Paracetamol intoxications:
A population-based study in Iceland

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Háskóli Íslands
Læknadeild
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Ágrip

Parasetamóleitranir og lifrarskaði: Lýðgrunduð rannsókn á Íslandi

Inngangur: Parasetamól er algengasta orsök bráðrar lifrarbilunar í Bandaríkjunum og mörgum löndum Evrópu en þetta hefur ekki verið rannsakað á Íslandi. Flestar eitranir af völdum parasetamóls tengjast of háum skömmtum af lyfinu. Það er óljóst hversu stór hluti sjúklinga með lyfjaeitrun af völdum parasetamóls hlýtur lifrarskaða og hverjar horfur sjúklinganna eru. Það er ennfremur óljóst hve stór hluti sjúklinga hefur fengið eitrun af völdum sjálfskaða eða óhapps. Markmið rannsóknarinnar var að kanna lýðgrundað nýgengi eitrana af völdum parasetamóls. Einnig að rannsaka afleiðingar parasetamóleitrunar svo sem áhættuþætti lifrarskaða, algengi bráðrar lifrarbilunar og afdrif sjúklinga.

Efniviður og aðferðir: Rannsóknin var lýðgrunduð afturskyggn og lýsandi cohort rannsókn sem náði yfir upptökusvæði Landspítala háskólasjúkrahúss (LSH) sem taldi u.þ.b. 220.000 manns. Gagna var aflað úr tölvukerfum LSH um alla þá sem leitað höfðu til spítalans vegna eitrana af völdum lyfja eða voru greindir með lifrarbilun á árunum 2004 til 2009. Upplýsingar um inntekin lyf, einkenni og blóðgildi sjúklinga voru unnar úr sjúkraskrám.

Niðurstöður: Í fyrri hluta rannsóknarinnar voru 1913 tilfelli vegna lyfjaeitrana frá 2004 – 2009 og þar af 346 (18%) af völdum parasetamóls. Nýgengi lyfjaeitrana fækkaði úr 200,5 í 117,3 fyrir 100.000 íbúa ($p<0.001$) á 6 árum. Einnig fækkaði nýgengi eitrana af völdum parasetamóls úr 32,8 í 17,3 fyrir hverja 100.000 íbúa, ($p<0,05$). Hlutfall kvenna á móti körlum var 2,8:1 og hlutfallslega flestar eitranir voru í aldurshópnum 16-25 ára.

Annar hluti rannsóknarinnar tók aðeins til fyrstu komu vegna parasetamól-eitrunar á LSH á árunum 2004 – 2009. Af 290 komum var hlutfall kvenna á móti körlum 2,7:1. Hlutfall sjúklinga sem lagðir voru inn á lyfjadeildir í kjölfar skoðunar var 22% og 11% þurftu að leggjast inn á gjörgæslu. Alls fengu 58% meðferð með N-acetylcysteine (NAC). Sjúklingar útskrifaðir beint heim eftir komu á bráðamótttöku voru 25%. Í sjö prósentum tilfella (20/285) var um óhappaeitrun að ræða og i þeim hópi var hlutfall karla hærra ($p<0,05$). Í óhappatilvikunum voru lifrarensím hærri ($p<0,005$) þrátt fyrir að blóðgildi parasetamóls hafi verið lægra. Bráð lifrarbilun var í 3,1% tilfella (9/290). Karlar voru marktækt eldri og hlutfall þeirra hærra en kvenna, en ekki var marktækur munur þar á, ($p=0,07$). Í vísvitandi tilfellum fengu 1,5% bráða lifrarbilun en í 15% óhappatilfella. Einn sjúklingur lést vegna bráðrar lifrabilunar af völdum parasetamóls.

Ályktanir: Nýgengi eitrunar af völdum parasetamóls var nokkuð hátt en tilfellum fækkaði á rannsóknartímabilinu. Konur í aldurshópnum 16-25 ára voru hlutfallslega flestar af þeim sem vísvitandi tóku inn ofskammt parasetamóls en í óhappatilvikunum var hlutfall eldri karla hærra. Tilfelli bráðrar lifrarbilunar voru fá og frekar tengd óhappaeitrunum. Notkun NAC var algeng og alvarleg tilfelli fá. Afdrif flestra sjúklinga voru góð.

Abstract

Paracetamol intoxications: A population-based study in Iceland

Background: Paracetamol is the most common cause of acute liver failure (ALF) in the US and many countries in Europe. Most data on paracetamol toxicity originate from liver transplant centres and tertiary referral institutions. The proportion of patients with paracetamol overdose who develop liver injury in a population-based sample is largely unexplored. The aim of this MPH thesis was to analyze the population-based annual incidence of paracetamol overdoses, prevalence of liver injury and the risk factors for hepatotoxicity and outcome in unselected patients presenting to hospital with paracetamol toxicity and/or overdose

Methods: This was a retrospective and descriptive cohort study. Search for the diagnosis of paracetamol toxicity and liver failure was undertaken in a teaching hospital serving a population of approximately 220,000 inhabitants in Iceland over a six-year period, from 2004 to 2009. Medical charts were reviewed for relevant characteristics, the proportion of intentional vs. unintentional toxicity, liver tests and outcome.

Results: In this population-based study 1913 visits were reviewed, and 346 (18%) involved paracetamol overdoses. The annual population incidence for all drug-related overdoses over the six years declined from 200.5 to 117.3 per 100,000 inhabitants ($p<0.001$). Likewise, the annual incidence of paracetamol overdoses declined from 32.8 to 17.3 per 100,000 inhabitants ($p<0.05$). The female/male ratio in the paracetamol cases was 2.8. The largest age-group by far was 16-25 years with 40% of the total cases.

There were 290 index visits by patients over the age of ten. The female to male ratio was 2.7. Of the total cohort 22% were admitted to the acute medical ward, and 11% needed intensive care. *N*-acetylcysteine was administrated in 59% of the cases. Twenty-five percent were discharged directly home after presentation to the emergency room. There was acute ethanol consumption in 41% of the cases. Visits caused by accidental overdoses constituted 7% (20/285) of the total cohort. Males were more likely to overdose due to therapeutic misadventures for medical effects ($p<0.05$). The accidental group had higher peak aminotransferase levels ($p<0.005$) in spite of lower serum paracetamol $P<0.05$). There was acute liver failure (ALF) in 3.1% (9/290) of the index visits. The proportion of males was higher although not significantly so ($p=0.07$). The median age for males was also higher ($p<0.05$). In the intentional group 1.5% developed ALF, compared to 15% of the accidental group ($p<0.05$). Only one patient died from ALF.

Conclusions: The annual incidence of paracetamol toxicity was high in this population-based study but declined over the period. Young females with intentional toxicity accounted for most of the cases, whereas accidental toxicity was more common in older males. The occurrence of ALF was low and associated with accidental overdose. The use of NAC was very frequent, and serious outcomes were very rare. Most patients had favourable outcomes.

ÞAKKIR

Höfundur vill færa eftirtöldum aðilum sérstakar þakkir: Leiðbeinanda mínum Einari S. Björnssyni fyrir vinsamlegt viðmót og skjót viðbrögð þegar leitað var til hans. Meistaranefndinni, þeim Magnúsi Jóhannssyni og Helgu Zoëga, fyrir margar góðar ábendingar og ráðleggingar á lokasprettinum. Þá vil ég þakka fyrir húsaskjól og aðstöðu hjá Helga Sigurðssyni og Nönnu K. Sigurðardóttur á Krabbameinsmiðstöð. Nönnu vil ég að auki þakka fyrir góða yfirferð í lokin. Ráðagóðu samnemendur mínir, Kristín K. Alexíusdóttir og Helga Norland, fá þakkir fyrir ánægjulegar stundir við rannsóknarvinnuna. Önnu Svanhildi Sigurðardóttir á rannsókarstofu í lífefnafræði á LSH Hringbraut þakka ég fyrir aðstoð við öflun klínískra gagna. Þá vil ég þakka Vísindasjóði Landspítalans,en sjóðurinn veitti fjárstyrk til rannsóknarinnar. Loks vil ég þakka eiginmanni og börnum fyrir þolinmæði og hvatningu, sem hefur verið mér mikils virði.

Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

ALF	Acute liver failure
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (ATC) classification system
ER	Emergency Room
F/M	Female/Male
GSH	Glutathion
HE	Hepatic encephalopathy
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICU	Intensive care unit
INR	International normalized ratio
KCC	Kings College criteria
LT	Liver transplant
NAC	*N*-acetylcysteine
NAPQI	N-acetyl-p-amino-benzoquinoneimine
NUH	National University Hospital
OTC	Over the counter
PT	Prothrombin time
SPSS	IBM SPSS statistics 19
US	United States
UK	United Kingdom

FOREWORD

The aim of this MPH thesis was to explore the extent of paracetamol overdoses in the area of the National University Hospital in Iceland. Paracetamol is one of the most widely used analgesics in Europe and USA. Over the last decade health authorities in UK, USA, Denmark and many other countries have sought diverse ways to decrease the ever-increasing incidence of overdoses. Paracetamol is an over-the-counter product in Iceland and only available in pharmacies. Although it is well recognised as a public health problem, little is known about the epidemiology the severity of paracetamol overdoses and the patients' outcomes. In addition, the proportion of unselected paracetamol overdose patients developing acute liver failure in an unselected population has not been well documented on a worldwide scale.

The thesis focuses on the above and is split into two halves. The first part is a review of the paracetamol drug itself, the toxicology and then the factors which can be either protective or worsen the outcome. The second half of the thesis is a study of paracetamol overdoses in a given population. This required a review of over 2500 medical records and lasted for over six months. This extensive work has added to the understanding of the extent of the overdose cases, which should be addressed as public health problem and is a considerable burden on the health care system.

INTRODUCTION

Paracetamol

Paracetamol is an analgesic commonly used worldwide and generally considered safe when consumed according to the maximum recommended dosage of 4g day^{-1}. Paracetamol is one of most commonly used analgesics in the United States[1] (US) and one of the most available over-the-counter (OTC) medicines.[2] The compound is found in over 100 OTC products and numerous preparations, commonly in combinations with opiates.[3] Paracetamol, or acetaminophen, which is the name used in the US, is the most common cause of acute liver failure (ALF) in the US[1,2] and many countries in Europe, such as United Kingdom (UK)[4] and Sweden.[5]

The fever-reducing effect of the forerunner of paracetamol, acetanilide, was discovered when Farbenfabriken Bayer began marketing a derivate of one of its by-products "phenacetin" as both antipyretic and analgesic. This has been described as the beginning of the pharmaceutical industry as we know it today. After studying the drug's metabolism in the 1950s, Brodie et al. introduced paracetamol in its final form, and it was put on the market by several producers.[6]

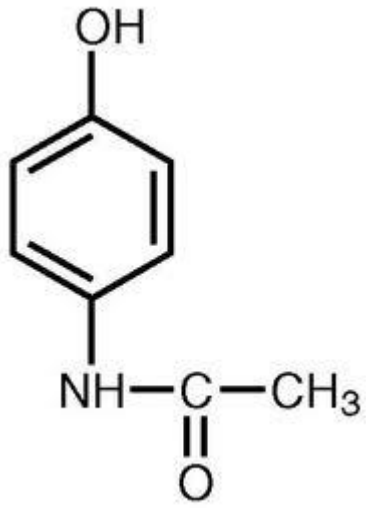


Figure 1: The structural formula of paracetamol[10]

Although the toxic effects of paracetamol have been extensively studied, remarkably little is known of its molecular mechanism.[3,6,7] Since 1966 it has been known that in cases of overdose paracetamol can lead to hepatic necrosis in a dose-related fashion.[8] This is in contrast with most other drugs leading to idiosyncratic liver injury that are generally dose-independent.[9] It was not until the 1990s that cases of paracetamol hepatotoxicity were reported and listed as a cause of liver transplants.[7]

Pharmacokinetics

Absorption

Paracetamol is classified as a mild analgesic with mechanisms which are not completely known. It has been found to be both antipyretic and analgesic and is produced in three forms; oral, rectal and intravenous.[11] When taken orally, it is absorbed beyond the stomach from the small bowel. The absorption is not affected by food when ingested with the drug, and the speed of absorption is independent of dose.[11] Serum paracetamol half-life is around two hours[11], with a time delay of peak plasma levels and maximum antipyretic effect is one to two hours.[12] The time delay between plasma concentration and analgesic effects is considered to be longer than in case of pyretic effects.[12]

The paracetamol is absorbed slowly when administered rectally and has a peak plasma concentration of 2-4 hours.[11] As paracetamol is not well soluble, it is not suitable for intravenous administration and is in the form of a pro-drug when so administered.[11]

Metabolism

Paracetamol has a plasma half-life of around two hours and is mostly metabolised in the liver. When ingested in safe doses, it is transformed by cytochrome P450 into N-acetyl-*p*-bezoquinoneimine (NAPQI) and further detoxified by Glutathion-S-transferase and Glutathion (GSH).[3] This compound is then excreted by the kidneys[8], and after 24 hours paracetamol can be recovered in the urine as a conjugate.[11]

When normal levels of GSH are depleted by an excess dose of paracetamol, or low levels of GSH are depleted by the NAPQI, the results can be loss of liver cell function and cell death.[3] It is not known if the depletion of GSH is itself toxic and leads to oxidative stress and loss of liver function, or the loss is caused by the reactive metabolites which attack critical protein thiols[3], leading to cell death.[13]

Reported hepatotoxicity when paracetamol intake has been under maximum daily dosage has been explained as an idiosyncratic reaction.[13] Raised alanine aminotransferase (ALT) levels of up to 8 x upper limits of normal (ULN) have been reported in a study where young healthy individuals were repeatedly administered 4g of paracetamol per day. The authors concluded that the raised levels were due to paracetamol as they ruled out all other known risk factors.[14] Although raised ALT levels are one of the factors indicating liver injury[15], the authors are not certain to what extent this indication has clinical relevance. It was assumed that the ALT elevations would have resolved with continued paracetamol administration.[14]

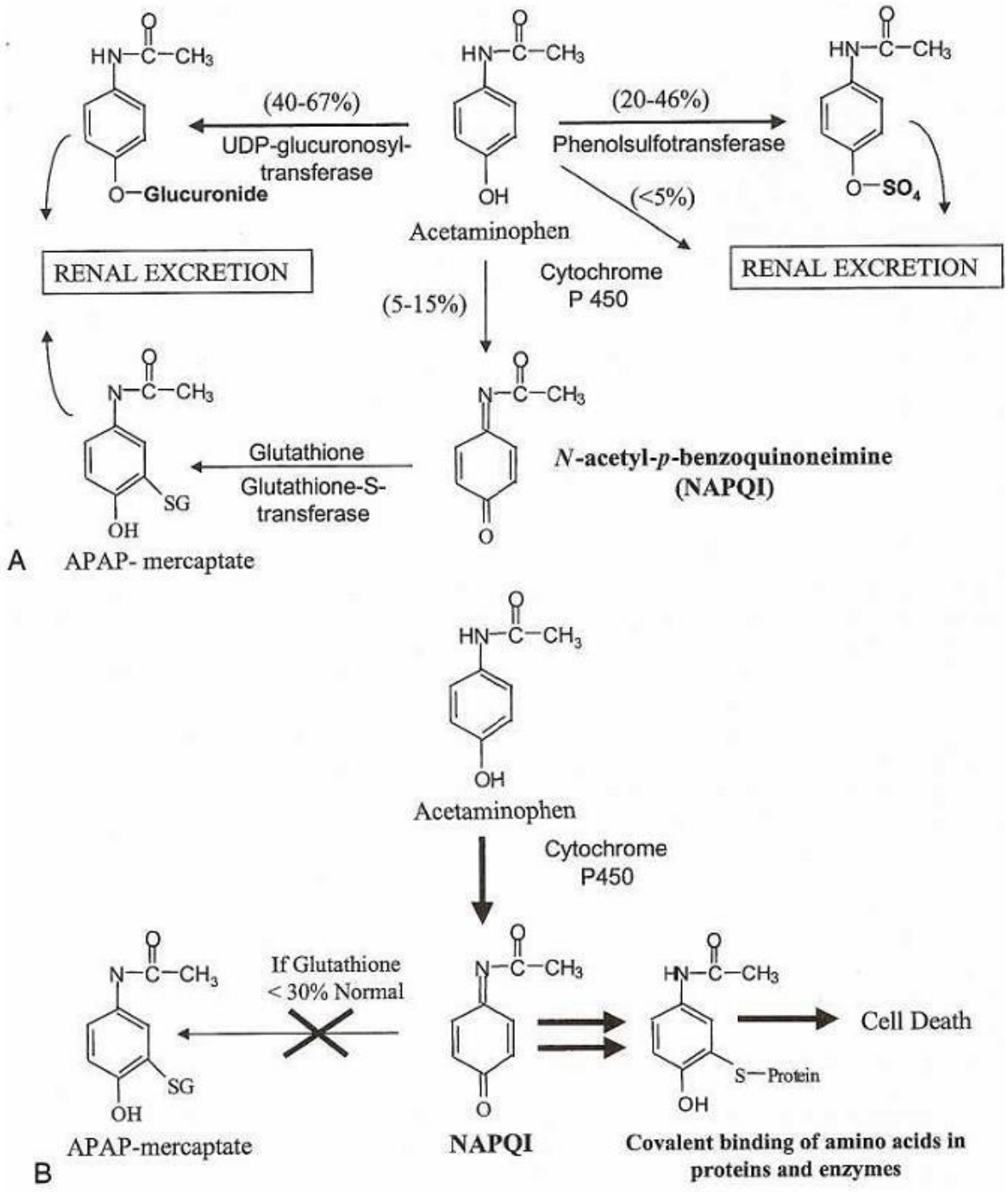


Figure 2: The paracetamol metabolism [16]

The mechanisms of paracetamol toxicity

Paracetamol is a direct hepatotoxin, i.e., the substance causes predictable dose-dependent hepatocellular necrosis.[2] Toxicity is unlikely when paracetamol is taken in daily dosages of 7.5 to 10g for adults or 150 mg/kg for a child.[4] Toxicity is possible or likely when dosage exceeds 12g over 24 hours or more than 250 mg/kg (150-250 mg kg^{-1}).[11] It has been observed that some individuals are able to adapt to the damaging effect of the drug.[9] It can be difficult to determine the safe dosage of the drug as the toxic mechanism of paracetamol is still unclear, as well as how the interplay of risk factors affects the toxic threshold.

The hepatotoxicity resulting from paracetamol overdose can be detected by raised serum paracetamol levels, increased liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and prolonged international normalized ratio (INR) or prothrombin time (PT).[4,15] There are numerous interfering factors that are of both genetic and environmental origin[3], i.e., the extent of cytochrome activation of other medications or the depletion of glutathion stores because of either malnutrition or alcohol use [2]

Hepatotoxicity

Hepatic toxicity may be experienced by adults after ingestion of more than 10g of paracetamol[17], but hepatotoxicity rarely develops at doses under 12g.[18] In the first two days after consumption, the symptoms may not reflect the complete extent of the toxicity. The progress of hepatotoxicity can be split into four phases:

Phase 1 : First 24 hours: Symptoms can include anorexia, abdominal pain, nausea, vomiting, lethargy, malaise and diaphoresis.[4]

Phase 2 (24-72h): Symptoms improve and even disappear. Clinical tests like liver enzymes, liver transaminases, bilirubin and prolonged prothrombin time become abnormal. Some patients might suffer from upper abdominal pain, and a liver biopsy will reveal centrilobular necrosis.[4,17]

Phase 3: Nausea and vomiting reappear and are accompanied by malaise, sometimes jaundice. In addition, there are symptoms from the nervous system, like confusion, somnolence or even coma. In this phase hepatocellular injury is common and, in severe cases, death.[4] Liver enzyme levels will peak at this stage[4], going as high as 10.000 IU/L.[19]

Phase 4 (4-14 days after intoxication): Almost 70% of those developing acute liver failure (ALF) can reach this phase and recover completely. When overdose is severe, and there is no treatment, most of the patients will die during these 4-18 days after paracetamol ingestion.[4]

Severe liver toxicity

If four hours have elapsed since ingestion, and serum paracetamol levels are above 2000µmol/L (300mg/L), or after 15 hours above 300µmol/L (50mg/L), there is a 90% chance of severe or fatal liver damage. If left untreated, 1-2% of patients with toxic paracetamol levels will develop fatal hepatic failure, and death will occur within 4 to 18 days.[4] When moderate to severe liver injury is suspected, a careful evaluation of mental status should be made and prothrombin time (PT) measured.[2] By definition, patients with PT > 15 seconds (or INR > 1.5)[20] and altered mental status have ALF. They require hospitalization and preferably intense monitoring at an intensive care unit (ICU).[2] Patients with hepatotoxicity from a paracetamol overdose and metabolic acidosis (pH below 7.3) often have poor outcome and should be immediately transferred to ICU.[2] However, the mortality of paracetamol overdose patient is less than 1%.[2]

Handling and follow-up of overdose cases

The Rumack-Matthew nomogram

Dose and time to presentation is the most vital information to predict prognosis after intoxication.[4] In case of a suspected paracetamol overdose, a serum paracetamol measurement should be taken at presentation and the result plotted against the Rumack-Matthew nomogram[4,21], see Figure 3. It was developed to help predict the risk of hepatotoxicity after paracetamol overdose and used to identify those requiring NAC-treatment.[4] The nomogram is a guide for first management of a single overdose but is not suitable for patients with chronic ingestion.[4,22]

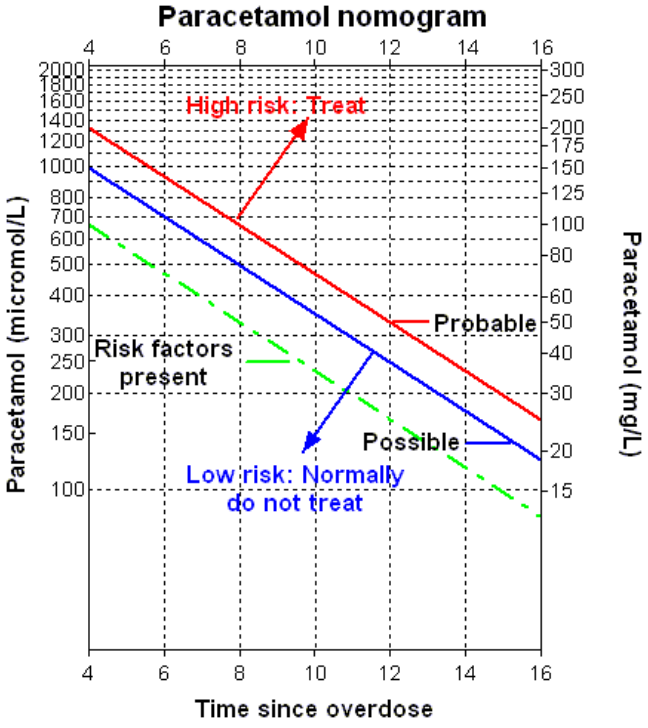


Figure 3: The Rumack-Matthew nomogram[21]

When the serum paracetamol level is below the Rumack-Matthew mark for possible hepatotoxicity, it is regarded safe to discharge the patient without any further treatment. In cases where the level of serum paracetamol is unknown and will not be known in 8 hours, it is advisable to treat all patients who have ingested more than 12g or 150mg/kg with N-acetylcysteine (NAC).[4] Measurements of serum aminotransferase levels can be used for guidance when paracetamol levels are not available and treatment provided for those showing elevated levels of AST and ALT.[4]

It has been advised to use a lower treatment threshold in the case of patients belonging to high risk groups, for example, involving chronic alcoholism, undernourishment, patients receiving medication inducing microsomal enzymes or with underlying hepatic-impaired function.[19,23] Intoxication is considered non-acute if ingestion is prolonged over more than 4 hours. In such cases the Rumack-Matthews nomogram becomes unsuitable.[4,19]

Use of activated charcoal

Activated charcoal is a safe and effective way of adsorbing drugs and chemicals in most toxic ingestions.[24] By inhibition of absorption, ingestion of charcoal is the most effective way of reducing gastrointestinal tract absorption of paracetamol though gastric lavage, and induced vomiting can also be used.[4] But concomitant administration of oral charcoal and *N*-acetylsysteine (NAC) is not recommended because of possible interaction as the charcoal can adsorb the NAC and reduce the antidote's ability.[24]

N-Acetylcysteine (NAC) treatment

NAC has been used for over 30 years as an antidote for paracetamol poisoning.[11] This treatment is considered to be the best way of reducing the risk of hepatotoxicity by detoxification.[2,4] NAC reduces toxic risk in two ways: first, by supplying additional sulfhydryl groups so that N-acetyl-p-amino-benzoquinoneimine (NAPQI) is neutralized and prohibited from damaging hepatic proteins.[11] Secondly the compound increases glutathione stores by deacetylation and thus enhances sulphate conjugation and acts as a glutathione substitute that binds to NAPQI[2], which adds further sulfhydryl.[11]

NAC treatment can prevent serious hepatotoxicity if administered within 8-10 hours after ingestion of a paracetamol overdose.[2,4] Results with NAC treatment are considered to be more uncertain after more than 15 hours from ingestion.[11] Reports have however shown that NAC given up to 24 hours or even later can be beneficial.[4] Intravenous treatment with NAC is preferable according to some reports as it has been shown to be more beneficial than oral treatment[2,15] since oral administration can cause nausea and vomiting.[4] The nausea can be reduced by administering anti-emetics.[15] However, it has been pointed out that no randomized trials have demonstrated the optimal way of administration.[4] A subsequent report recommended intravenous NAC especially in presentation within 12 hours from ingestion, but oral NAC treatment has been considered more favourable when presentation is late.[25] The NAC treatment duration is not clear, and it has been demonstrated with animal testing that the solution can delay recovery of the hepatocytes.[2] It is however recommended that the treatment be continued up to 72 hours, or until PT has fallen below 15 sec.

Patients receiving full NAC treatment within 4 hours of ingestion may be discharged when serum paracetamol levels fall below the treatment line of the Rumack-Matthew nomogram. Others may only be discharged when asymptomatic and liver tests and serum creatinine return to normal.[4] Patients suffering from coagulopathy need to be monitored more closely when creatinine levels are elevated.[4]

According to the standard guideline for treating patients suspected of paracetamol overdose presenting to the National University Hospital (NUH) of Iceland, the administration of intravenous NAC

(Mucomyst®) is advised when serum paracetamol exceeds the appropriate treatment line according to the Rumack-Matthew nomogram. Guidelines suggest that NAC is most effective during the first eight hours after ingestion and will protect the liver for up to 36 hours. When more than 10 hours have passed since ingestion of paracetamol, intravenous treatment exceeding 20 hours is recommended.[26]

Acute liver failure

Acute liver failure (ALF) is a multisystem disorder with coagulopathy, encephalopathy and sometimes acute renal failure, hypotension, sepsis, and cerebral oedema.[4] The causes of ALF are many, such as drugs, toxins, viral hepatitis, autoimmune hepatitis, vascular and metabolic diseases.[2]

The cause of ALF is the most important prognostic factor.[2] Patients with paracetamol-induced ALF have the best prognosis. ALF is defined as INR > 1.5 (corresponding to prolongation of PT >15 sec) due to liver injury in a patient with concomitant encephalopathy. When patients develop ALF, the need for ICU admission is determined by the mental status, coagulopathy as well as other complications of the liver failure, such as hypotension or acute renal failure.[2] Patients suffering from ALF need intensive care for frequent assessment as they can deteriorate rapidly and unpredictably.[15] The initial therapies consist mainly of intensive care support, and patients should have arterial and venous access for hemodynamic monitoring.[4]

Although paracetamol is the most common cause of ALF in the Western world, very few patients with paracetamol-induced hepatotoxicity need a liver transplant (LT). However, when patients develop ALF, the best long-term survival treatment is with a liver transplant.[4] The grade of hepatic encephalopathy is a good predictor of the chances of survival.[2] The most widely used and best validated[27] prognosis criteria for survival are the King's College criteria (KCC).[2,4]

Table 1: Kings College criteria for LT[28]

Paracetamol-induced ALF
• Arterial blood pH<7,30 (irrespective of encephalography grade)
or <u>all</u> of the following;
• Prothrombin time >100s (INR>6,5)
• Serum creatinine >300µmol/L
• Grade III or IV hepatic encephalopathy

The KCC are considered to be adequate for predicting the need for liver transplantation in patients with paracetamol-induced ALF,[2,29] (Table 1). The KCC have been found to have high positive predictive value for paracetamol-induced ALF but unfortunately exposed around 20% of patients to LT who might have survived without it.[27] Supplies of livers for transplant are scarce, and LT patients suffer long-term morbidity and mortality risk. The KCC are considered to have a short time frame for the paracetamol patients waiting for a suitable graft[29], resulting in many being unfit for operation at the time of resolution.[27] Because of this attempts have been made to add or modify some prognostic factors. Serum lactate is one of these factors and considered valuable in predicting transplant-free recovery in patients with paracetamol-induced ALF.[27] Subsequent studies have not confirmed the

increase in sensitivity, compared with the original KCC.[29] The number of patients in most of the studies that aimed at adding some prognostic factors has been deemed too low and therefore not suitable for generalization.[27]

Over 90% of all patients with paracetamol poisoning will survive, regardless of hepatotoxicity.[2] Even in cases where patients develop encephalopathy, the survival exceeds most other forms of ALF.[30] In a large retrospective cohort study from the Scottish Liver Transplantation Unit, patients with accidental overdose were at higher risk of mortality than patients with intentional paracetamol overdose. The accidental group had both lower serum paracetamol and ALT, and the authors recommend that these cases be treated as a high risk group because of their significantly higher risk of mortality.[31]

Factors contributing to prognosis of overdose/hepatotoxicity

Ethanol

The most featured underlying factors for increased and decreased hepatotoxicity is ethanol use (both chronic and acute), malnourishment or fasting and concomitant drugs. A genetic disorder resulting in decreased glutathione metabolic rate can also increase the risk of toxicity.[32] It has been of concern that alcohol-abusing individuals are at risk when consuming paracetamol in recommended daily dosage.[33,34] However, consumption of alcohol by chronic alcoholics has been found to be a significant protective factor, but only limited to the alcoholics.[35] In a study by Craig et. al, neither acute nor chronic alcohol consumption was found to be a predictor of poorer outcome after acute liver injury.[31] Contradicting this is the finding by Waring et. al that ethanol consumption at the time of acute ingestion of paracetamol lowers the risk of hepatotoxicity.[32]

Chronic alcoholics: Rumack addresses the question of the potentially increased effect of toxicity with concomitant ethanol use.[36] In a systematic review covering over 2000 cases, there seems to be only a few retrospective studies linking ethanol and toxicity, and there are no links between ethanol and paracetamol toxicity in any prospective study.[36] A 22% increase in the formation rate of the toxic metabolite has been reported in heavy drinkers.[36] The threshold for toxicity is still well over the recommended daily dosage (around 8g in a single dose).

Rumack draws the conclusion that chronic alcoholics are at more risk for overdose than non-heavy drinkers. Neither of these groups has elevated risk of toxicity when ingesting paracetamol in recommended daily doses.[36] Others have indicated that the main reason for increased risk of hepatotoxicity in chronic alcoholics is simply because of them having higher risk of exceeding the recommended dosages.[32]

It is conceivable that because of decreased hepatic glutathione, the production of the toxic metabolite of paracetamol might be enhanced in alcohol-abusing patients.[33] The results of a randomized prospective study did not support the theory that therapeutic doses of paracetamol cause severe liver injury in alcohol-abusing patients. The study covered paracetamol use in recommended daily doses (4g) by alcohol abusers with liver tests abnormalities but without severe liver failure.[33] Although there was a slight increase in ALT it was not considered a sign of hepatic synthetic

dysfunction. A subgroup with hepatitis C had a similar course of ALT increase, and administration of paracetamol to stable hepatitis C patients was considered possible for short periods.[33]

Acute overdose and ethanol consumption: A considerable proportion of the patients that overdose deliberately with paracetamol due to suicidal intent or self-harm has consumed ethanol simultaneously or around the same time.[32] Some studies have suggested that this kind of ethanol consumption can actually protect against the toxic effect leading to hepatotoxicity.[32] The mechanism thought to be behind this possible ethanol protection is its tendency to reduce cytochrome P450 function, thus minimizing production of toxic metabolites like NAPQI.[32] A lower proportion of patients consuming ethanol at the time of paracetamol overdose seemed to develop hepatotoxicity.[35] However, this happened only in patients chronically abusing alcohol, and the risk was unchanged in non-abusers. There were possible other important confounding factors; time to NAC was the most important one.[35] Results from other studies of paracetamol ingestion after ethanol intake have indicated that a slight increase in the ratio of paracetamol conversion to the toxic metabolite NAPQI occurs soon after the ethanol has been cleared from the body. Thus, social occasional drinkers consuming either recommended or supra-doses of paracetamol are thought to be at increased risk of hepatotoxicity.[37] However, few studies support this theory.

Ali et al. evaluated the risk of hepatotoxicity in acute overdoses by abstinent alcoholics. They used the peak serum paracetamol levels and time to NAC to estimate the risk with an earlier published logistic regression model from a Canadian Paracetamol Overdose Study.[23] They recommend that a threshold line at 660µmol/L (100µg/L) at 4h should be applied for the abstinent alcohol group instead of the usual 1000µmol/L (150µg/L) line which is recommended for the non-alcoholic group. The authors consider this to be only a platform for further studies to investigate whether abstinent alcoholics are actually at greater risk of hepatotoxicity.[23]

Nutrition

Data from the literature indicate that malnourished patients are at increased risk of toxicity.[36] The possible underlying mechanism could be that diets of individuals with eating disorders lack amino acids, resulting in deranged glutathion status.[38] Additionally, fasting affects hepatic glucose handling, causing reduction of non-toxic metabolism and thus increased NAPQI formation.[13] Results from a study of eleven anorexic patients and twelve controls pointed towards serum glutathione correlation with the individual body mass index.[38] It is worth mentioning that in this study, only cysteine was lower in the anorexic patients; all other amino acids did not differ between the groups. It is possible that the increased utilisation of glutathione requires the cysteine to form new supplies of glutathion, resulting in lower cysteine status in the malnourished patients.[38]

A study by Schenker et al. failed to show a connection between restriction of food intake by healthy but overweight individuals and paracetamol (2g) metabolism.[39] Another study suggests that recent fasting is a important factor for increased risk of toxicity when a dose of 4-10g (moderate overdose) of paracetamol was consumed within 24 hours.[40]

Chronic alcoholics are more likely to be recently fastening than non-alcoholics.[32,39] The primary cause of toxicity for them is thought to be decreased glutathion stores caused by ethanol use and, thus, increased toxic metabolism by the NAPQI pathway.[36,39] However, it has been suggested that when both CYP2E1 and glutathione decreases, the net result is no change in toxicity.[36] Patients with anorexia nervosa have been found to have 30% lower GSH levels than a control group[36], but simultaneous evaluation of CYP2E1 has never been done. The indications of reduced drug metabolism in malnourished individuals could explain why they seem not to have a higher risk of toxicity as production of the toxic reactive metabolite might also be reduced.[36]

Age

Age over 40 years is considered to be a risk factor for paracetamol-induced hepatic failure after overdose.[41] A study by Schmidt et al. concluded that not only was age itself an independent factor for severe outcome, but age was also associated with other risk factors like alcohol abuse, late arrival and higher incidences of benzodiazepine co-overdose.[41]

It has been recommended that paracetamol be administered to older and frail individuals in lower doses than the usual 4g per day.[42] Clearance of paracetamol, as well as aspirin and metoclopramide, seems to fall with age. The cause of the reduced clearance is assumed to be decreased activity of aspirin esterase and conjugative enzymes.[43] The aim of a recent study was to evaluate the impact of paracetamol on ageing and frailty in hospital patients. The authors concluded that although older and frailer patients had higher serum paracetamol concentrations than other hospitalized patients, they did not seem to be at higher risk for hepatotoxicity and could benefit from better pain relief from higher paracetamol dosage.[42]

Co-ingestion of other drugs

Simultaneous overdose of other drugs is found in a substantial number of paracetamol overdose cases. Documentation of interaction between concomitant drugs in overdoses is scarce. Some combinations are thought to be beneficial to the patient, and others are assumed to have the opposite effect.[44] Results from animal studies cannot be interpreted directly for humans, and it is thus difficult to make assumptions based on them as some effects have proven to be different in animals and humans.[44] The underlying cause of the pharmacokinetic interaction can be reduced paracetamol absorption, reduced conjugation, depletion of glutathione and inhibition of cytochrome-P450-mediated metabolism.[44]

Opiates: Codeine (hydrocodone) is classified as a weak opioid and commonly combined with paracetamol. This combination product is one of the most widely misused drugs and one of the most prescribed drugs in the USA.[45,46] Paracetamol combined with opioids, consumed by healthy adults in the recommended dosage of 4g pr day has not been found to increase serum ALT levels.[14] Although paracetamol in itself has no measurable psychotropic effects, the combination with codeine has some abuse- and liability-related subjective effects among recreational drug users.[45] Apart from hepatotoxicity,, overuse or abuse can be associated with rapidly progressive sensorineural hearing loss.[47]

Concomitant overdosing of opiates has been found to be an independent protective factor for hepatic encephalopathy (HE).[44] In supra-therapeutic dosage opiates have been thought to slow paracetamol absorption and thus have a protective effect.[48] However, in another prospective observational study the serum paracetamol concentration was measured over time in two groups, paracetamol overdose with and without opioid co-ingestion. No measureable difference was found between the groups, even when taking into consideration the stated dose and interval after ingestion.[32] These findings contradict the theory that opioid ingestion delays the absorption of paracetamol.

Benzodiazepines: Benzodiazepines are drugs frequently used for anxiety and bipolar disorders. Young adults on the club scene are among those most prone to misusing these drugs.[49] The interaction between benzodiazepine and paracetamol is not well documented. A Danish study found concomitant benzodiazepine overdose to be an independent risk factor for more severe outcome after co-ingestion with paracetamol.[44]

*NSAID*s: Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen and diclofenac, are widely used analgesics that can be purchased over the counter as well as with prescription. Although NSAIDs are well tolerated, there are some infrequent adverse effects, such as upper gastrointestinal bleeding and perforation, renal failure and heart failure.[50] In one study of concomitant NSAID and paracetamol, co-ingestion was linked with a tendency toward better outcome in these patients.[44]

Acetylsalicylic acid (ASA), better known as Aspirin®, is the most widely used salicylate. It has anti-inflammatory, antipyretic, antirheumatic and analgesic properties. Aspirin is also used in the prevention of ischemic stroke and cardiovascular diseases because of its antiplatelets effect.[46,51] The overdose symptoms can be variable and nonspecific.[52] Overdose of acetylsalicylic acid ingested with paracetamol has been found to be associated with markedly severe outcome like coma and death, even when paracetamol doses were lower, and other factors should have pointed towards reduced hepatotoxicity.[44] The increased mortality seems not to be related to hepatotoxicity, but rather increased ASA toxicity and severe acidosis.[44]

Genetic factors

Inter-individual difference in paracetamol-induced hepatotoxicity is partly explained by impaired DNA repair and apoptosis. Due to the lack of correlation of human and animal data, little is known about this.[13] Furthermore, human traits probably consist of more than 20 genetic changes through the genome so that a single genetic change is only representative in a small proportion of the trait. To manifest a genetic susceptibility to drug toxicity, more than 100 individuals with the same adverse effect would be needed.[53]

Acute versus chronic overdose

There are primarily two types of clinical syndromes associated with paracetamol overdose. The former is the acute overdose group where patients ingest large doses of paracetamol with suicidal or para-suicidal intent.[54] The latter group consists of patients consuming paracetamol over time, either in recommended dosages or exceeding the daily recommended dosage. Some individuals can be chronic paracetamol users for weeks or months without any problems. It is assumed that when these individuals develop symptoms from an overdose, it is caused by other underlying factors like fasting or illness.[32] These patients that accidentally overdose are more likely to abuse alcohol and have greater organ dysfunction and higher mortality.[31]

In a Canadian population-based study the acute intentional overdose group accounted for 69% and the accidental group for 25% of all paracetamol overdose-related visits to an emergency department.[55] Another related population-based study revealed that the intentional group accounted for 85% of all paracetamol overdose cases requiring hospitalization.[56] In many cases it is difficult to classify the overdose as either intentional or unintentional. The stigma associated with suicide attempts or deliberate self-harm can result in designating such cases as accidental overdoses.[57]

Intentional acute overdose: Paracetamol is the most common drug used by adolescents and young adults in many countries for first-time self-poisoning episodes.[41,58] Intentional overdose is often classified into subgroups; deliberate self-harm, medically serious suicide attempt or non-fatal drug overdose. This classification is problematic as the evaluation of intention can be unreliable.[56,59] Some patients are comatose at the time of hospitalization, and others might not want to admit the true reason for overdosing although most individuals do admit their misdeed[7], and/or the determination to die can vary over time.[59] A comparison between self-poison groups, one classified as suicidal and another as appeal-seeking patients revealed that the only significant difference was the percentage of females were higher in the appeal-seeking group.[59]

There are some characteristic differences between the intentional suicidal overdose and the accidental type. The intentional patients tend to be younger[17,54], present sooner to hospital and have higher serum paracetamol levels.[31,54]

Accidental overdoses, or therapeutic misadventures, are often caused by patients ingesting more than one drug containing paracetamol and, thus, accidentally exceeding the recommended daily dosage.[19] In such cases underlying pain is usually being treated.[7] These patients do not realise that something injurious has happened and only notice that they have become ill for an unknown reason.[7] Accidental overdose can likewise occur although the patient has followed the recommended dosage. Potential risk factors for overdose are: chronic alcohol use, malnutrition and induced cytochrome P450 enzymes.

A study by the ALF Study Group revealed that approximately one third of the accidental overdose patients consumed more than one narcotic-paracetamol drug or did not suspect that they had consumed additional paracetamol in combination with the narcotic substance.[7,60] This is likely to happen as the description of the contents on packages can be inconsistent, and in some cases abbreviations are used for paracetamol, like APAP.[19] In a UK study the majority (56%) of accidental

overdoses were due to a combination product of codeine and paracetamol.[31] The patients in the accidental group are considered to be a vulnerable interesting group that overdoses on narcotic-paracetamol compounds to relieve pain, and as they become addicted, they increase the doseage.[7] At presentation these patients tend to have more serious encephalopathy although the peak encephalopathy grade during hospitalization did not differ from the other group.[1] It is probable that gradual increase in paracetamol consuption can result in adaption to or protection from the toxic effect.[60] It has been suggested that over time patients increasing the doses build up tolerance to toxicity[7] and, at some point, experience a sudden breakthrough resulting in acute liver injury.[30]

In a study by the Acute Liver Failure Study Group of patients in 22 selected tertiary care centres in the US, the proportion of accidental paracetamol overdoses was 48% of the total cases of ALF patients, compared with 44% of intentional overdoses.[1] The outcome for the accidental group is worse than for the intentional overdose group although peak serum paracetamol levels are higher in the latter group.[31,54,61] Delayed presentation, older age and alcohol consumption can be confounding factors for increased risk of morbidity and mortality.[31]

Availability in Iceland

Availability of paracetamol is considered to be the key factor of widespread use in self-poisoning. In a UK study 48% of self-poisoned patients stated that the drug was purchased especially for the purpose of poisoning. The remaining 52% of the patients already had the paracetamol at their disposal.[62] Nearly half the patients ingesting more than double the recommended dosage of paracetamol acknowledged that they managed to buy the tablets although the purchase exceeded the maximum sales limit.[62]

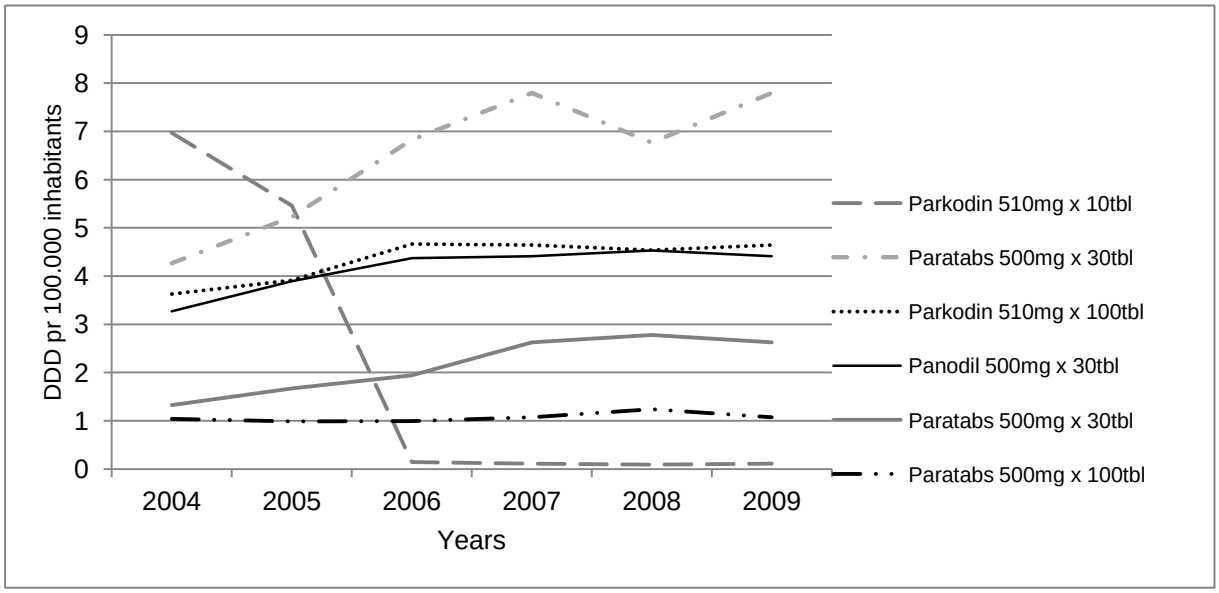


Figure 4: Wholesale of paracetamol-containing drugs in Iceland

To counter this problem some measures have been taken to reduce the availability. In 1998 sales restrictions were implemented in the UK.[62] The quantity allowed for purchase as OTC medicine both in pharmacies and supermarkets was restricted.[58,60] In addition, it was compulsory to deliver paracetamol in blister packs to reduce impulsive self-poisoning.[60] However, these restrictions have not reduced the paracetamol overdoses in Scotland.[63] In the US neither of these actions has been enacted, but instead packet labelling requirements have been tightened.[60] To reduce the risk of paracetamol-induced hepatotoxicity, last January the U.S. Food and Drug Administration asked drug manufacturers to limit the dose of paracetamol to 325mg per tablet in paracetamol-opioids compounds.[64] In a recent study an attempt was made to utilize several databases and estimate the result of an educational campaign aimed at informing the public of the safe use of OTC drugs. The conclusion of the study was that the promotion campaign had not reduced the overdose rate, for either intentional or unintentional cases.[57]

In Iceland paracetamol is available as an OTC drug in pharmacies. Wholesale turnover of paracetamol products increased by 17% in DDD*1000^{-1} from 2004 to 2009[65,66], see Figure 4. On 1 October 2005 the paracetamol combination product Parkodin, containing paracetamol 500mg and codeine 10mg, became available only as a prescription drug. Other changes in availability or regulation of paracetamol were not made over the period. The total number of pharmacy outlets has been almost stable since 2005 and the mean opening hours largely unchanged.[67]

The background of the current study

Most data on paracetamol toxicity originate from liver transplant centres and tertiary referral institutions. The proportion of patients with paracetamol overdose who develop liver injury in a population-based sample is largely unexplored. Population-based studies from Canada[55,56] have been published, but they were only aimed at the incidence and temporal variations of the paracetamol overdose frequency. However, one study from the US[68] was aimed at the outcome of paracetamol overdoses and the severity of liver injury as well as the incidence. No study was found in similar populations with as restricted paracetamol sales as Iceland's. A large number of visits to the NUH Emergency Room result from drug overdose, especially for young females.[69] This is a significant public health concern and burden on the health care system.

A prospective study of acute poisoning was undertaken in Iceland from 2001 to 2002, but intoxication with paracetamol was not a particular focus of the study.[69] In the study paracetamol was involved in 19% of all drug-related poisonings, and 80% of all poisonings were caused by non-opiate analgesics.[69] However, no detailed analysis was undertaken of the severity of toxicity and outcome of patients suffering from paracetamol overdose. No exact information on the nature of toxicity, such as deliberate vs. accidental toxicity, was presented in the study results.

The aims of the study

The overall aim of this retrospective study was to describe the proportion and annual incidence of paracetamol overdoses in the population of the NUH catchment area, as well as the association of risk factors and outcome of the paracetamol overdoses.

The specific aims were as follows:

Paper I

- Of all overdose cases presenting to the NUH in 2004 and 2009, estimate the proportion involving paracetamol.
- Estimate the annual incidence of paracetamol overdoses in the NUH catchment area. The annual incidence of interest was a) for all paracetamol incidences and b) for those patients with no former history of paracetamol overdose.
- Estimate the possible trend in the population-based annual incidence over time.

Paper II

- Analyze characteristics of all overdose patients presenting to the NUH and the risk factors of hepatotoxicity. These factors for more severe hepatotoxicity were: dosage of paracetamol, co-ingestion of other drugs, intentional vs. accidental overdosing and acute and chronic alcohol consumption.
- The secondary aims in Paper II were to evaluate the outcome after paracetamol overdose and the proportion of overdose cases resulting in acute liver failure in unselected patients presenting to the NUH hospital with paracetamol overdose.

METHODS

Study design and population

This was a descriptive and retrospective population-based study covering all patients presenting to the Icelandic National University Hospital (NUH) during the years 2004 to 2009. The study cases consisted of all patients who presented as instances of overdose or liver injury, as identified by the computerized hospital database LEGA, to the NUH Emergency Room or were hospitalized between 1 January 2004 and 31 December 2009.

In Paper I the source population was confined to all residents living in the NUH catchment area between 2004 and 2009. Therefore, all overdose cases were also restricted to residents of the catchment area. The mean population of the NUH catchment area over the six years was 219,249[70] residents. See Appendix 1 for details on mid-year population figures for each separate year covering the greater Reykjavik capital area and the South and Southwest region of Iceland.

The study population in Paper II consisted of all patients over the age of nine that presented to or were hospitalized at the NUH and fitted the search criteria, regardless of residence at the time of overdose.

Table 2: Clinical data variables

Clinical data collected:	Normal values
AST	<50 IU/L
ALT	<50 IU/L
Bilirubin	5-25 µmol/L
Amylase	25-120 µmol/L
Creatinine	60-100 µmol/L
Prothrombin time (PT)	12 -15 sec
Serum paracetamol	< 66 µmol/L
Serum ethanol	< 2.2 mm/L

AST: Aspartate transaminase, ALT: Alanine aminotransferase, IU/L: international units per litre, µmol/L: micromoles per litre, mm/L: millimol per litre.

Data collection and study measures

The computerized hospital database LEGA was used to retrieve cases matching the ICD-10 codes[71]; T50.9, T39, K71, K72, X60 – X64 & F19.1. (see Appendix 2). For each case in the LEGA database matching one or more of the ICD codes, the following information from their patient records in the Saga database were extracted: patient's initials, personal identification number, date of birth and date of admittance to the hospital. Further details on drugs ingested and acute alcohol consumption were also retrieved. Cases with matching ICD-10 codes, but not originating from overdose with drugs, were excluded (n=227), as were cases with missing information due to restricted access to psychiatric records or due to an unknown reason (n=246). Some cases had double entries as they were filed both as patients visits to the ER and as hospitalized incidences (n=185). Those cases were only entered once.

When reported paracetamol ingestion exceeded the recommended daily dose of 4g or the serum paracetamol was elevated above 66µmol/L, additional data were collected. For these patients data were collected for only the first presentation, i.e., the index visit. These additional data covered information on whether the overdose was intentional or accidental, the total dose of paracetamol digested and identification of other co-ingested drugs or substances. Further information regarding

reported histories of chronic alcohol consumption, psychiatric problems and drug abuse was collected. When patients had reports of previous or later overdoses, instances due to paracetamol or other drugs and substances were identified. Patients' medical records were reviewed regarding former or later visits to the NUH, to minimize the likelihood of missing vital information.

From the same Saga hospital registry clinical laboratory data were collected for serum paracetamol, serum ethanol, liver enzymes (AST and ALT), Bilirubin, Amylase, Creatinine and prothrombin time. In some instances when incidences originated in 2004 and the first six months of 2005, it was nessesary to retrieve clinical values directly from the NUH laboratory computers. Normal clinical values are shown in Table 2. Information was as well collected regarding; N-acetylcysteine therapy (NAC), transferrals, length of stay at the intensive care unit (ICU), discharge home or to other institutions. In all the cases of mortality the date and possible cause of death were registered.

Definition of study measures

Paper I

Annual Incidence was calculated as the number of paracetamol overdose cases/mid-year population x 100,000 separetely for each year in the study period, both as sex-specific and age-specific incidence and for the total patients. The annual incidence for first timers was calculated for new cases only. The population geographic area was defined as the greater Reykjavik capital area and the South and Southwest region of Iceland. The population mid-year numbers were retrieved from the Statistics Iceland website.[70]

- Personal identification number (includes date of birth) and date of presentation to the NUH.
- *Drugs digested in overdose:* Drugs digested in overdose cases as reported in patient records. Single co-ingested drugs were divided into groups by their ATC code[72], see Appendix 3. Concomitant drugs were the first four ingested drugs mentioned in the patient records in the overdose cases. One group was assigned for all combined ingestions when two or more drug groups were involved. The group "Other various ATC groups" was used in cases where single doses of more uncommon overdose drugs were ingested, like cardiovascular drugs, antihistamine and anti-infectives.
- *First timers:* Patients with no history of previous paracetamol overdose in the patient registry.

Paper II

- *Paracetamol overdose*: Paracetamol ingestion exceeding the recommended daily dosage of 4g over 24 hours or serum paracetamol levels greater than 66µmol/L.
- *Intentional overdose*: When patients were aware of exceeding the recommended daily dosage of paracetamol and/or intended self-harm. The overdose was registered as *accidental* when patients did not realize they were exceeding the recommended limits, and the ingestion was for a purely therapeutic reason.
- *Co-ingestion*: Other drugs were co-ingested along with paracetamol in an overdose. The drugs were classified by the ATC coding system.

- *Acute alcohol consumption*: Alcohol consumption reported at the time of overdose or serum ethanol above 2.2 mm/L.
- *Chronic alcohol problem*: Any report of patients having a history of alcoholic abuse over time. No distinction was made between those who had ceased consuming alcohol and those who had not.
- *Psychiatric problems*: Any report of patient having sought help for depression or another psychiatric problem.
- *History of previous or later overdose*: Any remark and the date of earlier or later overdose in the hospital registry. To be labelled as a paracetamol overdose, the same criteria were used as at the index visit (see first variable definition of Paper II).
- *Chronic paracetamol use:* Defined as ingestion of > 4g of paracetamol in repeated ingestions during a period exceeding 24 hours.
- *Liver tests:* Defined as not normal when either one or both AST or ALT exceeded 50 IU/L.
- *Hepatic injury:* Defined as when the AST level was between 50 and 1000 IU/L.
- *Severe hepatotoxicity:* Defined as peak ALT >1000 IU/L.

Other causes in flow chart (Figure 5) are explained by the causal agent of the ICD-10 coding having aetiology not related to drug overdose, including: cancer, cirrhosis, renal failure, viral hepatitis, poisoning by other than drug-related substances and ER visits made with the purpose of trying to obtain drugs due to addiction.

The primary outcome in Paper I was the annual population-based incidence of all drug-related and paracetamol overdoses. In these cases recurring incidences for each patient were allowed. Secondary outcome was the annual population-based incidence of patients with no history of former paracetamol overdose. The annual incidence was calculated per 100,000 inhabitants.

In Paper II the primary outcome was a description of the demography, clinical values and risk factors of unselected patients presenting to NUH with paracetamol overdose and related liver injury. The second outcome, but not the least, was the proportion of cases developing ALF and the outcome of those cases.

Data analysis

In Paper I Microsoft Excel was used to calculate incidences and proportions. The crude incidence was transformed to annual incidence per 100,000 inhabitants. For this purpose the sex-specific midyear population numbers by community were retrieved and calculated from the Statistics Iceland database[70] and can be seen in Appendix 1.

Descriptive statistics were used to present demographic data. The significance tests for time trend over the six years was Chi square test (Linear-by-linear) The data for the trend analysis were weighted by cases and calculated with IBM SPSS statistics 19 (SPSS).

In Paper II all data statistics were computed with SPSS. Demographical, and clinical values are presented as medians and inter-quartile ranges (IQR) or percentages unless otherwise stated. Descriptive statistical methods were applied in description of this data.

Frequency tables were used to present categorical data. Difference between categories and significance tests were compared with cross tables and Chi square or Fischer exact test. In the cases of continuous data the Mann Witney test of significance was used. Level of significance was set at 0.05 in both Paper I and Paper II.

Ethics

The study protocol was approved by the NUH Ethics Committee (63/2009) and the Icelandic Data Protection Authority (2009121155AT/-).

RESULTS

Study Population

A total of 2571 cases were retrieved from the computerized hospital database when searched for the specific diagnostic ICD-10 codes. Of those 1913 were visits to the NUH from 1 January 2004 to 31 December 2009 that were identified as drug intoxication fitting our ICD-10 coding criteria.

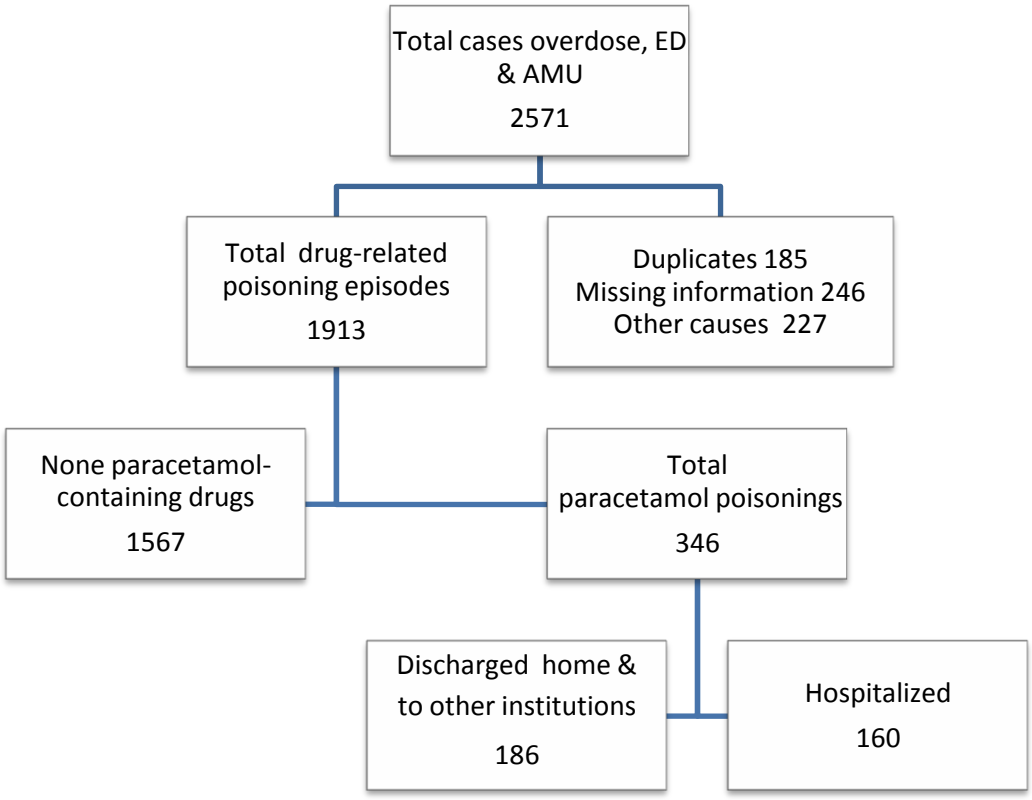


Figure 5: Flow chart explaining how cases were collected from hospital records.

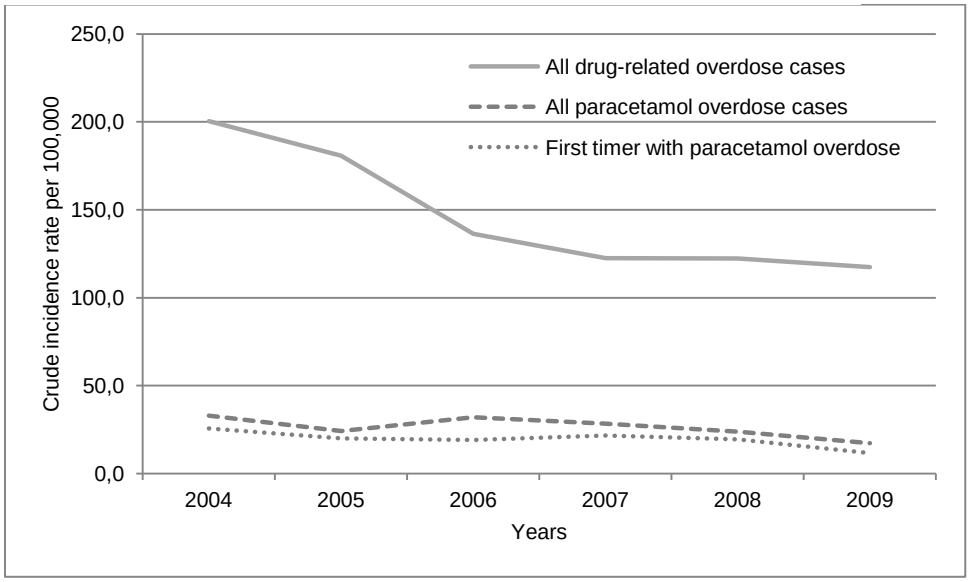
The 1913 drug-related visits were made by 1376 individuals (not shown). The 346 visits due to paracetamol overdose were made by 295 individuals (not shown). Among these 295 patients, 5 cases were by children under the age of ten.

Paper I

All drug-related overdoses: Incidence and temporal variations

The total number of visits due to drug-related overdose was 1913. The mean annual crude incidence from 2004 to 2009 was 145.4 per 100,000 inhabitants. This annual incidence of all drug-related overdoses in the NUH catchment area declined over the six years, from 200.5 to 117.3 per 100,000 inhabitants, see Table *3*. The sharpest decline of the incidence was between the 2005 and 2006. The trend test revealed that the decline of overdoses was significant compared to the population changes (χ^2=76.85, (p<0.001)).

Figure 6: Crude annual population incidence for all paracetamol and all drug-related overdoses.



The total visits due to paracetamol poisoning were 346/1913 (18%) of all cases due to drug-related poisonings. The median proportion of paracetamol over the six year was 18.4% in all. When tested for trend analysis, the proportion of all paracetamol overdoses did not decline significantly differently than all drug-related overdoses (χ^2=1.035, (ns)).

Table 3: Annual crude incidence per 100,000 population

Year	All overdoses	All paracetamol overdoses	First timers with paracetamol overdose
2004	200.5	32.8	25.6
2005	180.8	24.3	20.0
2006	136.3	32.0	19.0
2007	122.4	28.5	21.7
2008	122.4	23.9	19.5
2009	117.3	17.3	11.7

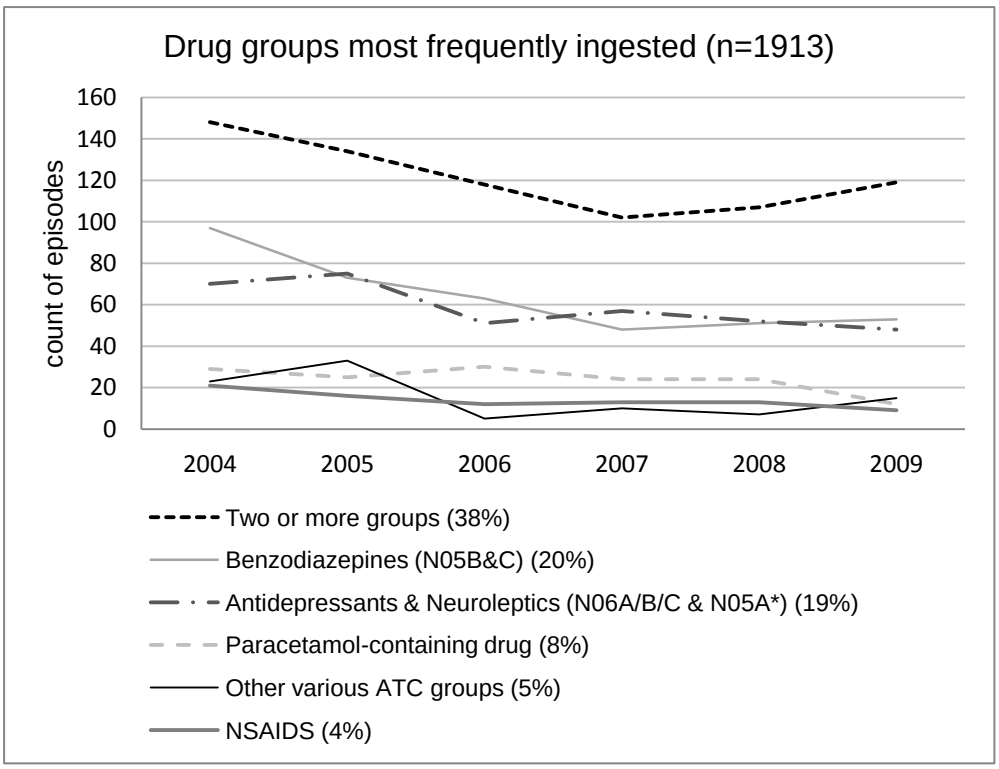


Figure 7: Drug groups most frequently ingested.
*N05A except N05A N01 (% of 6 years total drug poisoning).

The frequency of the six drug groups most frequently consumed can be seen in Figure 7. Illegal substance use without co-ingestion of drugs accounted for 4% of the overdose cases,. Concomitant acute ethanol use was reported in 21% (397/1913) of the cases. Overdose cases of opioids other than those combined with paracetamol accounted for 3% of the cases (not shown).

All paracetamol overdoses: Population-based annual incidence

Over the six years 346 cases presented to NUH, making the annual incidence per 100,000 inhabitants 32.8 in 2004, which fell to 17.3 in 2009 (see Table 3). The mean annual crude incidence was 26.3 per 100,000. Females made the most visits (255/346 (74%))(Table 4). The mean sex-specific annual incidence for all visits involving paracetamol overdose was 36.4 for females and 12.4 for males per 100,000 inhabitants.

Table 4: Sex-specific incidence from 2004 to 2009

	Female n=255		Male n=91		*p*-value
Age (mean ±SD)	30 ± 15.0		36 ± 15.6		<0.001
median (IQR)	25 (19 - 41)		33 (23 - 48)		
Year	n	Incidence *	n	Incidence *	
2004	46	44.6	22	21.2	
2005	38	36.3	13	12.3	
2006	53	49.6	16	14.7	
2007	52	47.7	11	9.8	
2008	36	31.0	19	16.1	
2009	30	26.4	10	8.5	

*per 100,000

The largest age group was 16-25 years with 40% (139/346) of the total cases. Females constituted the majority of the visits in this age group, 81% (113/139). The mean sex-specific annual incidence in this age group was 113.2 for females and 25.4 for males per 100,000 inhabitants. The F/M ratio was 86/23 or 3.7:1. The second largest age group was 26-35 years, or 18% (63/346), Figure 8. The F/M ratio in this group was 42/21 (2:1).

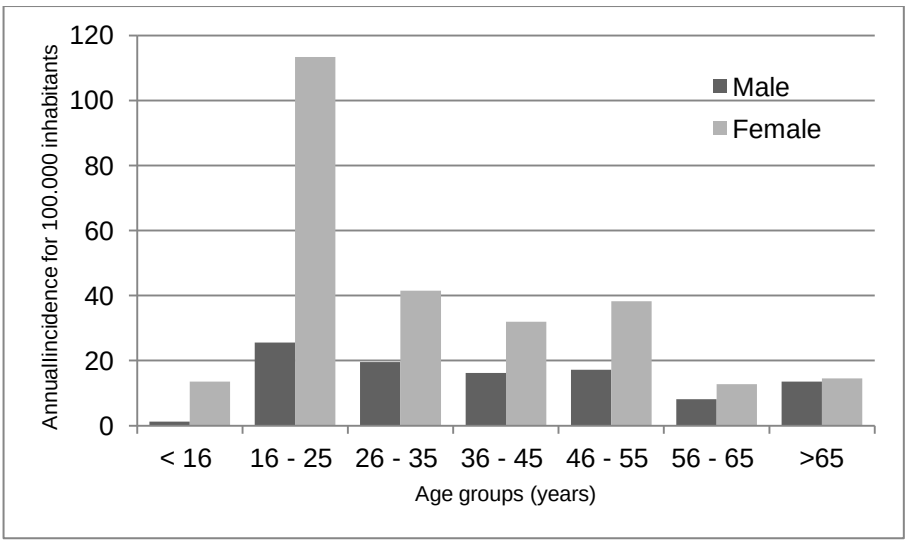


Figure 8: The annual age- and sex-specific incidence of all paracetamol overdoses

First timers

Of the paracetamol overdose visits 256/346 cases were by first timers (74%), i.e., patients with no history of former paracetamol overdoses. The crude annual incidence of the first-time paracetamol overdoses was 19.5 per 100,000. The annual incidence of the first timers, compared to the population, decreased from 25.6 to 11.7 per 100,000 between 2004 and 2009. (χ^2=7.6, p<0.01), Figure 9. The proportion of females in the group was 72% (184/256). The annual incidence for paracetamol overdoses was higher among females than males, 28.3 (± std 7.0) (females), compared with males 10.8 (± std 4.3) per 100,000 inhabitants (p<0.005).

When patients with first-time paracetamol overdose were divided into age groups, the largest one was for those aged 16-25, 96/256 (38%), with 78% females. The annual incidence in the 16-25 year age group was 75.1 for females and 20.5 males per 100,000 inhabitants.

Eighty-nine percent (227/256) of the group overdosed intentionally due to self-harm or drug abuse. Thirty-three percent of first timers ingested paracetamol only (non-mixed intoxication), compared with 42% of the patients with a history of former intoxication, but the difference was not significant.

There was no difference in history of psychiatric problems for the patients that overdosed for the first time and those having repeated incidences of paracetamol overdoses (data not shown). There was no difference in hospitalization for those with no former history of overdose with paracetamol and those with such a history, 73% vs. 71% (ns).

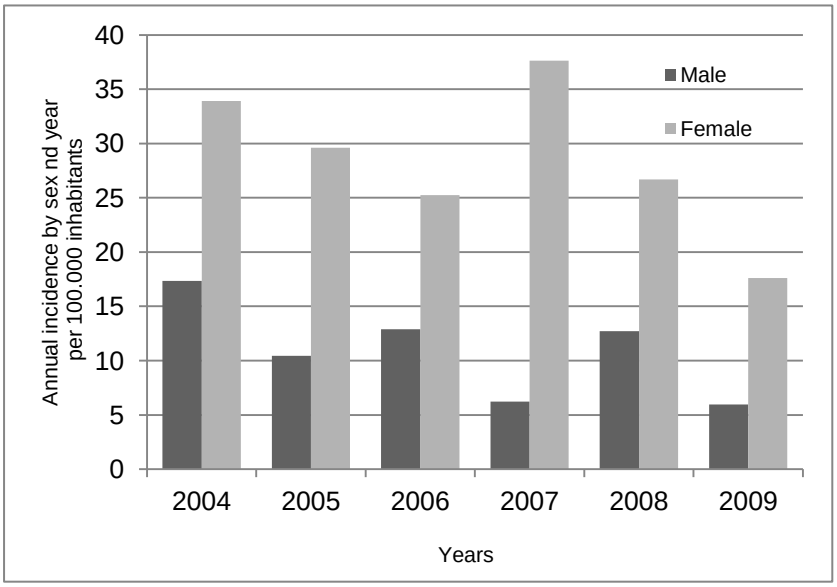


Figure 9: Annual Incidence of patients with no former paracetamol overdose (first timers).

Paper II

Paracetamol overdoses: Demography and characteristics

Over the six-year period there were 290 index visits to the NUH by patients above the age of nine. Patients with more than one visit due to paracetamol overdose were only entered in the study once in Paper II (on the first occasion). Females accounted for 73% (211/290) of the patients, compared with males being 27% of the total group; thus, the F/M ratio was 2.7:1. The median age of all index visits was 26 years (IQR 19-42). The largest age group was between 16 and 25 years of age (38%), and 79% (86/109) were females. The proportion of females in this age group was 41% of all female patients with paracetamol overdoses, compared to 29% of all males. The second largest age group was between 26 and 35 years of age, with 21% (60/290) of all patients.

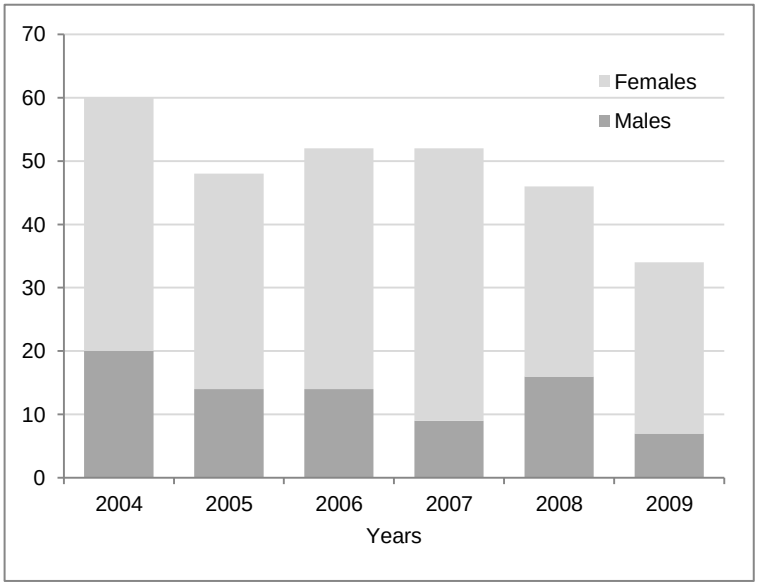


Figure 10: Admitted paracetamol index visits

Table 5: Characteristics of all NUH paracetamol overdose patients 2004 to 2009

	Male n=80	Female n=212	*p* value
Age, mean (SD)	36 (14)	30 (15)	<0.005*
Intentional overdose	67 (87)	198 (95)	<0.05**
Concomitant drug ingestion	49 (64)	135 (66)	ns**
Acute ethanol ingestion	33 (44)	82 (40)	ns**
Chronic alcohol abuse	35 (47)	44 (22)	<0.001**
Previous psychiatric problem	45 (58)	128 (64)	ns**
NAC treatment	44 (61)	116 (58)	ns**
Admitted to ICU	12 (15)	20 (10)	ns**
Discharged to psychiatric dept.	23 (30)	34 (17)	<0.02**
Discharged from ER directly home	18 (23)	54 (26)	ns**

SD: standard deviation, ICU: intensive care unit, ns: not significant, ER: emergency room
Significance test by; *Mann-Whitney **Chi square,

N-acetylcysteine was administered in 59% of the total cases. Acute ethanol consumption was observed in 41% (115/280) of the total cohort and was more common in patients reporting a history of alcohol abuse 49/74 (66%) (χ^2=33.3; p<0.001).

The proportion of accidental toxicity was 7% (20/285) and was significantly higher among males (13% vs. 5%, $p<0.05$). Multiple drug ingestion was found in 66% (184/281) of the cases. A significantly higher proportion of the males had a history of chronic alcohol abuse (Table 5).

No gender difference was found regarding a history of former paracetamol poisoning: 6% females and 4% males (ns). Twenty-nine percent of the study population (80/278) had repeated visits due to self-poisoning with some drug within the six years. In the case of re-admittance with an overdose with some drug, the proportion of females was also higher, 32% females vs. 21% males ($p=0.06$). Recurrent incidences caused by paracetamol poisoning after the index visit occurred in 29/276 of the patients (11%). The greatest number of visits by a single patient with paracetamol overdose was 18 over the six years. Almost 93% of the patients had only one visit due to paracetamol overdose, 5% had two visits, 1% made three visits. Females were slightly more prone to repeated paracetamol overdoses (13% vs. 5%, $p=0.07$).

Twenty-two percent were transferred to an acute medial ward, and 11% had to be transferred to the ICU. Six percent were admitted to a psychiatric ward directly after the ER examination (significantly more males than females). Sixteen percent of the patients did not receive any psychiatric assistance after the overdose. Overall, 25% (72/288) of the patients were discharged directly home after initial examination at the emergency room.

Doses of paracetamol ingested

The reported doses of ingested paracetamol by patients ten years and older was available in 216/290 (74.5%) cases. In fourteen cases (4.8%) the dose could not be predicted due to the nature of chronic paracetamol use and in 20.7% of the cases the dosage was unknown. The range of reported ingested paracetamol was 1-50g. The mean paracetamol ingestion was 14.0g (male) and female 12.3g (ns). Approximately 57% of the patients (124/216) with known dosages digested 4-12g of paracetamol. The maximum serum paracetamol in this group was 1789 µmol/L (median 219, IQR 105-434). Abnormal liver tests in this rage (4 – 12g) were observed in 9/126 cases (8%).

Table 6: Paracetamol dosage and liver tests.

Dosage (g)	N=290 n	Peak serum paracetamol† median (mean±SD)		Normal liver tests* n	(%)	Elevated liver tests** n	(%)
<4	9	109.5	182 ±159	9	(3.1)	0	(0.0)
4-7.9	63	211.0	238 ±155	58	(20.0)	5	(1.7)
8-11.9	52	304.5	390 ±362	48	(16.6)	4	(1.5)
12-15.9	44	347.0	493 ±375	36	(12.4)	8	(2.8)
16-19.9	7	387.0	452 ±313	6	(2.1)	1	(0.3)
20-23.9	13	280.0	732 ±980	10	(3.4)	3	(1.0)
24-27.9	12	519.5	662 ±561	10	(3.4)	2	(0.7)
>28	16	513.0	995 ±953	10	(3.4)	6	(2.1)
Chronic use	14	168	203 ±168	4	(1.4)	10	(3.5)
Unknown	60	223	354 ±368	51	(17.6)	9	(3.1)

† µmol/L, *Both AST and ALT < 50IU/L, ** AST and/or ALT > 50 IU/L

When tested for serum paracetamol, the mean level was 495 µmol/L for females, (median 336; IQR 198-610) and 394 µmol/L for males (median 237; IQR 145-427), ($p<0.05$).

Concomitant intoxication

In 66% (184/290) of the cases, co-ingestion of other drugs was reported, but there was no gender difference. Acute alcohol consumption along with intoxication accounted for 41% (115/280) of the cases, and there was again no gender difference.

The most frequent drug group was opioids analgesics, nearly 20% of the co-ingested drugs. Seventy-two percent of the opioid analgesic cases were due solely to the prescription of Parkodin Forte, a combination drug of paracetamol and codeine. Other dominating drug groups were Benzodiazepines, Non-steroid anti-inflammatory drugs and antidepressants, (Table 7). Illegal substances were present in 12/284 cases (4%) and were significantly more common in males than females, 10% vs. 2%, (p<0.005). The proportion of patients with elevated liver tests that did not have concomitant intoxication was 56% (24/43). In the case of normal liver enzymes, the proportion of no co-ingestion was 31% vs (73/248), (χ^2=10.2, p<0.001).

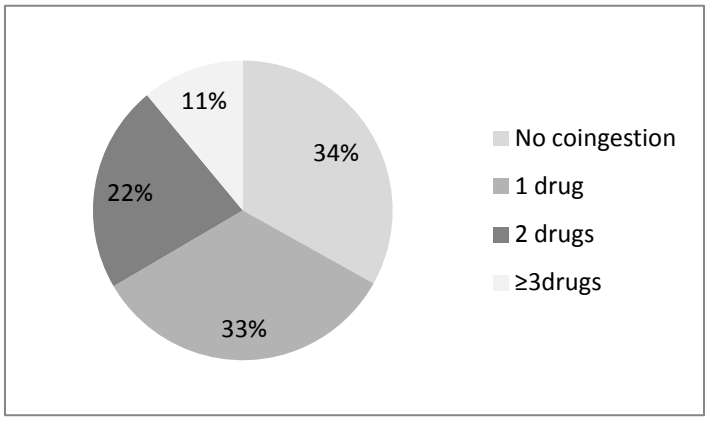


Figure 11: Number of co-ingested drugs with paracetamol

Table 7: Most frequent drug groups with ATC code in concomitant ingestion with paracetamol

Opioid Analgesics	N02A	19.4%
Benzodiazepines	N05B & C	18.4%
NSAIDS	M01A	18.2%
Antidepressants	N06A	13.7%
Cardiovascular drugs	C	4.5%
Neuroleptics	N05A	4.0%
Acetylsalicylic acid	N02B A	3.8%
Antihistamines	R06	3.5%
Antiepileptics	N03	2.4%
Gastrointestinal	A	2.1%
Psychostimulants	N06A	1.9%

Intentional versus accidental overdoses

The patients with intentional overdose were 93% (265/290) of the total group of paracetamol overdoses. Thus, accidental overdoses occurred in 7% of the cases (20/290). In five cases (1.7%) it was not possible to assess from the medical records whether the overdose was intentional or not. Among the reported explanations for misadventure in the accidental group were relief of pain in: arms and feet, migraine, and toothache three times. The group characteristics are presented in Table 8.

Table 8: Characteristics of patients with intentional vs. accidental overdose.

	Intentional n=265 (100%)		*Accidental n=20 (100%)*		p-*value*
Sex F/M	198/67	(95/87)	10/10	(5/13)	<0.05**
Age, years, mean/median (IQR)†	30/26	(18-40)†	44/41	(27-60)†	0.001 *
NAC therapy	144	(58)	12	(63)	ns**
Multiple ingestion	177	(68)	6	(32)	0.001**
Chronic alcohol abuse	68	(27)	7	(37)	ns**
Concurrent alcohol consumption	108	(42)	6	(30)	ns**
Intensive care	30	(11)	1	(5)	ns**
History of former intoxication	86	(34)	0	(0)	0.001**
History of psychiatric problems	162	(64)	7	(39)	<0.05**

*F/M:female/male, ns: not significant, Significance test by; *Mann-Whitney **Chi square*

Accidental overdose patients tended more often to be older males, who were less prone to multiple drug intoxication and less likely to have history of psychiatric problems (Table 8) at the time of the index visit. Only one patient with accidental overdose had a history of recurrent poisoning, which was also by paracetamol ingestion. None had a history of former poisoning in the hospital records.

Table 9: Clinical values in intentional and accidental overdose

	Intentional		Accidental		*p*-value
	mean	(median;IQR)	mean	(median;IQR)	
Peak s#. paracetamol, µmol/L	433	(275:125-536)	198	(139:65-265)	<0.05*
Peak AST, IU/L	306	(25:20-34)	1383	(48:29-754)	<0.005*
Peak ALT, IU/L	224	(26:20-35)	1262	(48:40-534)	0.001*
Peak Bilirubin	54	(7:4-12)	84	(35:10-66)	<0.005*
Peak PT, seconds	16	(14:13-16)	18	(16:14-22)	ns*
Serum ethanol, mm/L	33	(31:21-42)	36	(39:15-55)	ns*

*s#:serum, ns: not significant, Significance test by; *Mann-Whitney*

Liver enzymes values were significantly higher in those with accidental poisoning although peak serum paracetamol was lower than in the intentional group, Table 9. The proportion of the patients needing intensive care was 30/263 (11%) of intentional cases vs. only 1/20 patients (5%) in the accidental cases (ns) even though the liver enzymes, AST and ALT, were more unfavourable in the latter group.

Clinical values in alcohol versus non-alcohol group

Acute alcohol consumption was reported in 115/280 (41%) cases at the time of paracetamol ingestion. There was no gender difference between the groups concerning acute alcohol consumption while overdosing, Table 5. Patients with chronic alcohol abuse were more likely to have consumed ethanol with paracetamol, 66% vs. 28% (p<0.001).

In 55% (159/290) of the cases serum ethanol levels were measured. Serum ethanol values above 2.2 mm/L were measured in 93/290 instances (32%). The maximum serum ethanol level was 84mm/L (median 32, IQR 19-42). The only clinical values that tested significantly differently were the peak creatinine levels (see Table 10).

Table 10: Clinical variables seen in no alcohol vs. acute alcohol groups

	No alcohol consumption	Acute alcohol consumption	*p*-value
Age (years)			
Mean ± SD	29 ±15	35 ± 14	< 0.001*
Median (IQR)	24 (18 - 37)	32 (21 - 45)	
NAC treatment n(%)	90 (58)	67 (63)	ns**
Elevated liver tests[1], n(%)	26 (16)	21 (18)	ns**
Peak Serum paracetamol, µmol/L			
Mean ± SD	427 ± 463	423 ± 497	ns*
Median (IQR)	267 (118 -550)	278 (105 - 521)	
Peak AST, IU/L			
Mean ± SD	314 ± 1822	821 ± 3234	ns*
Median (IQR)	25 (20 - 34)	27 (21 – 38)	
Peak ALT, IU/L			
Mean ± SD	253± 1221	544 ± 2050	ns*
Median (IQR)	27 (20 - 38)	28 (21 - 46)	
PT sec			
Mean ± SD	15.5 ± 3.3	18.8 ± 10.4	ns*
Median (IQR)	14.4 (13.2 – 16.1)	14.6 (13.8 – 17.9)	
Peak Bilirubin			
Mean ± SD	53 ± 186	67 ± 195	ns*
Median	7 (4 - 14)	8 (5 - 18)	
Peak Creatinine			
Mean ± SD	78 ± 102	91 ± 100	<0,05*
Median (IQR)	66 (57 - 76)	70 (59 - 82)	

*[1]: Peak AST and/or ALT > 50IU/L, ns: not significant, Significance test by; *Mann-Whitney **Chi square*

Table 11: Clinical profiles of the patients with ALF

	Age/Sex	Intentional overdose	Ingested para-cetamol (g)	Peak serum paracetamol (µmol/L)	ALF	Peak PT (sec)	Peak AST (IU/L)	Peak ALT (IU/L)	Days in ICU	Acute ethanol con-sumption	Chronic alcohol problem	History of psychiatric problem	Earlier para-cetamol overdose	Later para-cetamol overdose
1	48/F*	Y	Chronic	620	Y	61,4	19996	6372	1	Y	Y	Y	N	N
2	33/F	U	Missing	<66	Y	44,4	14680	7931	0	Y	Y	Y	N	N
3	20/F**	Y	40,0	<66	Y	42,8	11854	13016	U	Y	N	U	U	N
4	44/M	Y	45,0	173	Y	34,0	13986	9608	5	Y	N	Y	N	N
5	54/M	Y	Chronic	186	Y	32,3	6451	3096	6	Y	Y	Y	Y	N
6	57/M	U	Chronic	168	Y	26,9	17150	8844	0	N	Y	Y	?	N
7	65/M	N	Missing	<66	Y	24,7	1424	2778	6	N	Y	Y	N	Y
8	44/F	N	Missing	83	Y	24,5	9851	7402	0	Y	Y	N	N	N
9	51/M	N	Missing	<66	Y	20,4	11544	8687	0	N	Y	Y	N	N

Indication: C: Chronic use, F: female, M: male, Y: yes, N:no, NA: not available, ICU: Intensive Care Unit, U: Unknown

*All patients received NAC-treatment. *Patient died after 24hours in ICU. **Patient in potential need of LT and transferred to a Danish institution.*

Hepatotoxicity and acute liver failure

Acute liver failure due to paracetamol overdose occurred in 9/290 (3.1%) of the index visits, four females and five males. The proportion of male patients developing ALF was higher but not significantly, 6.3% vs. 1.9% (p=0.07). The median age for males was 54 (IQR 48-61) and for females 39 (IQR 23-47), the mean age, respectively, was 54 and 36 (p<0.05).

Intentional overdose occurred in 44% of the cases, accidental in 33% (p<0.005) but in 22% of the cases it was not possible to determine the cause. Fifteen percent of the patients who overdosed accidentally while trying to self-medicate and reduce pain developed ALF vs. only 1.5% of the intentional overdoses (p<0.05). The ALF patients were much more likely to have a history of alcohol abuse, 89% vs. 27% (p<0.001).

It was impossible to determine the ingested dose of paracetamol in seven of the cases, but in the two remaining instances the ingested dose was above 28g. The mean peak serum paracetamol in the ALF patients was 166µmol/L (median 83; IQR 65 -180) and was significantly lower than in non-ALF cases (mean: 425µmol/L, p<0.02). Four (44%) of the patients had admission paracetamol levels below 66 µmol/L. In three of these cases there was an elapsed time of 2 – 3 days from ingestion before the patient sought help at the emergency room. In one instance the patient was transferred from another institution, which resulted in delay in the initial clinical measurement at the NUH. All patients received NAC treatment regardless of the time from ingestion.

Four patients had ingested paracetamol as the only drug, and in one case the ingestion was mixed with aspirin (acetylsalicylic acid). In four cases it remained unclear whether the patients had co-ingested other drugs with the paracetamol.

The clinical profiles of the nine ALF patients are presented in Table 11. The outcome of the ALF patients was as follows: Five patients recovered and were discharged from the hospital. Two patients were transferred to other institutions. One patient was transferred to another hospital (in Denmark) as he was considered to be in at great risk of requiring a liver transplant. One patient died from acute liver failure after one day in intensive care. The death involved a 48-year-old female with a known history of depression, chronic alcohol problem and history of overdoses (see patient no. 1 in Table 11.)

DISCUSSION

We are not aware of any other population-based study of paracetamol overdoses that have both shed light of the incidence in a given population and provided information on the characteristics and clinical information as well as the outcome after paracetamol overdose.

Paper I

The paracetamol cases accounted for a total of 18.4% of all drug-related overdoses in the NUH catchment area. Over the six years, from 2004 to 2009, the proportion of paracetamol overdoses compared to other overdoses remained constant. This proportion is in agreement with an earlier prospective study of toxic exposure in Iceland, showing these to be 18.7% of drug-associated overdoses.[69] This is similar to the most severe poisoning cases in Norway, where 18% were caused by paracetamol, including paracetamol and opioid combination drugs.[73] These findings are somewhat higher than those found in other studies from Norway (Oslo)[74] and USA[61], where paracetamol was the main poisoning agent in 12% of the cases.

The annual incidence rate for total paracetamol overdoses for the catchment area decreased by nearly 20% over the six years, from 32.8 to 17.3 per 100,000 inhabitants. This reduction remains unexplained and was in line with the reduction of all drug-related overdose cases. Although results of the calculated incidence cannot be compared directly between regions, our annual incidence seems to be far lower than reported in Canada, 46 cases per 100,000 inhabitants annually,[55] but slightly higher than in another population-based study from the US, where the approximate annual incidence was 21 per 100,000 inhabitants.[68]

Likewise, the annual incidence of patients presenting for the first time with paracetamol overdose decreased over the period. We do not have any obvious plausible explanation for these results. No major differences in coding or other administrative alterations were found during the study period that might explain this. A multicentre study from England also revealed a decline in presentation to emergency departments caused by non-fatal self-harm due to self-poisoning from 2000 to 2007.[75] However, this decline followed changes in legislation in 1998 to limit the availability of paracetamol. Thus, if Icelandic authorities had made similar changes in the legislation at the beginning of the study period, this decline would probably be attributed to them.

This downward trend in the annual incidence is at odds with some results showing the incidence of paracetamol poisoning to be in direct relationship to the availability of the drug.[76,77] Paracetamol is available as an OTC drug in Iceland, but only in pharmacies, and the number of pharmacy outlets hardly changed during the period.[67] A Canadian population-based study found a decline in paracetamol incidences 1997-2002,[55] in both overdose cases presenting to hospitals[56] and phone calls to poisoning centres.[56] This decline was both where changes in legislation and/or prevention programs had been implemented[75] and in areas where nothing at all had changed regarding these matters.[78] Others have reported that hospitalizations due to paracetamol overdoses had not increased even though sales restrictions on paracetamol had been lifted.[78] The study results of trends in non-fatal self-harm in the UK from 2000 to 2007 indicated a decrease in presentation of

self-poisoning and self-cutting to health care centres towards more violent methods such as hanging. The authors assume that the trend might imply a change in individual characteristics.[75] In this study we did not attempt to find such a shift in self-harm methods to explain the decrease in overdoses.

Wholesale figures of paracetamol, as both an OTC drug and a prescription combination drug with opioids, revealed a 12% sales increase in DDD/1000 inhabitants over the six years.[65] This increase might point towards an increase in paracetamol overdoses, which was not the case in the present study. A UK study reported results indicating a decrease in hospitalization and admittance to liver units due to paracetamol when restrictions of paracetamol packages were implemented.[76] The authors emphasise the fact that it is difficult to draw a firm conclusion due to the short follow-up time and lack of comparison groups.[76]

When all paracetamol overdoses were divided into age groups, the age group most affected by paracetamol self-poisoning was 16-25 years with predominantly female patients. This age and sex distribution is as expected as paracetamol overdoses are most frequent in young people and those overdosing for the first time.[41,58] It was not surprising to find that young females represented over 70% of the total paracetamol overdose cases. This is in line with numerous studies concentrating on paracetamol overdoses[56,73,79] and in mixed poisoning epidemiology, where female patients have been in majority.[58,69,80] Although not statistically significant, the first timers were more likely to take multiple drug combinations than those who had earlier reports of self-poisoning. This is at odds with other studies that have demonstrated that paracetamol has been found to be the choice of first timers and young people due to easy availability.[58,81]

Paper II

This part of the study was designed to evaluate characteristics and risk factors in relation to the outcome of paracetamol overdosing. The population in this part consisted of the index visits of all patients over 10 years of age presenting to the NUH regardless of their residence. More than half of the overdose patients had histories of psychiatric problems with no gender difference, which is similar to the hospitalized patient population in a Canadian study.[56]

As expected the vast majority of the index visits were young females who overdosed intentionally. The age group between 16 and 25 was by far the largest one. This is of concern as young patients who self-harm with paracetamol have been observed to be at increased risk of mortality[82], and up to half of the mortality cases are caused by preventable conditions[82]. It is thus advisable at the time of the index visit to implement preventive and interventional strategies, apart from the routine handling of overdose patients.

In the current study 25% of the patients were discharged home without further hospitalization. This is a much lower proportion than discharged directly home after representation to an emergency department in Canada (67%).[55] In the current study patients needing transferral to the ICU were 11% of the index visits to the NUH, compared to 4.1% of the Canadian patients.[55] If the rate of hospitalization and transferral to the ICU are to be markers of the severity of the overdoses, the NUH patients' toxicity was more serious than in the Canadian study population. The fact that the annual

incidence is much higher in the Canadian study than in ours, and the severity of the overdoses appears much less, this could indicate that the Canadian population is more vigilant towards the possible harmful consequences of paracetamol.

The case with highest reported paracetamol dosage (50g) had a measured serum paracetamol level of only 80µmol/L. The serum ethanol was also quite high, with more than 2 promille (41 mmol/L), and the patient was a frequent drinker. In this extreme intentional overdose case the AST and ALT were not elevated. In fact, in 10 of 16 cases with reported paracetamol doses ≥ 28g (all but one was intentional), the AST and ALT levels remained normal. There are similar reports of cases with high dosages of paracetamol and normal AST levels[22], but in those cases the paracetamol ingestion was prolonged over time.[22,83] An acquired tolerance of paracetamol has been suggested to occur in humans and has been demonstrated in animal models.[60] However this has been linked to cases where multiple doses have been increased over time.[60,83]

Recently concerns have been raised that therapeutic as well as supra-therapeutic doses of paracetamol can cause clinically relevant impairment of liver function.[13] Furthermore, a recent study in healthy volunteers demonstrated ALT elevations in therapeutic doses of paracetamol.[14] Our results suggest that the therapeutic use of paracetamol is very safe as no patient using it in therapeutic doses had abnormal liver tests.

Concomitant intoxication was observed in 66% of the cases and with no gender difference. This was twice the proportion of concomitant overdoses in a Danish study (31%).[44] The most frequent drug group ingested along paracetamol was opioid analgesics, benzodiazepins and NSAIDs. A significantly higher proportion of patients had abnormal liver tests when the intoxication was not mixed with other drugs.

Accidental overdoses accounted for seven percent of the paracetamol cases, which is a similar proportion to that reported in a population-based study from the US (8%).[68] In a Canadian study by Myers et al. the proportion of accidental overdose was reported to be 13% of the overdose cases.[82] In the current study the accidental overdose cases were more common in older males, but chronic alcohol abuse not more likely than in the intentional group. None had a history of former intoxication, compared to 34% in the intentional group. Only one patient was found in the accidental group with a recurrent poisoning incident.

The mean serum levels of the liver enzymes were significantly higher in the accidental group although the mean serum paracetamol was lower. It is in line with other studies[68] that the chronic users of paracetamol were found to have higher AST and ALT liver enzymes than those with intentional overdose. The accidental group had lower mean paracetamol levels, which is expected and is caused by the long-term ingestion type of paracetamol overdose.

Neither the proportion of patients with acute ethanol consumption nor serum ethanol levels were found to differ between intentional and accidental poisonings. Reports of acute alcohol consumption were found in 41% of the paracetamol overdose cases, which is somewhat higher than in a US study[61] and reported in the Icelandic prospective study from 2001 to 2002, in which alcohol was a co-ingestant in 28.3% of all drug-related overdoses.[69] A history of alcohol abuse was common (40%) and significantly more common in males than females. This is a higher percentage than in other

reports from the US[68] and Canada[55] and nearly double the findings in a Danish study[44]. The AST and ALT levels were not significantly different when compared between those with and without concomitant acute ethanol consumption. Thus the results indicate neither protective nor harmful effects of alcohol consumption in paracetamol overdose cases.

In this Icelandic population-based study of the characteristics and outcome after paracetamol overdose, 3% (9/290) of the visits to NUH resulted in acute liver failure. It has been estimated that less than 5% of paracetamol overdoses will develop into acute liver failure although the basis for that statement has been rather unclear until now.[82] In line with other studies[31,61] patients with accidental overdose were at higher risk than those with intentional overdose to develop ALF.

The median age of the ALF patients was higher than non-ALF patients. Because of the nature of ingestion of paracetamol, i.e., ingestion of paracetamol over several days, it was not possible to estimate the doses ingested in the majority (7/9) of the ALF cases. All patients developing ALF received NAC treatment upon arrival to the NUH. There was neither a significant gender difference nor difference in history of psychiatric problems. However a considerable higher proportion of alcohol abuse was among the ALF patients than those patients without ALF.

The mean serum paracetamol at admission was much lower in the ALF group and thus corresponds poorly with the severity of the hepatic toxicity. In fact 19% of the total paracetamol overdose group patients had higher serum paracetamol levels than the highest ALF patient.

Five of the nine ALF patients were transferred to the ICU, but four remained in an acute medical ward. The outcome of the patients with ALF was as follows: one died after one day in ICU; in one case (intentional) information on outcome was missing, where the patient was considered at risk of needing LT and was transferred to another institution, but all other patients (7) recovered.

The current study demonstrates that although paracetamol overdose is a common causal agent for emergency room visits and hospitalizations, serious liver injury is very rarely associated with these cases. Thus, serious liver-related morbidity and mortality due to paracetamol seems to be the tip of the iceberg of these intoxications. The two other population-based studies from Canada and the US show similar results but population-based studies from other Nordic countries have not been available for comparison.

Paracetamol is the most common cause of acute liver failure (ALF) in many countries.[1,5,20,84] Those results are based on data from highly specialized tertiary referral centres. The results of this study demonstrate that in the vast majority of cases with paracetamol overdose, clinically important liver injury is extremely rare.

Strength and limitations

This current study had a retrospective design with the known drawbacks of these kinds of studies, such as lack of systematic data collection, and sometimes relevant data were missing from medical records. The accuracy of our results relies on this data. On the other hand, all data from the patient records were collected by one person, so there should be internal consistency in the data handling.

Another limitation of this study is the variability of the ICD-10 coding praxis over the years. Some temporal trends were observed in the use of different codes. However, most of the cases were coded T50.9 (64%), which is a very unspecific code. All information on chronic alcohol abuse, illegal substance use and ingested paracetamol and/or ethanol is based on patient history or speculation by the ambulance staff. This can result in information of some sort not being mentioned in the medical records that we have assumed o be non-existent. Thus, it is possible that alcohol abuse is likely to be under-reported. This should however be neither more nor less than occurs in comparable studies, which have also been mostly retrospective[34,55,56,61,68].

Other limitations are that the more severe cases from neighbouring hospital areas were transferred to the NUH. This could cause some skewing in the distribution of severity of paracetamol poisoning. However, one of the strengths of the study is that since it was possible to use personal identification numbers and connect them to the patients' postal codes, we were able to calculate with good accuracy the annual population incidence.

An additional strength of the study is that it is population-based incidence study which has clinical data added to the incidences. The inclusion of clinical data adds to the validation of the diagnoses. This gives a much fuller picture of the paracetamol overdose problem.

The National University Hospital is the only hospital serving the overdose population that was defined in this study. Its emergency room is also the only one in the area so it is very unlikely that patients would have sought help elsewhere. All residents in the area have a unique personal identification number and are thus easy to trace in the hospital patients registry. Regarding mortality it is unlikely that patients from the index visit who died of paracetamol overdose were overlooked as all causes of mortality occurring within weeks of the overdose were checked.

CONCLUSIONS

Compared to other studies the annual incidence of paracetamol poisoning is high in Iceland and a significant public health problem. This high incidence is somewhat surprising as the access to paracetamol is more restricted than in the other populations studied. The drop in the annual incidence of both all drug-related overdoses and paracetamol overdoses between 2004 and 2009 is not explained by market changes or regulations by the authorities. It thus remains unexplained.

In short, young females tend to be in majority of those overdosing intentionally with paracetamol, and a majority of the group has a history of psychiatric problems. Although intentional overdoses are much more common, the outcome of the accidental overdose group is more severe and around 15% of them develop ALF. Compared to other studies, the frequency of accidental overdoses in our study seems to be rather low. The mortality following a paracetamol overdose is extremely low, and the patients have a good chance of recovery.

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Appendix 1: Population numbers of the NUH catchment area

	2004		2005		2006		2007		2008		2009	
Age groups (years)	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
<10	17822	17176	17832	17253	18002	17460	18157	17628	18620	18119	19019	18358
11-15	8560	8235	8658	8308	8694	8251	8610	8196	8690	8268	8488	8110
16-25	15958	15758	16182	15873	16640	16288	17373	16704	18240	17544	18078	17676
26-35	16157	15803	16513	16135	17599	16811	18728	17487	20396	18142	19775	18108
36-45	15924	16016	15950	16021	16246	16125	16756	16145	17767	16520	17303	16620
46-55	14066	13924	14471	14339	15080	14725	15711	15054	16571	15508	16352	15856
56-65	9167	9312	9672	9809	10291	10377	10928	10878	11495	11362	11898	11755
>65	6151	6980	6179	6953	6190	6854	6164	6834	6268	6898	6460	7085
Total by gender	103805	103204	105457	104691	108742	106891	112427	108926	118047	112361	117373	113568
Total population		207009		210148		215633		221353		230408		230941

Appendix 2: ICD-10 codes

International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [71]

Mental and behavioural disorders (F00-F99)

F19.1 Mental and behavioural disorders due to psychoactive substance use

F32.9 Depressive episode, unspecified

F55.0 Abuse of non-dependence-producing substances

Diseases of liver (K70-K77)

K71.1 Toxic liver disease with hepatic necrosis

K72.0 Hepatic failure, not elsewhere classified

K72.9 Hepatic failure, unspecified

Poisoning by drugs, medicaments and biological substances (T36-T50)

T39.0 Poisoning by nonopioid analgesics, antipyretics and antirheumatics. Salicylates

T39.1 4-Aminophenol derivatives

T39.3 Other nonsteroidal anti-inflammatory drugs [NSAID]

T39.8 Other nonopioid analgesics and antipyretics, not elsewhere classified

T39.9 Nonopioid analgesic, antipyretic and antirheumatic, unspecified

T50.9 Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances

Intentional self-harm (X60-X84)

X60.0 Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics

X60.6 Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics. Industrial and construction area

X60.9 Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics. Unspecified place

X61.0 Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified. Home

X63.8 Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances. Other specified places

X64,9 Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances. Unspecified places

Appendix 3: ATC-Codes used in concomitant overdose cases

1st level, anatomical main group	ATC-codes
Benzodiazepines	N05B*
	N05C*
Neuroleptica	N05A*
Opioids	N02A*
	N02A*+
Analgesics and antipyretics	N02B*+
	N02B*
	N02B A51*
Acetylsalicylic A	N02B A*
Anti-inflammatory and Antirheumatic products, Non-steroids	M01A*
Muscle relaxants	M03*
Anti-gout preparations	M04*
Antidepressants	N06A*
Psychostimulants	N06B*
Psycholeptics	N06C*
Antibiotics	J01*
Anticonvulsants	N03*
Antihistamine	R06*
Cough and cold preparations	R05*
Cardiovascular	C*
Alimentary tract and metabolism	A*
Blood and blood-forming organs	B*
Dermatologicals	D*
Genito-urinary system and sex hormones	G*
Systemic hormonal prep, exl. sex hormones	H*

*ATC-code not specified more precisely