 84 | 132 | 20 | - | - | - | - | 366 | 139 | 505 |
| M (+/-SD) | 125.1 (78.6) | 142.5 (139.0) | 127.6 (99.1) | 110.1 (50.5) | 120.2 (54.6) | - | - | - | - | 122.1 (84.7) | 116.1 (80.5) | 120.5 (83.5) |
| Median (IQR) | 106.0 (72) | 107.0 (59) | 98 (68) | 98.5 (58) | 107.5 (77) | - | - | - | - | 102.0 (63) | 95 (73) | 100 (65) |
| Min - Max | 41 – 457 | 54 – 900 | 31 - 656 | 40 - 331 | 64 – 243 | - | - | - | - | 31 - 900 | 0 -523 | 0 - 900 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal range | 62 (72.9%) | 36 (80.0%) | 61 (72.6%) | 103 (78.0%) | 15 (75.0%) | - | - | - | - | 277 (75.7%) | 103 (74.1%) | 380 (75.2%) |
| Abnormal range | 23 (27.1%) | 9 (20.0%) | 23 (27.4%) | 29 (22.0%) | 5 (25.0%) | - | - | - | - | 89 (24.3%) | 36 (25.9%) | 125 (24.8%) |

*BD = twice a day; *IRP = Immediate Release Paracetamol; *M = Mean; *NP = No Paracetamol *OD = overdose; *P = Paracetamol, *PRN = percentage as required; *QID = four times a day; *SD = Standard Deviation; *SRP = Sustained Released Paracetamol; *TDS = three times a day