Paracetamol-induced hepatotoxicity after normal therapeutic doses in the Hong Kong Chinese population

WH Tsang *, CK Chan, ML Tse

ABSTRACT

Introduction: Paracetamol is generally safe at normal therapeutic doses of ≤4 g/day in adults. However, paracetamol-induced hepatotoxicity after normal therapeutic doses use has been reported. We investigated the epidemiology of this adverse drug reaction in the Hong Kong Chinese population.

Methods: This territory-wide retrospective observational study included adult patients with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use from January 2011 to June 2022. We evaluated the demographic characteristics; paracetamol dose, duration, and reason for use; preexisting hepatotoxicity risk factors; laboratory findings; and their relationship with clinical outcomes.

Results: We identified 76 patients (median age: 74 years, 23 males) with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use. There were 14 cases with significant clinical outcomes (five deaths and nine cases of acute hepatic failure), with an incidence of 1.2 cases per year. For patients with significant clinical outcomes, they were significantly older (age >80 years), had a lower body weight (<50 kg), exposed to longer durations (>2 days) and higher daily doses (>3 g), and with higher proportion of malnutrition.

Conclusion: Paracetamol-induced hepatotoxicity can occur at normal therapeutic doses in the Hong Kong Chinese population. The identified risk factors are consistent with international guidelines regarding susceptible patients. Considering the widespread local use of paracetamol and low incidence of severe hepatotoxicity, the current dosage recommendations are considered safe for the general population. For susceptible patients, a reduced maximum dose of ≤3 g/day is recommended, with liver function and serum paracetamol monitoring in place.

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New knowledge added by this study

- Paracetamol can induce hepatotoxicity at normal therapeutic doses in high-risk groups.
- Dosage reduction to ≤3 g/day may reduce the incidence of serious liver injury.

Implications for clinical practice or policy

- Physicians should consider a maximum dosage reduction from 4 g/day to 3 g/day in high-risk groups.
- High-risk groups included older age, lower body weight, malnutrition, exposure to longer duration of drug use, and higher daily dose.

Introduction

Paracetamol is a non-opioid analgesic recommended as a first-line treatment for mild to moderate pain and fever.[1] It is one of the most widely used over-the-counter medications worldwide. In Hong Kong, >600 registered pharmaceuticals contain paracetamol.[2] Adverse drug reactions in healthy individuals are rare within the therapeutic dose range. According to the British National Formulary, the recommended daily dose of paracetamol is 4 g/day in divided doses for adults with body weight ≥50 kg.[3] Special precautions are needed for individuals with a high risk of hepatotoxicity, including those with body weight <50 kg, chronic alcoholism, chronic dehydration, chronic malnutrition, hepatocellular insufficiency, and/or concomitant use of P450 liver enzyme inducers (eg, antituberculosis drugs, antiepileptic drugs, and herbs/dietary supplements such as St John's wort).

Paracetamol is metabolised through various pathways in the liver. In healthy individuals taking normal therapeutic doses, >90% of paracetamol undergoes glucuronidation and sulphation, followed by renal excretion.[4] Only 5% to 10% is oxidised by

香港華人服用正常治療劑量撲熱息痛後引起的肝損傷

曾永康、陳志強、謝萬里

引言：一般成人每天服用≤4克撲熱息痛是安全的，然而有報告指出小部分人服用正常劑量撲熱息痛後會引起肝損傷。我們在香港華人群體進行了流行病學調查，了解這種藥物的不良反應。

方法：這項全港性回顧觀察納入了2011年1月至2022年6月期間正常服用撲熱息痛後疑似誘發肝損傷的成年患者。我們收集及分析了患者的人口特徵；撲熱息痛服用劑量、使用時間和原因；預先存在的肝損傷危險因子；實驗室檢查結果；及它們與臨床結果的關係。

結果：在研究中，我們找到76名患者（年齡中位數：74歲，男性23人）在使用正常劑量後疑似出現撲熱息痛引起的肝損傷。14例有顯著的臨床結果（5例死亡，9例急性肝衰竭），發生率為每年1.2例。具有顯著臨床結果的患者的年齡明顯較大（>80歲），體重較低（<50公斤），服用時間較長（>2天），每日劑量較高（>3克），營養不良的比例亦較高。

結論：香港華人在服用正常劑量撲熱息痛後有可能會引起肝損傷。在高風險患者中找到的危險因素與國際準則一致。考慮到撲熱息痛被廣泛使用，嚴重肝損傷的發生率低，目前的建議劑量對一般人來說是安全的。對於高危群組，建議將最大劑量降低至每天≤3克，並進行肝功能和撲熱息痛血清監測。

cytochrome P450 to the toxic metabolite N-acetyl-p-benzoquinone imine, which is subsequently neutralised by glutathione and undergoes renal excretion. However, in cases of paracetamol overdose or glutathione depletion, excessive production and accumulation of N-acetyl-p-benzoquinone imine in hepatocytes can result in acute liver injury. N-acetylcysteine, the primary antidote in such situations, acts by replenishing hepatic glutathione.[5] Theoretically, paracetamol hepatotoxicity can occur after normal therapeutic dose use in patients with critically depleted glutathione levels.

There have been few reports of paracetamol-induced hepatotoxicity after normal therapeutic doses use.[6-8] Most of these cases had at least one of the aforementioned risk factors. In 2022, the United Kingdom's Healthcare Safety Investigation Branch published a report recommending a prescription alert for individuals with body weight <50 kg who are prescribed paracetamol.[9] The Queensland Government's Department of Health of Australia also revised its paracetamol use guidelines, recommending ≤3 g/day for adults with risk factors such as advanced age or low body weight.[10] When risk factors are present and treatment continues beyond 48 hours, liver function test and international normalised ratio (INR) monitoring is recommended.[10] The United States Food and Drug Administration states that it is safe to consume ≤4 g of paracetamol within 24 hours,[11] whereas the Irish Health Products Regulatory Authority recommends ≤2 g of paracetamol for patients with mild to moderate hepatic insufficiency or chronic alcoholism.[12]

Isolated cases of paracetamol-induced hepatotoxicity causing death or acute hepatic failure after normal therapeutic doses use have been reported to the Hong Kong Poison Information Centre (HKPIC). However, no local reports have been published concerning the incidence of this rare adverse drug reaction in the Hong Kong population. This study aimed to describe the epidemiology and incidence of paracetamol-induced hepatotoxicity in the Hong Kong Chinese population.

Methods

Study design

This territory-wide retrospective observational study included adult patients with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use reported to the HKPIC from 1 January 2011 to 30 June 2022 (11.5 years in total).

Study setting and data sources

The HKPIC was the only poison control centre in Hong Kong during the study period. This centre provides round-the-clock phone consultations regarding poisoning cases to local healthcare professionals and receives voluntary reports of poisoning from all public emergency departments.[13,14] The HKPIC maintains an electronic database, the Poison Information and Clinical Management System (PICMS), that contains information about all consultations and reports received. Clinical data from consultations and reports are entered into the PICMS by staff trained in clinical toxicology.[14] The data source for this study consisted of data retrieved from the PICMS. When PICMS data were incomplete, supplementary data were retrieved from the Hospital Authority's electronic Patient Record system, which contains all medical records (ie, clinical data, laboratory results, and outcomes) of patients treated in public hospitals in Hong Kong.

Study population

All cases of paracetamol poisoning recorded in the PICMS during the study period were identified. Exclusion criteria were applied to ensure the inclusion of only adult patients with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use. These exclusion criteria were age <18 years, intentional self-harm with paracetamol, daily paracetamol consumption >4 g, unknown paracetamol dose, co-ingestion with other hepatotoxic drugs, or hepatotoxicity unrelated to paracetamol.

Data collection

For the included cases, the following data were collected: demographic characteristics including age, sex, and ethnicity; duration of paracetamol use, daily paracetamol dose, and reasons for paracetamol use; risk factors including history of preexisting liver disease, chronic alcoholism, use of P450 liver enzyme-inducing medications, and malnutrition; poisoning data including peak serum paracetamol concentration, peak alanine transaminase (ALT) level, peak INR, and receipt of N-acetylcysteine; and clinical outcomes including death, acute liver failure, mildly deranged liver function, and minimal effect.

Definitions

The diagnosis of paracetamol-induced hepatotoxicity was established on the basis of compatible clinical and biochemical features, excluding other causes of deranged liver function (eg, acute viral hepatitis, autoimmune causes, and other drug- or herb-induced hepatitis). All cases were reviewed by at least one clinical toxicologist working in the HKPIC. Clinical outcomes were defined as follows: 'death' was defined as poisoning-related death, as judged by a clinical toxicologist, within 30 days after hospitalisation; 'acute hepatic failure' was defined as severe acute liver injury with an ALT level >1000 IU/L, associated with encephalopathy and impaired synthetic function within 26 weeks[15]; 'mildly deranged liver function' was defined as a peak ALT level >2 times the upper limit of normal, without encephalopathy or impaired synthetic function; and 'minimal effect' was defined as a peak ALT level <2 times the upper limit of normal, along with normal mental status. 'Significant clinical outcome' cases were those with a clinical outcome of death or acute hepatic failure. Malnutrition was defined as documented insufficient energy intake for >1 week.[16]

Statistical analysis

Data were analysed using SPSS software (Windows version 29.0; IBM Corp, Armonk [NY], United States). Continuous data were expressed as medians (interquartile ranges); the Mann-Whitney *U* test was used to compare the death and acute hepatic failure groups with the minimal effect group. Categorical variables were expressed as frequencies and percentages; they were compared using the Chi squared test or Fisher's exact test, as appropriate. All statistical tests were two-sided, and P values <0.05 were considered statistically significant. Due to the small sample size and low incidence of significant clinical outcomes, multivariable logistic regression was not performed.

Results

Within the study period, 3873 cases of paracetamol poisoning were identified. Reasons for exclusion were intentional paracetamol poisoning, age <18 years, other causes of deranged liver function, daily paracetamol dose >4 g, and unknown paracetamol dose (Fig). In total, 76 patients were included in the analysis; these patients were grouped according to clinical outcomes. During the study period, five patients died, nine patients developed acute hepatic failure, one patient developed mildly deranged liver function without coagulopathy or altered mental status, and 61 patients showed minimal effect; no patients underwent liver transplantation. The incidence of significant clinical outcomes (including death and acute hepatic failure) was 1.2 cases per year. Baseline demographic and clinical characteristics are summarised in Table 1.

Most patients were women (69.7%). The median age was 74 years and the median body weight was 54.2 kg. All patients were of Chinese ethnicity. Compared with the minimal effect group, patients in the death group were older (median age: 83 vs 72 years; P=0.003), had a longer duration of paracetamol use [median duration: 7 vs 1 day(s); P=0.001], and had a higher daily paracetamol dose (median dose: 4 vs 2 g; P=0.004). Their body weights tended to be lower, but this difference was not statistically significant (median: 50 vs 56.4 kg; P=0.11). Moreover, a higher percentage of patients in the death group suffered from malnutrition (80% vs 31.1%; P=0.04), and their peak serum paracetamol concentrations were higher (median peak concentration: 410 vs 0 μmol/L; P<0.001), exceeding the normal range of <130 μmol/L despite the use of normal therapeutic doses (Table 1).

Patients with significant clinical outcomes were evaluated by combining the death and acute hepatic failure groups. Five risk factors for significant clinical outcomes were identified, namely,

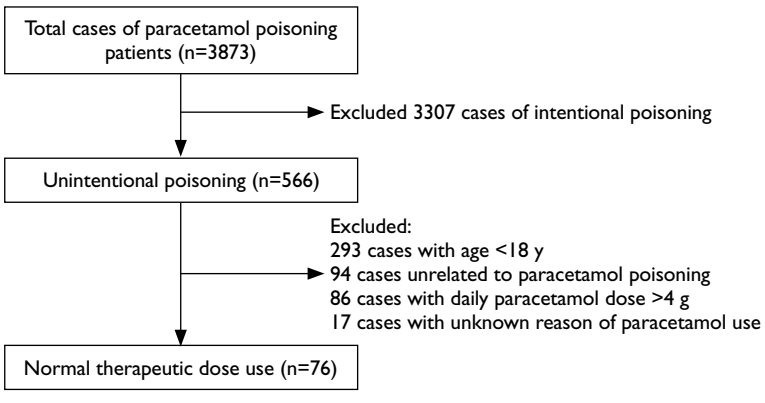

FIG. Selection of adult patients with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use

TABLE 1. Demographic data, clinical characteristics, and clinical outcomes of included cases*

	All cases (n=76)	Death (n=5)	Acute hepatic failure (n=9)	Mildly deranged liver function (n=1)	Minimal effect (n=61)
Male sex	23 (30.3%)	0	2 (22.2%)	0	21 (34.4%)
Age, y	74 (49-83)	83 (83-91)	82 (49-83)	77	72 (37.5-82)
Body weight, kg	54.2 (47-61.3)	50 (40-53)	50 (41-56.5)	31.9	56.4 (50-62.0)
Chinese ethnicity	76 (100%)	5 (100%)	9 (100%)	1 (100%)	61 (100%)
Duration of paracetamol use, d	1 (1-1.25)	7 (5-7)	5 (4-7)	4	1 (1-1)
Daily paracetamol dose, g	2 (2-3.5)	4 (3.5-4)	4 (4-4)	4	2 (1.5-2.5)
Peak serum paracetamol concentration, μmol/L	31 (0-174)	410 (350-640)	195 (103-221)	42.9	0 (0-66.5)
Peak ALT level, IU/L	21 (13-44)	4525 (1896-5432)	2020 (1284-2647)	210	18 (13-25)
Peak INR	1 (1-1)	4.8 (4.3-5.11)	2.1 (2-2.6)	1.3	1 (1-1)
Reasons for paracetamol use					
Relief for pain or fever	46 (60.5%)	4 (80%)	9 (100%)	1 (100%)	32 (52.5%)
Accidental exposure after ethanol intoxication	1 (1.3%)	0	0	0	1 (1.6%)
Accidental exposure due to cognitive impairment	26 (34.2%)	1 (20%)	0	0	25 (41.0%)
Therapeutic error	3 (3.9%)	0	0	0	3 (4.9%)
Risk factors					
Preexisting liver disease	2 (2.6%)	1 (20%)	1 (11.1%)	0	0
Chronic alcoholism	1 (1.3%)	0	1 (11.1%)	0	0
Malnutrition	28 (36.8%)	4 (80%)	5 (55.6%)	0	19 (31.1%)
P450 inducer use	1 (1.3%)	0	0	0	1 (1.6%)

Abbreviations: ALT = alanine transaminase; INR = international normalised ratio

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

age >80 years (odds ratio [OR]=7.2, 95% confidence interval [CI]=2.0-26.2), body weight <50 kg (OR=3.8, 95% CI=1.0-12.1), duration of paracetamol use >2 days (OR=16.9, 95% CI=2.1-136.9), daily paracetamol dose >3 g (OR=7.2, 95% CI=2.0-26.2), and malnutrition (OR=4.07, 95% CI=1.2-13.8). A summary of the risk factors is provided in Table 2.

Discussion

The maximum recommended daily dose of paracetamol for healthy adults is 4 g/day in divided doses.[17] As one of the most widely used analgesics worldwide for decades, this dosage recommendation is considered safe and generally has not been questioned by most healthcare professionals. Physicians have been taught to use the convenient dosing of 1-g paracetamol four times daily as a first-line analgesic in adults. Historically, paracetamol-induced hepatotoxicity was solely regarded as a consequence of overdose. Paracetamol-induced hepatotoxicity after normal therapeutic doses use was considered a therapeutic misadventure of doubtful existence.[7] However, case reports of this adverse drug reaction were published.[6-8] The situation becoming clear after a single-blind randomised controlled trial by Watkins et al[18] revealed elevated ALT levels in 40% of healthy individuals who had received 4 g/day of paracetamol for 2 weeks. Subsequent studies confirmed this observation and showed that continuous use of paracetamol by individuals with high ALT levels did not result in hepatotoxicity.[19,20] Their ALT levels returned to baseline after continuous paracetamol use, suggesting hepatic adaptation.[21] Nevertheless, the mechanisms underlying hepatic adaptation are not fully understood, and paracetamol-induced hepatotoxicity after normal therapeutic doses use may represent a rare adverse drug reaction due to failed hepatic adaptation. In a prospective study in Spain,[22] the incidence of this adverse drug reaction was estimated to be 10 per million paracetamol users-year (95% CI=4.3-19.4). Prior to the present study, there has been little information on how often paracetamol-induced hepatotoxicity occurs in the Hong Kong Chinese population.

Our study confirmed the existence of this rare adverse drug reaction, with an incidence of 1.2 cases

TABLE 2. Risk factors for significant clinical outcomes in patients with suspected paracetamol-induced hepatotoxicity after normal therapeutic doses use*

	Significant clinical outcome (death or acute hepatic failure) [n=14]	OR (95% CI)	P value	Mildly deranged liver function/minimal effect (comparison group) [n=62]
Age >80 y	10 (71.4%)	7.2 (2.0-26.2)	0.0028	16 (25.8%)
Body weight <50 kg	6 (42.9%)	3.8 (1.0-12.1)	0.049	11 (17.7%)
Duration of paracetamol use >2 d	13 (92.9%)	16.9 (2.1-136.9)	0.008	27 (43.5%)
Daily paracetamol dose >3 g	10 (71.4%)	7.2 (2.0-26.2)	0.0028	16 (25.8%)
Malnutrition	9 (64.3%)	4.07 (1.2-13.8)	0.02	19 (30.6%)

Abbreviations: 95% CI = 95% confidence interval; OR = odds ratio

* Data are shown as No. (%), unless otherwise specified

of significant clinical outcomes per year in the Hong Kong population (approximately 7 million people). Because the vast majority of the local population is served by public hospitals included in our poisoning surveillance protocol, we believed that this figure accurately reflects the rare occurrence of this adverse drug reaction. Concerning patient characteristics predictive of significant clinical outcomes, we found that age >80 years, body weight <50 kg, duration of paracetamol use >2 days, daily paracetamol dose >3 g, and malnutrition were associated with a higher risk of paracetamol-induced hepatotoxicity leading to death or acute hepatic failure. The median daily dose was 4 g of paracetamol, consistent with the convenient maximum therapeutic dosing (eg, 1 g four times daily) for adults. Additionally, the median duration of paracetamol use was 5 to 7 days, indicating that life-threatening paracetamol-induced hepatotoxicity can develop and rapidly progress within a few days in susceptible individuals receiving convenient paracetamol dosing. The supratherapeutic serum paracetamol concentrations detected in these cases provide evidence of impaired hepatic paracetamol metabolism, leading to gradual accumulation of paracetamol within the body. The subsequent pathophysiology of hepatotoxicity is considered identical to that of paracetamol overdose. Therefore, the use of the antidote N-acetylcysteine is recommended in all identifiable cases of paracetamol-induced hepatotoxicity after normal therapeutic doses use.

One argument against the existence of this adverse drug reaction has been the accuracy of documentation concerning paracetamol dosage.[7] Because the clinical presentation of paracetamol-induced hepatotoxicity is indistinguishable from that of paracetamol overdose, it has been suggested that the hepatotoxicity cases actually represent undeclared or undiagnosed instances of paracetamol overdose, which are more common in clinical practice. The present findings exclude this possibility. All five patients who died had exhibited normal liver function upon or prior to hospital admission; they were prescribed therapeutic doses of paracetamol for various indications during their inpatient stay. The possibility of intentional or accidental paracetamol overdose was excluded in each case.

The association between older age and paracetamol-induced hepatotoxicity has been addressed in previous studies. In 2021, a prospective study by Louvet et al[23] showed that older age was an important risk factor associated with acute liver injury after therapeutic doses of paracetamol. Paracetamol pharmacokinetics in older adults reportedly differ from those in younger adults. Although absorption from the gastrointestinal tract is not significantly reduced, paracetamol clearance is 46.8% lower in frail older individuals than in healthy older individuals.[24] In another observational study,[25] the effects of ageing and frailty on serum paracetamol and ALT levels were assessed in hospitalised patients after continuous exposure to therapeutic doses for 5 days. The results showed that serum paracetamol concentrations were higher in older frail patients.[25]

Limitations

This study had some limitations. First, its retrospective nature required reliance on the accuracy and completeness of medical records. Incomplete information in medical records, particularly missing data concerning the daily dose and duration of paracetamol exposure, could substantially affected the results. Second, because all consultations were voluntarily reported, underreporting may contribute to reporting bias. Third, the sample size was relatively small, hindering analysis of confounders via logistic regression. Finally, the effects of some potential risk factors (eg, chronic alcoholism and concomitant use of P450 inducer) could not be quantified due to their low reported incidence and the small sample size.

Conclusion

Paracetamol-induced hepatotoxicity can occur

at normal therapeutic doses in the Hong Kong Chinese population. Our study identified risk factors associated with significant clinical outcomes. Considering the widespread use of paracetamol in Hong Kong, the incidence of paracetamol-induced hepatotoxicity is low; current dosage recommendations are considered safe for the vast majority of the general population. Nevertheless, a maximum daily dose of ≤3 g is recommended for susceptible patients. Paracetamol dosage, especially if consumed at 4 g/day for >48 hours, should be reviewed; liver function and INR monitoring should be considered in susceptible patients.[10]

Author contributions

Concept or design: All authors.
Acquisition of data: WH Tsang.
Analysis or interpretation of data: WH Tsang, CK Chan.
Drafting of the manuscript: WH Tsang.
Critical revision of the manuscript for important intellectual content: WH Tsang, CK Chan.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This research was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: KC/KE-23-0041/ER-4). The requirement for informed patient consent was waived by the Committee due to the retrospective nature of the research and the use of anonymised data in the research.

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