Paracetamol Misuse and Dental Pain: Results from the French Observational DAntaLor Study

E. Pape, C. Collin, F. Camelot, L. Javot, N. Petitpain, E. Puskarczyk, D. Anastasio, E. Gérard, N. Gambier, J. Scala-Bertola, et al.

Paracetamol misuse and dental pain. Results from the French observational DAntaLor Study.

Running title: Paracetamol misuse and dental pain

E.PAPE[1,2] , C.COLLIN[3], F.CAMELOT[3,4], L.JAVOT[1], N. PETITPAIN[1], E.PUSKARCZYK[5], D.ANASTASIO[6], E.GERARD[7], N.GAMBIER[1,2], J.SCALA-BERTOLA[1,2], C.CLEMENT[3,4*]

[1] CHRU Nancy, Department of Clinical Pharmacology and Toxicology, Nancy, F-54000, France

[2] Université de Lorraine, UMR 7365 CNRS-UL, IMoPA, Vandoeuvre-lès-Nancy, F-54505, France

[3] Université de Lorraine, Faculty of Odontology, Nancy, F-54004, France

[4] CHRU Nancy, Emergency Dental Service, Nancy, F-54000, France

[5] CHRU Nancy, Poison Information and Toxicovigilance Center, Nancy, F-54000, France

[6] CHR Metz-Thionville, Department of Odontology, Thionville, F-57100, France

[7] CHR Metz-Thionville, Department of Odontology, Metz, F-57000, France

*Corresponding Author: Céline CLEMENT

Address: Faculté d'Odontologie
Avenue du Maréchal De Lattre De Tassigny - BP 50 208
54004 NANCY
FRANCE

Telephone: +33(0) 6 62 73 79 47

Fax number: +33(0) 3 72 74 67 81

Email: celine.clement@univ-lorraine.fr

Key words: Paracetamol, Acetaminophen; Acute dental pain; Misuse; Unintentional intoxication.

Conflict of Interest statement: None

Abstract

Aims: Dental pain is one of the main reasons for paracetamol consumption by the patients. The aim of the DAntaLor study was to evaluate the risk of hepatotoxicity due to unintentional paracetamol misuse occurring in patients with acute dental pain. **Methods:** A prospective multicentre observational survey was performed on patients consulting without appointment odontology department of three main French hospitals of the Lorraine region over a three-month period. Patients were asked to fill a medical questionnaire while seating in the waiting room. Those who fulfilled the questionnaire, had dental pain and took paracetamol were included in the DAntaLor study. Misuse was defined as a daily dose of more than 4 grams of paracetamol per day. The risk of hepatotoxicity was considered high if the supposed ingested dose was above the threshold of 150 mg kg^{-1} $24h^{-1}$, 125 mg kg^{-} $24h^{-1}$ or 100 mg kg^{-} $24h^{-1}$ over a period of 24h, 48h or 72h, respectively. Hepatotoxicity was suspected in the presence of clinical symptoms. **Results:** Of the 1,810 patients consulting the odontology departments 741 were included in the study. Painkillers were used in 74.4% of the cases and paracetamol was taken by 81.7% of the patients. Paracetamol was self-medicated in 85.5% and misused by 6.0% of the patients. Clinical symptoms were observed in 1.6% of the patients with no paracetamol misuse. For patients consuming more than 4g per day, mild unspecific clinical symptoms of hepatotoxicity were experienced by 11.8% and 40.0% of the patients if the corresponding supposed ingested dose was below or above one of the three previously defined thresholds, respectively. **Conclusion:** Patients with dental pain are at risk of paracetamol overdose and hepatotoxicity.

1. Introduction

Paracetamol, also known as acetaminophen, is the most prescribed analgesic drug. In 2012, the analysis of selling medicines performed by the French National Agency for Medicines and Health Products Safety estimated that paracetamol represented 18 % of all ambulatory prescribed medicines, that is around 500 million packages per year.[1] Considered as a safe and well-tolerated drug, paracetamol is easily and largely prescribed, delivered or consumed, the risk of hepatotoxicity being too often forgotten although paracetamol still remains the first cause of acute liver failure.[2] Paracetamol is used to treat different types of pain (back, fever, headache, musculoskeletal,…) where dental pain is one of the main reasons for accidental paracetamol overuse or overdose.[3-8] Paracetamol overdose associated with dental pain is mainly the result of unintentional repeated supratherapeutic intake rather than of intentional acute paracetamol exposure.[9] In this particular clinical situation, the risk of hepatotoxicity is hardly identifiable and it is not easy to recognize hepatotoxicity because clinical signs as nausea, vomiting or abdominal pain are mild and unspecific and the alanine aminotransferase (ALT) level can be normal or slightly elevated.[2,10] Furthermore, the risk of hepatotoxicity cannot be assessed by testing the plasma paracetamol concentration using the Rumack-Matthew nomogram - only validated for acute paracetamol poisoning with immediate-release oral preparations within the first 24 hours after ingestion - since liver damage can occur even if levels of paracetamol are undetectable.[9-11] Summing up, the evaluation of hepatotoxicity following repeated unintentional paracetamol overdoses is far from obvious and administration of N-acetylcysteine therapy should be considered in patients with excessive paracetamol intake - 10g/24h or 6g/24h over a period of 24h or 48h, respectively and 4g/day for patients with predisposing risk factors of hepatotoxicity (chronic ethanol misuse, dehydration, prolonged fasting)[12] - and presenting clinical manifestations of hepatotoxicity (abdominal pain, fatigue, anorexia, and fever) or paracetamol plasma concentration greater than 20 mg/L or elevated levels of alanine aminotransferase (ALT) that should be checked in case of suspected overdose.[10] If the risk of hepatotoxicity associated with unintentional repeated supratherapeutic ingestion of paracetamol is described, the risk of hepatotoxicity in patients taking this drug to control dental pain has never been assessed.

Therefore, the aim of the DAntaLor study was to evaluate the frequency of hepatotoxicity due to unintentional paracetamol misuse or overdose occurring in patients with acute dental pain consulting the odontology department of three main French hospitals of region Lorraine over a three-month period.

2. Materials and Methods

The patients were recruited among the patients consulting without appointment the odontology department of three main regional hospitals of Lorraine (France) during a three month period between April and June 2011.

The DAntaLor study was designed as a prospective survey. Included in the study were patients who filled the questionnaire (see below), consulted for dental pain and used paracetamol. Patients who declined research participation, with memory disorder or with a diagnosed mental disorder, with impaired communication skills or lack of French language understanding and unaccompanied minor patients were excluded. The DAntaLor study was authorized by the local research ethics committee (CRENHU).

Questionnaires

Two specific questionnaires were designed in order to select the patients. One questionnaire that the patient had to fill out in the waiting-room prior to the consultation and a second one to be filled out by the dental practitioners. The two medical questionnaires were developed to standardize data collection.

The patients' questionnaire included 3 parts recording administrative and medical information, the reason for consultation and the list of pain medications taken to control the dental pain. The first part collected information about profession, age, gender, size and weight of the patient as well as the name of the family dentist to check the existence of regular dental visits. The second part assessed whether the patient consulted the clinic for dental pain or another reason. In case of dental pain, the patient had to rate the pain intensity at the time of consultation and the maximum pain felt by the patient since its inception by means of a numeric pain rating scale (NPRS)[13] with the anchor points 0 (no pain) and 10 (worst possible pain). The third part concerned the intake of pain killers (type, quantity, prescription type (self or prescribed)) taken in the last two weeks including the day of consultation. A catalogue with the picture of the drug package of the 21 most frequently bought analgesics in the Lorraine region was provided to the patient in order to facilitate remembering the name of the used analgesics and to improve the quality of the data collection.

The questionnaire to be filled by the dentist was designed in order to standardize, check and complete the information provided by the patient in particular regarding the period and the

amount of ingested paracetamol in order to calculate the supposed ingested dose (see below) necessary for the assessment of paracetamol misuse or overdose. The questionnaire also included questions about the first clinical symptoms of paracetamol intoxication (anorexia, epigastric and right hypochondrium pain, nausea, vomiting, pallor, sweat), dental diagnosis and treatment. An instruction leaf was provided to the dentist to help identify situations of paracetamol overdose based on the first clinical symptoms of intoxication or on the calculated supposed ingested dose over a period of 24h, 48h or 72h. This instruction leaf also contained a list of the most frequently consumed painkillers containing paracetamol, alone or in association and the instruction for the management of paracetamol overdose, including the hepatotoxicity evaluation by the Regional Poison Center and spontaneous reporting to the Regional Pharmacovigilance Centre of Lorraine. If necessary, patients were referred to the Emergency Department of the same hospital. Finally, the dental practitioner had to add the final diagnosis and to let the patient rate pain intensity after therapy using NPRS.

Calculation of supposed ingested dose

To standardize the ingested doses, the supposed ingested dose (SID) was determined as explained by Clement *et al.*[9] using three values provided by the patient: the supposed period of ingestion (*i.e.* time elapsed between the first and last paracetamol intakes), the total ingested amount of paracetamol over the period of ingestion, and the weight of the patient.

$$SID\ (mg.kg^{-1}.24\,h^{-1}) = \frac{ingested\ \ amount\ \ (mg) \times 24}{weight\ \ (kg)\ \times\ \ period\ of\ \ ingestion\ \ (h)}$$

Assessment of paracetamol misuse and risk of hepatotoxicity

Paracetamol misuse was considered if paracetamol intake exceeded the recommended maximum dose of 4 grams per day and overuse or high risk of hepatotoxicity if the calculated supposed ingested dose greater than the corresponding threshold doses (T_{SID}) defined by Daly *et al.*[12]: 150 $mg.kg^{-1}.24h^{-1}$, 125 $mg.kg^{-1}.24h^{-1}$ or 100 $mg.kg^{-1}.24h^{-1}$ over 24h, 48h or 72h, respectively.[12]

Criteria for suspecting paracetamol hepatotoxicity

Paracetamol hepatotoxicity was suspected only based on the presence of symptoms: nausea, vomiting, sweating, pallor, anorexia or epigastralgia.

Statistical Analysis

Frequency data were analysed using descriptive statistics. Linear regression with ordinary least squares was used to assess the relationship between pain intensity and paracetamol intake. Differences in pain intensity among the three diagnoses (pulpitis, pulp necrosis and cervicofacial cellulitis) were assessed by means of ANOVA. A p-value < .05 was considered as statistically significant. Analyses involved use of SAS® (version 9.3) statistical software (SAS Institute, Cary, NC, USA).

3. Results

During the 3 months of the study period, 1810 patients consulted the odontology departments without appointment: 510 in the hospital of Thionville, 525 in the hospital of Metz and 775 in the university hospital of Nancy. Among the 1810 patients, 862 accepted to fill the medical questionnaire and dental pain was the reason for consultation in 741 patients of them (86.0%). Out of these 741 patients, 551 used analgesics and the 450 patients who used paracetamol were included in the DAntaLor Stdy (Figure 1). Patients were mainly under 45 years of age (75 %) and mainly men (55.6 %). Median and mean age were respectively 30.0 and 35.1±17.1 years-old. The majority of the patients (67.4 %) did not visit the dentist routinely. The two most frequent pathologies were pulpal pathologies (51.9%) and cervicofacial cellulitis (18.1%) (Table 1). Pulpal pathologies included pulpitis (35.8%) and pulp necrosis (16.1 %). The mean pain intensity was 6.0±2.6 on the day of the consultation with more than 75 % of the patients reporting a score above 4.0. The maximum mean pain intensity score was 7.5±2.3 regardless of pathology (Table 2). No statistical difference in pain intensity score was found between the three pathologies pulpitis, pulp necrosis and cervicofacial cellulitis (p>.05).

Analgesics were taken by 74.4 % of the patients presenting dental pain and paracetamol was the most commonly used by them (81.7 %), especially in the last 24 hours (98.0 %). The mean intake dose of paracetamol was 3.8±3.3 g (median value = 3.0 g) for a period of ingestion ranging from 0 to 72 hours before the consultation (median = 48 h). Paracetamol mean intake dose was found to be correlated with the intensity of dental pain at the time of consultation and the linear correlation coefficient was 0.77 (Figure 2). In contrast, no correlation was observed between the maximal dental pain and the paracetamol mean ingested dose (r=0.35). Paracetamol was self-medicated in 85.5% of the patients: obtained without prescription, e.g. as an OTC (over-the-counter) drug in 44.7 %, obtained from a previous prescription in 29.9 % and from a close person or a family member in 10.9 %. Paracetamol

misuse - corresponding to a daily dose greater than 4g per day - was observed in 27 of the 450 patients using paracetamol (6.0 %) (Figure 1). Ten of them were considered to have taken an overdose and therefore to be at a high risk of hepatotoxicity since the calculated supposed ingested doses were greater than the established threshold doses previously described. The supposed ingested dose of paracetamol observed in these patients ranged from 119.1 to 327.3 mg kg^{-1} 24 h^{-1} (median value: 169.1 mg kg^{-1} 24 h^{-1}) for intake periods ranging from 48 to 72 hours. Hepatotoxicity was suspected in 4 of them (40.0%) according to clinical symptoms (nausea, vomiting, sweating, pallor, anorexia, epigastralgia). Despite the fact that the patients were referred to the emergency department after the dental treatment, only three patients went there. As for the 17 patients with paracetamol misuse but considered at low risk of hepatotoxicity, clinical symptoms of hepatotoxicity were observed in 2 of them (11.8%) and hepatotoxicity was suspected. Finally, clinical manifestations of hepatotoxicity were observed in six out of the 27 paracetamol misuser patients (22.2%). Hepatotoxicity was suspected in seven out of the 423 patients (1.6 %) who did not exceed the maximum therapeutic daily dose of 4g. Thus, the use of a daily dosage of paracetamol of more than 4 grams per day and greater than the threshold dosages defined by Daly *et al.*[12] is associated with a 13-fold and 24-fold higher risk of hepatotoxicity, respectively. None of the 13 patients experiencing clinical symptoms of hepatotoxicity presented hepatotoxicity risk factors such as alcoholism, chronic liver disease or malnutrition. Taken together 2.9% of the patients with dental pain using paracetamol presented clinical symptoms of hepatotoxicity. All the patients presenting clinical manifestations of hepatotoxicity recovered spontaneously.

4. Discussion

Patients consulting the odontology departments of the three regional hospitals in Lorraine presented characteristics consistent with those reported by previous epidemiological studies on patients consulting French emergency dental care facilities.[14,15] These patients are usually described as young adults with poor oral hygiene who did not go to the dentist on a regular basis.[8]

Dental pain was the reason for consultation for three out of four patients and pulpitis and pulp necrosis were the two most frequent dental pathologies and were found in one in 2 patients. This is consistent with the fact that 67.4% of the patients did not have regular check-ups by a dentist. Indeed, early diagnosis and treatment of dental and periodontal pathologies contributes to avoiding emergency consultations. Furthermore, as reported but not assessed in

the previous case series by Clement *et al.*[9], the present study confirmed the particularly high intensity of pain caused by dental pathologies. Indeed, the mean intensity at time of the consultation was 6.0±2.6 and the maximum 7.5±2.3.

The results of this study that was performed between April and June to avoid the risk of involving patients with an over-consumption of paracetamol due to winter diseases indicate a positive linear relationship between the amount of paracetamol intake and the dental pain intensity at the time of the consultation but not with the maximum dental pain. This suggests that pain at the time of the consultation was a better marker for paracetamol consumption and that is likely more associated with the persistence of the dental pain than with its intensity. In addition, even if the present study was not designed to evaluate the influence of paracetamol on dental pain relief, it highly suggests, as previously reported[16,17], that a common antalgic treatment does not sufficiently resolve the dental pain. Indeed, despite paracetamol intake during one or several days, the mean pain intensity at the time of the consultation was still high (6.0±2.6) and only the dental treatment was able to decrease dental pain by an average score of 4 points. Nevertheless, and in accordance with previous studies,[4,6-8,15] patients with dental pain often use paracetamol to control it as demonstrated in this study: 3 out of 4 patients used analgesics and paracetamol was the analgesic of choice in 82 % of these patients. Paracetamol was self-medicated in 85.5% of the patients proving that this drug escapes any medical or pharmaceutical control. Despite the prevention campaigns about the hepatotoxicity risk of paracetamol conducted by the French National Agency for Medicines[18] in 2008 or the Food and Drug Administration (FDA)[19] in 2009, paracetamol was misused by 6.0% of the patients in the present study. Even if this percentage was lower than that reported by Heard *et al.*[5], efforts in France should be continued to warn the population against the risk of paracetamol misuse. US programs like Know Your Dose (Acetaminophen Awareness Coalition)[20], Medicines in My Home (FDA)[21], and Get Relief Responsibly (McNeil Consumer Healthcare)[22] - dealing with different aspects of OTC medication errors and accidental unsupervised ingestions in a context of dental pain - should be implemented also in France. Among the preventive information, the strict respect of the maximum daily dose of 4 grams per day is probably the most important information. Indeed, clinical manifestations of hepatotoxicity were observed in 1.6 % of the patients with a therapeutic use of paracetamol and in 22.2% of the paracetamol misuser patients, which is in accordance with the study of Watkins *et al.*[23] who reported an increase of more than 30% of aminotransferase levels in healthy adults receiving 4 grams of paracetamol daily during 14 days. The clinical signs

presented by the patients were mild and unspecific and associated nausea, vomiting, sweating, pallor, anorexia or abdominal pain.

In accordance with other studies[2,9,10], paracetamol plasma concentrations, assessed in the three patients who went to the emergency department, were undetectable or lower than 10 mg/L whereas serum ALT levels was normal or varied less than 3-fold. This finding reinforces the difficulty in diagnosing hepatotoxicity in patients with repeated supratherapeutic paracetamol intake suggesting that the clinical evaluation still remains the best diagnostic tool in current practice. Likely, assessment of other biological markers such as N-acetyl-p-benzoquinone imine (NAPQI), the reactive metabolite of paracetamol, or paracetamol protein adducts would have been helpful to confirm paracetamol overdose due to repeated supratherapeutic ingestions but these tests are currently insufficiently used in routine care.[24-26]

Using the supposed ingested dose thresholds proposed by Daly *et al.*[13] 10 of the 27 paracetamol misuser patients were at high risk of hepatotoxicity. Clinical manifestations of hepatotoxicity were observed in 4 of these 10 patients. Conversely, only 2 of the 17 paracetamol misuser patients at low risk of hepatotoxicity and 7 of the 423 patients with a therapeutic use of paracetamol experienced clinical symptoms of hepatotoxicity. None of the patients with clinical symptoms of hepatotoxicity presented risk factors of hepatotoxicity. Thus, patients using paracetamol at a daily dosage of more than 4 grams per day have a 13-fold higher risk of hepatotoxicity than patients without paracetamol misuse. The risk increases to a 24-fold factor when the paracetamol dose was greater than the threshold dosages defined by Daly *et al.*[12]. These results suggest that the threshold proposed by these authors could constitute a very useful tool in the evaluation of the risk of hepatotoxicity in a context of unintentional overdose due to repeated supratherapeutic paracetamol intake. Another tool which may be useful for the dental practitioners to diagnose patients at risk is the dose proposed by Nayyer *et al.*[27] e.g. 150 mg/kg or 75 mg/kg over a 24h period in presence/absence of risk factors of hepatotoxicity, respectively. All the patients with clinical evidence of hepatotoxicity of this study recovered spontaneously without administration of N-acetylcysteine antidote. Even if this observation could be considered as reassuring, it should not be overlooked that the patients with clinical symptoms of paracetamol hepatotoxicity probably presented saturated glucuronidation and sulfonation pathways resulting in glutathione depletion associated with the production of paracetamol protein adducts.[10] It has to be highlighted that the patients of this study did not present any other risk factors of

hepatotoxicity and that their risk was relatively low due to the limited duration of the dental pain of no more than three days.

Finally, it is important to point out a possible limitation of the DAntaLor, e.g. the low rate of participation (47.6%). As mentioned by Galea *et al.*[28], the rate of participation in epidemiologic studies has been declining over the past 30 years and the participation rate observed in this study is in accordance with the participation rates reported in other epidemiologic studies since 2000. Possible reasons are: the proliferation of research studies, the fear of intrusion on personal lives or highly solicited individuals in an "oversurveyed" society especially by telemarketing. The patients that are more likely to participate are women, employed persons and married persons and they participate more easily to simple and not time consuming studies with immediate benefit to themselves and salient to their lives. Interestingly, patients with lower socioeconomic status, poorer health or concerned with a risk behaviors such as smoking, alcohol or drugs, are less likely to participate to studies. Taken together it cannot be excluded that the relatively low participation rate could have led to an underrepresentation of the patients at risk of hepatotoxicity and therefore of the calculated risk.

Conclusion

The study showed that patients with dental pain were at risk of paracetamol overdose. Clinical symptoms of hepatotoxicity were found in only 1.6% of the patients using therapeutic dose of paracetamol whereas they were found in 22.2% of the patients using more than 4 grams of paracetamol per day. Clinical symptoms were observed in 40% of the patients who ingested more than 150 $mg.kg^{-1}.24h^{-1}$, 125 $mg.kg^{-1}.24^{-1}$ or 100 $mg.kg^{-1}.24h^{-1}$ over a period of ingestion of 24h, 48h or 72h, respectively. Clinical symptoms were mild, unspecific and resolved without sequelae and antidote administration.

References

1. ANSM. Analyse des ventes de médicaments en France en 2011. ANSM: 2012. http://ansm.sante.fr/var/ansm_site/storage/original/application/0e689f733291d5ddbb09f0cccf93e438.pdf. Accessed 30 January, 2018.

2. Tittarelli R, Pellegrini M, Scarpellini MG, Marinelli E, Bruti V, Di Luca NM et al. Hepatotoxicity of paracetamol and related fatalities. Eur Rev Med Pharmacol Sci 2017; 21: 95-101.

3. Hargreaves K, Abbott PV. Drugs for pain management in dentistry. Aust Dent J 2005; 50: S14–22.

4. Thomas MBM, Moran N, Smart K, Crean S. Paracetamol overdose as a result of dental pain requiring medical treatment - two case reports. Br Dent J 2007; 203: 25–28.

5. Heard KJ, Ries NL, Dart RC, Bogdan GM, Zallen RD, Daly F. Overuse of non-prescription analgesics by dental clinic patients. BMC Oral Health 2008; 8: 33.

6. Matusiak R, Harley KE. Paracetamol overdose in a teenager following placement of a fixed appliance. Dent Update 2009; 36: 33–35.

7. Vogel J, Heard KJ, Carlson C, Lange C, Mitchell G. Dental pain as a risk factor for accidental acetaminophen overdose: a case-control study. Am J Emerg Med 2011; 29: 1125–1129.

8. Siddique I, Mahmood H, Mohammed-Ali R. Paracetamol overdose secondary to dental pain: a case series. Br Dent J 2015; 219: E6.

9. Clement C, Scala-Bertola J, Javot L, Royer-Morrot MJ, Gillet P, Trechot P et al. Misuse of acetaminophen in the management of dental pain. Pharmacoepidemiol Drug Saf 2011; 20: 996–1000.

10. Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update. J Clin Transl Hepatol 2016; 4: 131-142.

11. Dargan PI, Ladhani S, Jones AL. Measuring plasma paracetamol concentrations in all patients with drug overdose or altered consciousness: does it change outcome? Emerg Med J 2001; 18: 178-182.

12. Daly FFS, Fountain JS, Murray L, Graudins A, Buckley NA, Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust 2008; 188: 296–301.

13. Beebe A, Latham J. Pain: clinical manual for nursing practice. Mosby, 1994.

14. Roger-Leroi V, Laléchère-Lestrade C, Tubert-Jeannin S. [Characteristics of the patients needing emergency dental treatment at the hospital of Clermont-Ferrand (France)]. Rev Epidemiol Sante Publique 2007; 55: 197–202.

15. Tramini P, Al Qadi Nassar B, Valcarcel J, Gibert P. Factors associated with the use of emergency dental care facilities in a French public hospital. Spec Care Dentist 2010; 30: 66–71.

16. Radeva E. Emergency treatment of irreversible pulpitis. J of IMAB 2008; 14: 3-103.

17. McDougal RA, Delano EO, Caplan D, Sigurdsson A, Trope M. Success of an alternative for interim management of irreversible pulpitis. J Am Dent Assoc 2004; 135: 1707–1712.

18. ANSM. Fiche d'aide à l'automédication : Le paracétamol en bref - information patient. ANSM: 2008. http://ansm.sante.fr/var/ansm_site/storage/original/application/b69723fdab668e3ee857d2b4e4805382.pdf. Accessed 30 January, 2018.

19. Food and Drug Administration. Acetaminophen: Avoiding Liver Injury. US Food and Drug Administration: 2009. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm168830.htm. Accessed 30 January, 2018.

20. The Acetaminophen Awareness Coalition. Know Your Dose Campaign. KnowYourDose: 2017. http://www.knowyourdose.org/the-acetaminophen-awareness-coalition/. Accessed 30 January, 2018.

21. Food and Drug Administration. Medicines in My Home. US Food and Drug Administration: 2014. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm. Accessed 30 January, 2018.

22. McNeil Consumer Healthcare. Adult acetaminophen dosage chart. Get Relief Responsibly: 2016. https://www.getreliefresponsibly.com/use-pain-medicine-safely/adult-acetaminophen-dosing. Accessed 30 January, 2018.

23. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 2006; 296: 87–93.

24. Heard K, Green JL, Anderson V, Bucher-Bartelson B, Dart RC. Paracetamol (acetaminophen) protein adduct concentrations during therapeutic dosing. Br J Clin Pharmacol 2016; 81: 562–568.
25. McGill MR, Jaeschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. Pharm Res 2013; 30: 2174–2187.
26. Cook SF, King AD, Chang Y, Murray GJ, Norris HR, Dart RC et al. Quantification of a biomarker of acetaminophen protein adducts in human serum by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry: clinical and animal model applications. J Chromatogr B Analyt Technol Biomed Life Sci 2015; 985: 131–141.
27. Nayyer NV, Byers J, Marney C. Identifying adults at risk of paracetamol toxicity in the acute dental setting: development of a clinical algorithm. Br Dent J 2014; 216: 229–235.
28. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007; 17:643-653.

List of Figures

List of Tables

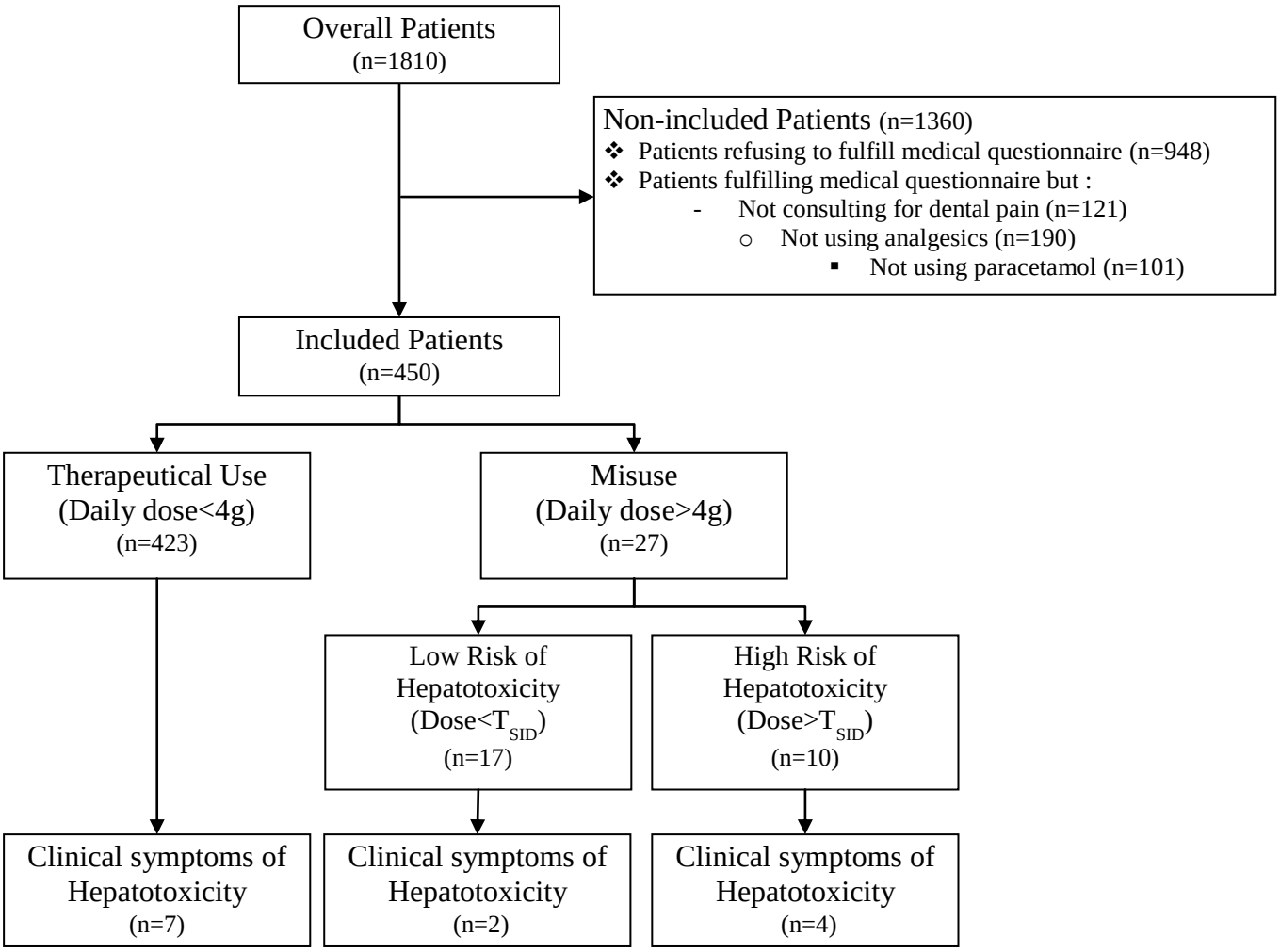

Figure 1: Flowchart of the DAntaLor cohort population. T_{SID} threshold dosages of 150 mg/kg/24h, 125 mg/kg/24h or 100 mg/kg/24h over a period of 24h, 48h or 72h, respectively.

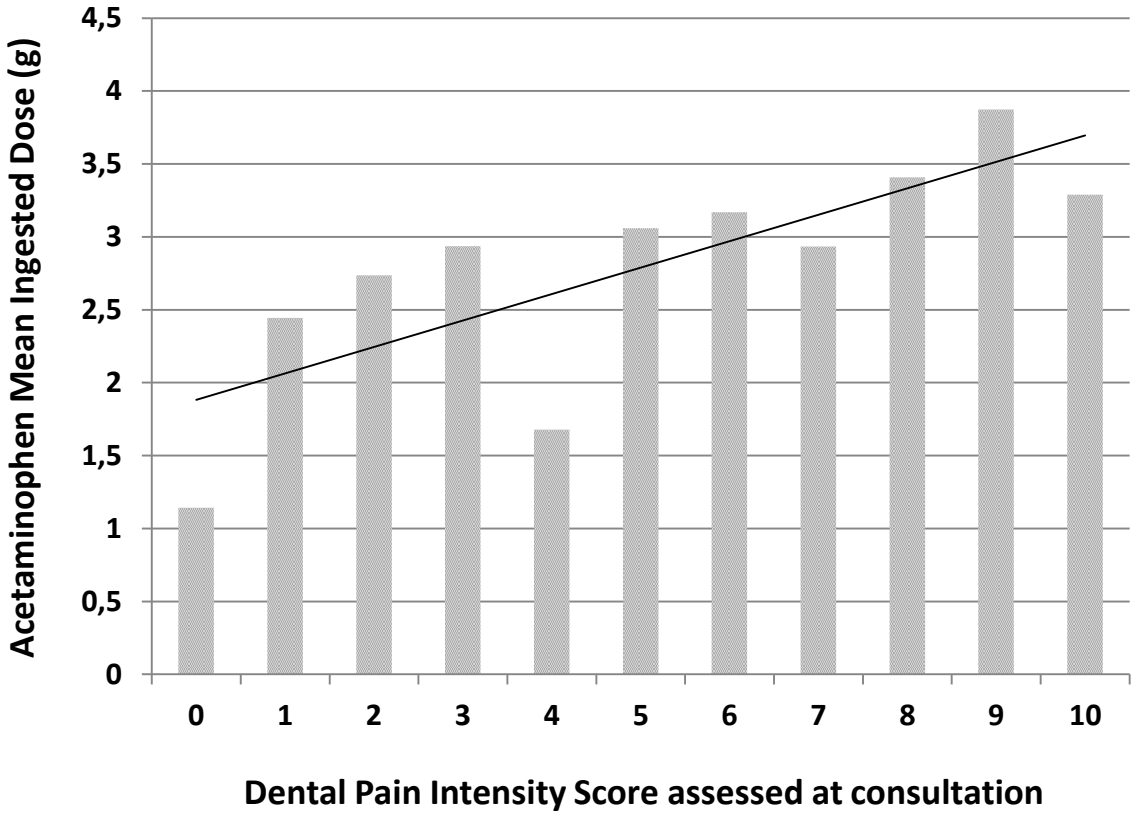

Figure 2: Positive correlation between paracetamol mean ingested dose and dental pain intensity score assessed at the time of the consultation (r=0.77).

Table 1: Diagnoses in patients consulting for pain

	n	(%)
Pulpitis	213	(35.8)
Cervicofacial cellulitis	108	(18.1)
Pulp necrosis	96	(16.1)
Mucosal lesion	31	(5.2)
Tooth mobility	30	(5.0)
Dentin hypersensitivity	30	(5.0)
Periodontal infection	27	(4.5)
Dental trauma	24	(4.0)
Interproximal pain	13	(2.2)
Pain causing by teeth prosthesis	10	(1.7)
Alveolitis and Postoperative pain	12	(2.1)
Necrotizing Ulcerative Gingivitis	2	(0.3)

Table 2: Mean Intensity of pain felt by the patients in the three most painful pathologies.

Intensity of Pain with the numeric pain rating scale from 0 to 10	**Overall Pathologies**	**Pulpitis**	**Pulp necrosis**	**Cervicofacial cellulitis**
Mean intensity of pain at the consultation	6.0±2.6 (n=727)	6.3±2.4 (n=211)	6.2±2.5 (n=96)	6.5±2.6 (n=107)
Maximum intensity of pain from the beginning of the pain	7.5±2.3 (n=693)	7.8±2.0 (n=204)	7.9±2.0 (n=91)	8.1±1.8 (n=105)
Decrease of pain intensity after dental care	-4.0±3.1			