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Case Report

Paracetamol misusing to dental pain: a case-report and recommandations for treatment

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Abstract – Introduction: The paracetamol is the most widely used painkiller to dental pain. Patients self-medicating with paracetamol for dental pain had 12.8 more times lead to overdose than patients with other pains. The aim of this work was to propose a standardized management in case of paracetamol overdose from a clinical case report. **Observation:** A 56-year-old man was referred to the General Emergency Department because he had ingested 32 grams of paracetamol in less than 24 hours due to a dental pain. He was in a state of haemodynamic and hypothermic shock. He was placed on the liver transplant list due to fulminant hepatitis. The dental check-up found juxta-pulpal carious lesions on the four wisdom teeth which were removed before the transplantation. **Conclusion:** Paracetamol overdose is one of the leading causes of liver failure. The estimated toxic dose was 150 mg/kg/day or about 10 g/day. N-acetylcysteine treatment should be leaded early, between 8 and 10 hours after ingestion. The paracetamol-aminotransferase, as a risk prediction tool, reproductibles methods and biomarkers can identify overdoses and lead to a faster medical care. Information campaigns and warning articles on overdosing risk must be continued to strengthen the prevention message for the population.

Introduction

Drug poisoning is a serious public health issue. Pain associated with dental conditions, including acute pulpitis and pericoronitis, is very common in the global population. The pain intensity can lead to analgesic self-medication above the recommended doses. The paracetamol is the analgesic the most widely used in the world in 2016 (49 000 Metrics Tons (MT) in USA, 34 600 MT in China, 48 400 MT in Europe) [1]. This drug was broadly used in mild to moderate pain by self-medication since 2008 and got analgesic and antipyretic effects. It is responsible for 2–7% of all cases of drug poisoning.

After benzodiazepines, it is the second most common drug involved in cases of drug poisoning (2–7%). Its antidote is N-acetylcysteine (NAC) [2].

The aim of this paper is to discuss the epidemiology, triggers, clinical and biological symptoms, as well as the treatment in order to propose a treatment regimen of acute paracetamol overdosing in dentistry.

Observations

A 56-year-old man was referred to the emergency department by his home care worker who found him at the morning in a confused and icteric state in a context of dental pain motivating the intake of 3 boxes of 8 tablets of paracetamol 1g during the night.

The anamnesis highlights: history of myocardial infarction leading to a septo-apical necrosis where angioplasties of the middle anterior interventricular artery and of the right coronary were performed; atrial fibrillation treated with fluindione, acetylsalicylic acid; hypertension treated with bisoprolol, perindopril; hypercholesterolemia treated with a combination of ezetimibe and simvastatin. He was also taking a proton pump inhibitor (lansoprazole).

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Table I. Biological vitals at different times of hospitalization.

	Exam T Time			Constants
	T1	T2	T3	
pH	7.18			7.38–7.42
PCO_2	16 mmHg			40 mmHg
HCO^{3-}	6 mmol/L	20.7	19	22–28 mmol/L
Creatinin	231 µmol/L	336	122	64–104 µmol/L
GFF	26 mL/min/1.73 m^2	16.72	56.81	90–120
Total Bilirubine	157 µmol/L	145	4	3–21 µmol/L
Conjugated Bilirubine	107 µmol/L L	106		0–9 µmol/L
ASAT	>4202 U/I	5578	19	5–34 U/I
ALAT	2784 U/I	2868	26	0–55 U/I
GGT	250 U/I	170	31	21–64 U/I
Lipase	87–U/I	235	77	8-78 U/I
INR	>10	2.01	1.22	2–3
Platelets	20 G/L	65	360	150–400 G/L
Factor V	9 mg/L	0.14	1.43	0–5mg/L
PT	18	37	79	>70
Paracétamol	20.4 mg/L			

T1: entry into emergency department; T2: morning of transplantation; T3: at discharge.

The patient had risk factors such as active smoking (40 pack-years) and chronic alcoholism (minimum 10 doses of alcohol per day).

On arrival at the emergency room, the patient was in shock (Blood Pressure: 76/40 mmHg; tachycardia: 120 bpm; marbling; polypnea at 30 cycles/minutes; oliguria) and a grade II encephalopathy (flapping and ideomotor slowing). He presented hematemesis and melena. The biological examination showed a hepatocellular insufficiency associated with an acute renal insufficiency and acidosis. The evolution of the biological data is summarized in Table I at three times of the hospitalization: T1 (entry into emergency department), T2 (morning of transplantation), T3 (at discharge).

An N-acetylcysteine protocol was initiated. He was transferred to intensive care. Upon diagnosis of fulminant hepatitis and according to the king's college criterias, the patient was placed on the waiting list for a priority liver transplant according to a national super emergency protocol.

Dental consultation revealed carious lesions ICDAS 6 on 18/17/28/38, ICDAS 3 on 48 and 35 (Fig. 1).

At the time of transplantation, viral status is negative.

Wisdoms teeth and 17 were extracted during hospitalization under local anesthesia and under antibiotic prophylaxis and therapy (amoxicillin) for 7 days. A local hemostasis protocol was implemented using collagen sponges and absorbable sutures. A scaling was performed and the 35 was preserved and restored in a conventional way.

The patient's new treatment at discharge, 2 months later, was: Acetylsalicylic acid, bisoprolol, atorvastatin, pantoprazole, alfuzosin, mycophenolic acid, tacrolimus, valganciclovir (donor was CMV+).

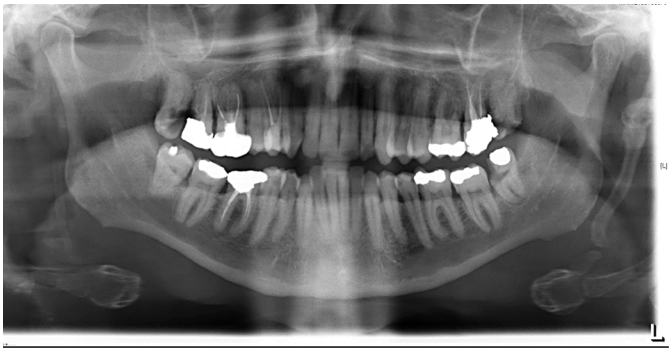

Fig. 1. Dental panoramic.

Discussion

Literature review

A narrative review of the literature (Medline and Web of science databases) about paracetamol overdose related to dental pain found 10 articles (published between 2002 and 2019) representing 331 patients [3–12].

The reasons given during anamnesis in supratherapeutic doses were all causes of dental pain (pulp necrosis, acute pulpitis, alveolitis or cellulitis with an apical lesion [4,5,12].

Patients were seen in dental or general emergency departments within 1 to 2 weeks of the appearance of symptoms [5,13]. These patients were classified as relative emergencies, and therefore did not require prompt treatment, which increases the risk of overdose [10].

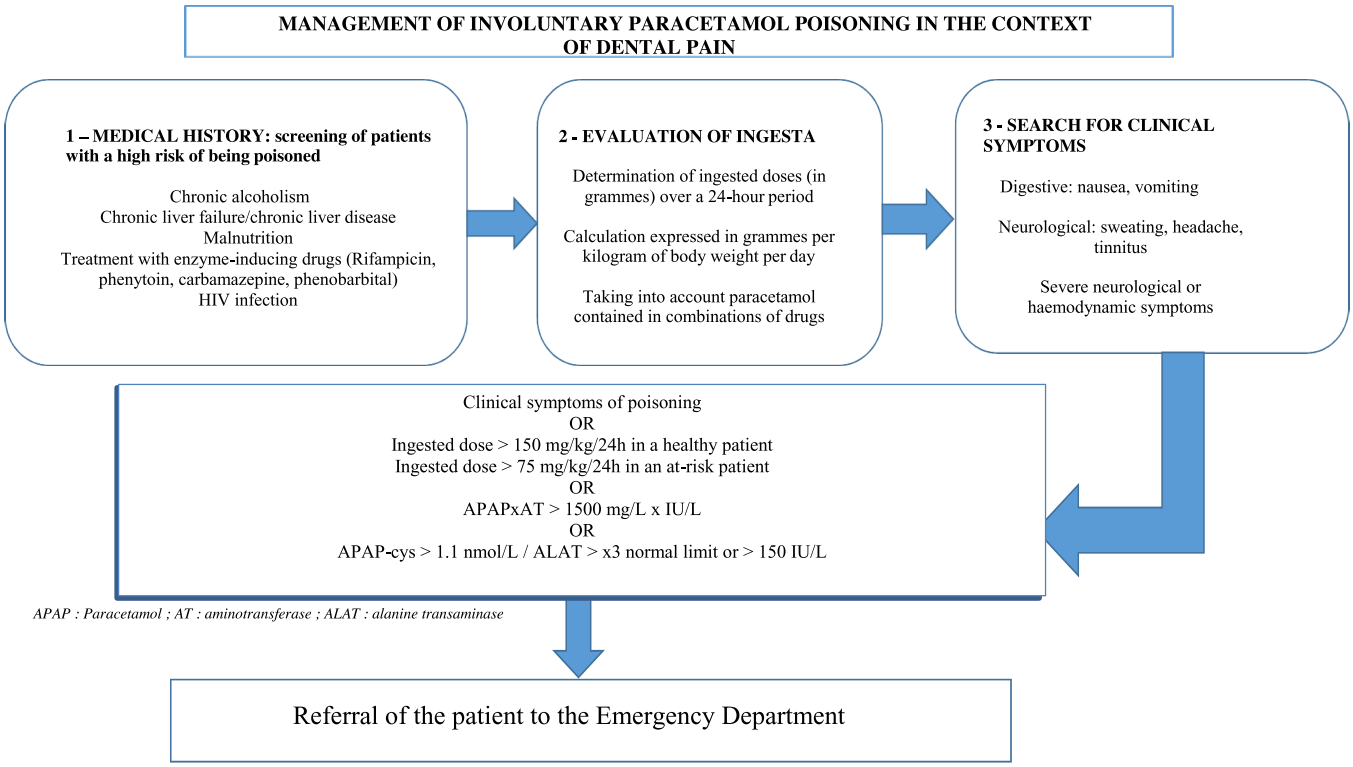

Fig. 2. Proposed treatment regimen for paracetamol poisoning inspired from Nayyer *et al.* [8].

The main clinical manifestations of overdose are digestive and neurological: abdominal pain, vomiting, or tinnitus [5–7]. Biological signs included acute liver failure with elevated transaminases [9,11] and decreased prothrombin (PT) [5] and even hepatic necrosis with paracetamolemia [9,11,12]. In the United Kingdom, paracetamol overdose is one of the leading causes of liver failure [6–8]. Georges and Meldrum showed in a survey that one in four patients were unaware of a maximum dose of paracetamol and 36% chose an incorrect amount. [14].

Diagnosis and treatment

The critical threshold varies between 10 and 15 grams of paracetamol per 24 hours [6,8], or about 150 to 250 mg/kg [9,15]. This threshold was half as high for patients with underlying diseases (cirrhosis, hepatitis) or those at risk (HIV, anorexia, undernutrition, cachexia, liver fibrosis, consumption of hepatotoxic drugs such as carbamazepine, phenobarbital) [8].

In the first prospective study describing the characteristics of paracetamol poisoning, the toxic dose was at least 4 grams within a 24-hour period. Symptoms and consequences of poisoning were dose-dependent [15]. Therefore, any patient who has ingested more than 150 mg/kg/day should be referred promptly to an emergency department.

NAC treatment is leaded when dose of paracetamol is upper or equal of 150 mg/kg in adults and 200 mg/kg in child. This injection could be administered immediately if the patient was seen within the hour [6] or in all cases of ingestion of 2 or more supratherapeutic doses of paracetamol over a period of 8 hours [7]. Compared to acute cases of poisoning involving a single dose, repeated poisonings have a higher mortality rate and a higher incidence of encephalopathy and hepatic and renal damage, despite the lower serum concentrations of paracetamol involved [16]. NAC only protects the liver if the injection takes place within 24 hours of ingestion. It is administered intravenously with an electric syringe at the initial dose of 150 mg/kg in 200 ml of 5% glucose solution for 15 minutes, then 50 mg/kg in 500ml for 4 hours and 100 mg/kg in 1000 ml for 16 hours [12]. Hypersensitivity reactions to NAC occur in 6 to 23% of cases [7] and appear within one hour of injection, ranging from skin rash to anaphylactic shock. Patients were allowed to return home as soon as their liver function had returned to normal [15]. Per os or intraveinous galenics can be used but per os need a longer treatment and can be difficult if vomiting [17]. A part of hepatic metabolism is transformed in a metabolit named N-Acetyl-p-benzoquineimine reacting with glutathione which decreased its rate. The depleting in glutathione leads to oxidative stress can causing centrolobular necrosis hepatic. NAC is the predecessor to glutathione to absorb toxic metabolites of paracetamol to prevent acute poisoning. It restores glutathione concentration by means of hydrolysis of cysteine

Predictor risk of hepatotoxicity

However, Wong and Graudins [18] reported that the use of paracetamol concentration is not a reliable predictor of the risk for this developing hepatotoxicity, unlike the paracetamol-

aminotransferase product which is calculated by multiplying the concentration of paracetamol by the aminotransferase activity measured at the same time (APAP x AT). This product does not require any knowledge of the exposure time, its reproducibility is better (laboratory measurements) and has a high sensitivity in the period less than 8 hours after ingestion.

The other solution evoked is biomarkers. Biomarkers are sensitive laboratory tests specific to confirm drug-related nature of a liver injury. A hepatotoxicity biomarker is not only the signature of a liver lesion but can also identify the xenobiotic involved or at least one class of chemical entities. They are used to confirm liver damage, severities, prognosis or define the type of liver injury [19]. Two major groups of biomarkers studied in paracetamol overdosing: paracetamol protein adducts (APAP-cys) and liver-specific micro-RNA (miR122-5p defining ALAT value) [18]. They are readily detectable and have better sensivity compared with ALAT and ASAT [20,21]. Nevertheless, higher cost and times requirements of genetic testing limit their use [22].

Conclusion

Based on the literature review and this work, we are proposing a treatment regimen for paracetamol poisoning, which is summarized in Figure 2: Management of involuntary paracetamol poisoning in the context of dental pain.

Patients self-medicating with paracetamol for dental pain had 12,8 more times lead to overdose than patients with other pains [23]. It appears there is a significant lack of knowledge among practitioners about the critical threshold for paracetamol ingestion and drug combinations containing paracetamol, as well as among the general population about the risks of overdose [5,7,8,12]. Information campaigns and warning articles on overdosing risk must be continued in order to strengthen the prevention message for the population.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Ethical approval was not required.

Consent for publication

Written informed consent was obtained from all patients and/or families.

Availability of data and materials

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Authors' contributions

CD, RL, JL, FC, JHC wrote and read the article and approved the final manuscript.

List of Abbreviations

MT	Metric Tons
NAC	N-Acetylcysteine
ASAT	Aspartate aminotransferase
ALAT	Alanine aminotransferase
PT	Prothrombin
HIV	Human Immunodeficience Virus
APAP	Paracetamol
AT	Aminotransferase
GFF	glomerular filtration flow
INR	international normalized ratio
HB	hepatitis B
HC	hepatitis C
CMV	cytomegalovirus

References

1. Global paracetamol market 2019 by manufacturers, regions, types and application forecast to 2024; available on https://www.360researchreports.com/global-paracetamol-market-13881939 Accessed Dec. 23, 2020
2. Yamamoto T, Spencer T, Dargan PI, Wood DM. Incidence and management of N-acetylcysteine-related anaphylactoid reactions during the management of acute paracetamol overdose. Eur J Emerg Med Off J Eur Soc Emerg Med 2014;21:57–60.
3. 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;29:1125–9.
4. Leader R, Hackett J, Al-Naher A. Supra-therapeutic oral paracetamol overdose in adults: an update for the dental team. Dent Update 2017;44:409–10, 413-4.
5. 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.
6. Siddique I, Mahmood H, Mohammed-Ali R. Paracetamol overdose secondary to dental pain: a case series. Br Dent J 2015;219:E6.
7. O'Sullivan LM, Ahmed N, Sidebottom AJ. Dental pain management – a cause of significant morbidity due to paracetamol overdose. Br Dent J 27 2018;224:626–624.
8. 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;216:229–35.
9. Pape E, Collin C, Camelot F, Javot L, Petitpain N, Puskarczyk E, *et al.* Paracetamol misuse and dental pain: results from the French

observational DAntaLor study. J Oral Facial Pain Headache 2019;33:123–9.
10. Dodd MD, Graham CA. Unintentional overdose of analgesia secondary to acute dental pain. Br Dent J 2002;193:211–2.
11. Lee SKY, Quinonez RB, Chuang A, Munz SM, Dabiri D. The case for improved interprofessional care: fatal analgesic overdose secondary to acute dental pain during pregnancy. Case Rep Dent 2016;2016:7467262.
12. 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;203:25–8.
13. Hommez G, Ongena B, Cauwels RGEC, Paepe PD, Christiaens V, Jacquet W. Analgesia (mis)usage on a dental emergency service: a patient survey. Clin Oral Investig 2017;1–6.
14. George I, Meldrum J. A study to assess the prevalence of unintentional paracetamol overdose among patients presenting in dental pain in primary care. Br Dent J 2020
15. Daly FFS, O'Malley GF, Heard K, Bogdan GM, Dart RC. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med 2004;44:393–8.
16. Craig DGN, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol 2012;73:285–94.
17. Bannwarth B, Pehourcq F. Bases pharmacologiques de l'emploi du paracetamol: aspects pharmacocinétiques et pharmacodynamiques. Drugs 2003;63:5–13.
18. Wong A, Graudins A. Risk prediction of hepatotoxicity in paracetamol poisoning. Clin Toxicol 2017;55:879–892.
19. Andrade RJ, Aithal GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, *et al.* EASL clinical practice guidelines: drug-induced liver injury J Hepatol. 2019.
20. Thulin P, Nordahl G, Gry M, Yimer G, Aklillu E, Makonnen E, *et al.* Keratin-18 and microRNA-122 complement alanine aminotransferase as novel safety biomarkers for drug-induced liver injury in two human cohorts. Liver Int 2014;34:367–378.
21. Thulin P, Hornby RJ, Auli M, Nordahl G, Antoine DJ, Starkey Lewis P, *et al*. A longitudinal assessment of miR-122 and GLDH as biomarkers of drug-induced liver injury in the rat. Biomarkers 2017;22:461–469.
22. Fu S, Wu D, Jiang W, Li J, Long J, Jia C, Zhou T. Molecular biomarkers in drug-induced liver injury: challenges and future perspectives. Front Pharmacol 2020;10:1667.
23. Thomas MB, 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.