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

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Aims: To evaluate the risk of hepatotoxicity due to unintentional paracetamol misuse in patients with acute dental pain. **Methods:** A prospective multicenter observational survey was performed in patients consulting, without appointment, the odontology departments of three main French hospitals in the Lorraine region over a 3-month period. Patients were asked to fill out a medical questionnaire while seated in the waiting room. Those who completed 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 g 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 $mg.kg^{-1}.24h^{-1}$, or 100 $mg.kg^{-1}.24h^{-1}$ over periods of 24, 48, and 72 hours, 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%. Paracetamol was self-medicated in 85.5% of the patients and misused by 6.0%. Clinical symptoms were observed in 1.6% of the patients with no paracetamol misuse. For patients consuming more than 4 g per day and experiencing mild unspecific clinical symptoms of hepatotoxicity, the suspected ingested dose category was below one of the three previously defined thresholds for 11.8% and was above for 40.0%. **Conclusion:** Patients with dental pain are at risk of paracetamol overdose and hepatotoxicity. *J Oral Facial Pain Headache 2019;33:123–129. doi: 10.11607/ofph.1861*

Keywords: *acetaminophen, acute dental pain, misuse, paracetamol, unintentional intoxication*

Paracetamol, also known as acetaminophen, is the most prescribed analgesic drug. In 2012, the analysis of sold medicines performed by the French National Agency for Medicines and Health Products Safety estimated that paracetamol represented 18% of all ambulatory prescribed medicines, which represent approximately 500 million packages sold every year.[1] Paracetamol, considered a safe and well-tolerated drug, is easily and largely prescribed, delivered, and consumed, so the risk of hepatotoxicity is too often forgotten despite paracetamol remaining the major cause of acute liver failure.[2] Paracetamol is safely used to treat different types of pain such as back pain, fever, headache, and musculoskeletal pain. Nevertheless, 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 hard to identify, as its clinical signs (such as nausea, vomiting, or abdominal pain) are mild and unspecific and because the alanine aminotransferase (ALT) level might appear normal or only slightly elevated.[2,10] Furthermore, the risk of hepatotoxicity cannot be assessed by testing the plasma paracetamol concentration using the Rumack-Matthew nomogram, which is 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]

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 (10 $g.24h^{-1}$ or 6 $g.24h^{-1}$ over periods of 24 and 48 hours, respectively; and 4 g/day for patients with predisposing risk factors for hepatotoxicity [chronic ethanol misuse, dehydration, prolonged fasting]),[12] presenting clinical manifestations of hepatotoxicity (abdominal pain, fatigue, anorexia, fever), or with a paracetamol plasma concentration greater than 20 $mg.L^{-1}$ or elevated levels of alanine aminotransferase (ALT), which 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 departments of three main French hospitals of the Lorraine region over a 3-month period.

Materials and Methods

The patients were recruited among the patients using services without an appointment in the odontology departments of three main regional hospitals of the Lorraine region (France) during a 3-month period between April and June 2011.

The DAntaLor study was designed as a prospective survey. Included in the study were patients who completed the questionnaire (see below), accessing dental services due to dental pain, and subsequently using paracetamol. Patients who declined to participate in the research, patients with memory disorder or with a diagnosed mental disorder, patients with impaired communication skills or limited knowledge/understanding of the French language, and unaccompanied minor patients were excluded. The DAntaLor study was approved by the local research ethics committee (CRENHU).

Questionnaires

Two specific questionnaires were designed in order to select the patients. One questionnaire had to be completed in the waiting room prior to the dental appointment, and the second questionnaire was completed by the dental practitioners. The two medical questionnaires were developed to standardize data collection.

The first questionnaire consisted of three parts: recording administrative and medical information, the reason for accessing services, 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 and confirm the existence of regular dental visits. The second part assessed whether the patient used the clinic for dental pain or any another reason. In cases of dental pain, the patient had to rate the pain intensity at the time of the visit and the maximum level of pain experienced by the patient since its inception by means of a numeric pain rating scale (NPRS)[13] ranging from 0 (no pain) to 10 (worst possible pain). The third part of the questionnaire analyzed the intake of painkillers (type, quantity, prescription type [self- or physician-prescribed]) taken in the last 2 weeks, including the day of the visit. A catalog with the picture of the drug packs of the 21 most frequently bought analgesics in the Lorraine region was provided to the patient to help him/her remember the name of the used analgesics and to improve the quality of the data collection.

The questionnaire to be completed by the dentist was designed in order to standardize, check, and complete the information provided by the patient, in particular regarding the period and amount of ingested paracetamol in order to calculate the supposed ingested dose (SID; see below) necessary for the assessment of paracetamol misuse or overdose. The questionnaire also included questions about the first clinical symptoms of paracetamol intoxication, including anorexia, epigastric and right hypochondrium pain, nausea, vomiting, pallor, and sweat, and also about dental diagnosis and treatment. An instruction leaflet was provided to the dentist to help identify situations of paracetamol overdose based on the first clinical symptoms of intoxication or on the calculated SID over periods of 24, 48, and 72 hours. This leaflet also included a list of the most frequently consumed painkillers containing paracetamol, solely or combined, 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 let the patient rate their pain intensity after therapy using the NPRS.

Calculation of SID

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

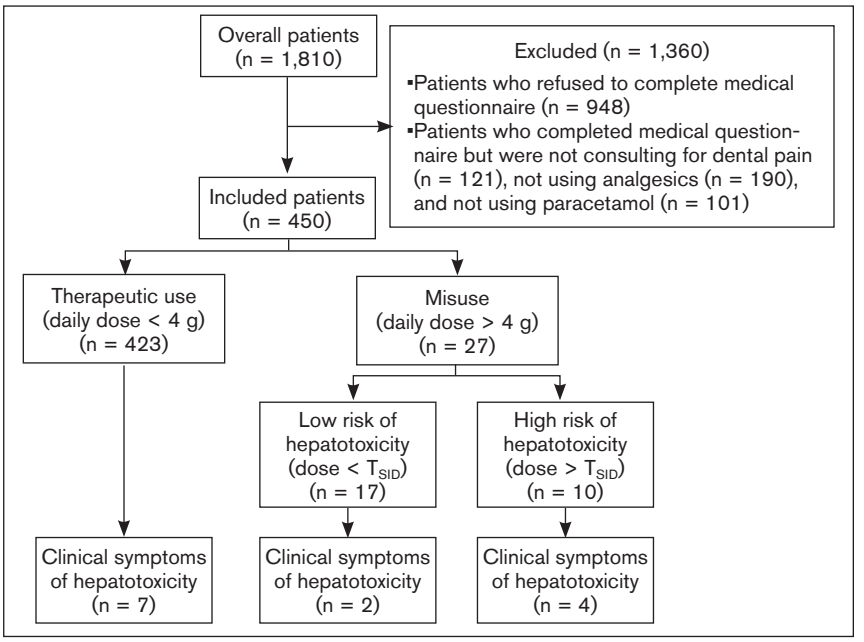

Fig 1 Flowchart of the DAntaLor cohort population. T_{SID} = threshold dosages of 150 $mg.kg^{-1}.24h^{-1}$, 125 $mg.kg^{-1}.24h^{-1}$, or 100 $mg.kg^{-1}.24h^{-1}$ over periods of ingestion of 24, 48, and 72 hours, respectively.

of paracetamol over the period of ingestion, and the weight of the patient. The formula was as follows:

$$\text{SID } (mg.kg^{-1}.24h^{-1}) = \frac{(\text{Ingested amount [mg]} \times 24)}{(\text{Weight [kg]} \times \text{Period of ingestion [h]})}$$

Assessment of Paracetamol Misuse and Risk of Hepatotoxicity

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

Criteria for Suspecting Paracetamol Hepatotoxicity. Paracetamol hepatotoxicity was diagnosed only based on the presence of symptoms such as nausea, vomiting, sweating, pallor, anorexia, and/or epigastralgia.

Statistical Analyses

Frequency data were analyzed 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 using analysis of variance (ANOVA). A P value < .05 was considered statistically significant. Analyses involved use of SAS (version 9.3) statistical software (SAS Institute).

Results

During the 3 months of the study period, 1,810 patients used the odontology services without appointment: 510 in the hospital of Thionville, 525 in the hospital of Metz, and 775 in the university hospital of Nancy. Of these patients, 862 completed the medical questionnaire, and dental pain was the reason for accessing services in 741 of these cases (86.0%). Of these 741 patients, 551 used analgesics, and the 450 who used paracetamol were included in the DAntaLor study (Fig 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. Of the 551 patients using analgesics, 596 diagnoses were listed, and the two most frequent pathologies were pulpal pathologies (56.0%) and odontogenic infections (infection of the alveolar bone, jaws, or face through maxillofacial spaces originating from a tooth or its supporting structures that is secondary to pulp necrosis, apical lesions, pericoronitis, periodontal disease, or iatrogenic complications of a dental procedure) (19.6%) causing cervicofacial cellulitis (Table 1). Pulpal pathologies included pulpitis (38.6%) and pulp necrosis (17.4%). The mean pain intensity as rated on the 0–10 NPRS 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).

Table 1 Diagnoses in Patients Using Services for Pain Management

	n	%
Pulpitis	213	38.6
Cervicofacial cellulitis	108	19.6
Pulp necrosis	96	17.4
Mucosal lesion	31	5.6
Tooth mobility	30	5.4
Dentin hypersensitivity	30	5.4
Periodontal infection	27	4.9
Dental trauma	24	4.3
Interproximal pain	13	2.3
Pain caused by teeth prosthesis	10	1.8
Alveolitis and postoperative pain	12	2.1
Necrotizing ulcerative gingivitis	2	0.3

Note: 8.1% (45/551) of the patients presented more than one diagnosis.

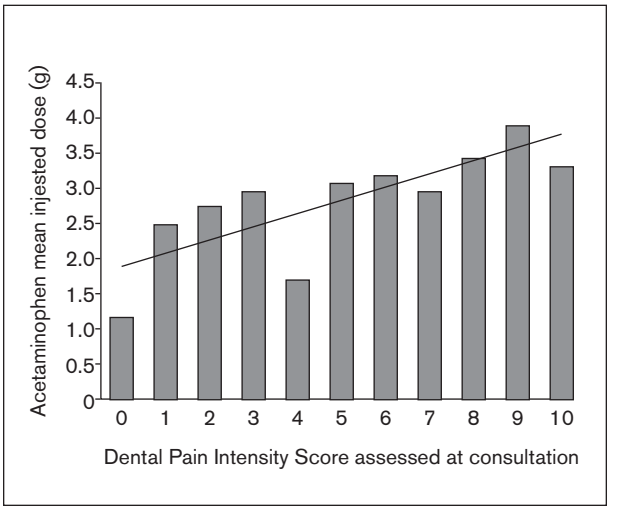

Fig 2 Positive correlation between mean ingested dose of paracetamol and dental pain intensity score assessed at the time of the visit (r = 0.77).

Table 2 Mean ± Standard Deviation Pain Ratings on a 0–10 Numeric Pain Rating Scale of Patients with the Three Most Painful Pathologies

	Overall pathologies	Pulpitis	Pulp necrosis	Cervicofacial cellulitis
Mean intensity of pain at 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	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 in pain intensity after dental care	−4.0 ± 3.1			

Of the patients suffering from dental pain, 74.4% took analgesics. Paracetamol was the most commonly used in 81.7% of these cases, 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 visit (median 48 hours). Paracetamol mean intake dose was found to be correlated with the intensity of dental pain at the time of the visit, and the linear correlation coefficient was 0.77 (Fig 2). In contrast, no correlation was observed between 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 (eg, as an over-the-counter [OTC] drug) in 44.7%, obtained from a previous prescription in 29.9%, and from a close person or family member in 10.9%. Paracetamol misuse corresponding to a daily dose greater than 4 g per day was observed in 27 of the 450 patients using paracetamol (6.0%) (Fig 1). Ten of them were considered to have taken an overdose and therefore to be at high risk of hepatotoxicity, since the calculated SIDs were greater than the established threshold dosages previously described. The SID of paracetamol observed in these patients ranged from 119.1 to 327.3 $mg.kg^{-1}.24h^{-1}$ (median value: 169.1 $mg.kg^{-1}.24h^{-1}$) for intake periods ranging from 48 to 72 hours. Hepatotoxicity was suspected in four of these patients (40.0%) according to clinical symptoms such as nausea, vomiting, sweating, pallor, anorexia, and epigastralgia. These four patients were referred to the emergency department after the dental treatment, but only three patients went. As for the 17 patients with paracetamol misuse but considered at low risk of hepatotoxicity, clinical symptoms of hepatotoxicity were observed in two (11.8%), and hepatotoxicity was suspected. Finally, clinical signs of hepatotoxicity were observed in 6 out of the 27 paracetamol misuser patients (22.2%). Hepatotoxicity was suspected in 7 of the 423 patients (1.6%) who did not exceed the maximum therapeutic daily dose of 4 g. Thus, the use of a daily dosage of paracetamol of more than 4 g per day or greater than the thresholds 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.

Discussion

Patients accessing the odontology departments of the three main hospitals in the Lorraine region presented characteristics consistent with those reported by previous epidemiologic studies on patients accessing 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. Pulpitis and pulp necrosis were the two most frequent dental pathologies and were found in one out of every two 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 might prevent unnecessary 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 the time of consultation was 6.0 ± 2.6, and the maximum 7.5 ± 2.3.

The results of this study were performed between April and June to avoid the risk of involving patients with an overconsumption of paracetamol due to winter diseases. This demonstrates 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 visit was a better marker for paracetamol use and that it is likely to be 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 visit 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 to warn the population of the risk of paracetamol misuse should be continued. 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 g per day is probably the most important information. Indeed, clinical signs 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. This is in accordance with Watkins et al,[23] who reported an increase of more than 30% of aminotransferase levels in healthy adults receiving 4 g of paracetamol daily during 14 days. The clinical signs presented by the patients were mild and unspecific, with 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 $mg.L^{-1}$, whereas serum ALT levels were 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 biologic 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]

According to the TSIDs proposed by Daly et al,[12] 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 g per day have a 13-fold higher risk of hepatotoxicity than patients without paracetamol misuse. This risk increased 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 that may be useful to dental practitioners to diagnose patients at risk is the dose proposed by Nayyer et al[27] (eg, 150 $mg.kg^{-1}$ or 75 $mg.kg^{-1}$ over a 24-hour period in absence/presence of risk factors of hepatotoxicity, respectively). All the patients with clinical evidence of hepatotoxicity in 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 must be highlighted that the patients of this study did not present with 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 3 days.

Finally, it is important to point out a possible limitation of the DAntaLor study—the low rate of participation (47.6%). As mentioned by Galea and Tracy,[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 and the fear of intrusion on personal lives or highly solicited individuals, especially by telemarketing, in an "oversurveyed" society. The patients more likely to participate are women, employed people, and married people who willingly participate in simple and not time-consuming studies with an immediate benefit to themselves and that are salient to their lives. Interestingly, patients with lower socioeconomic status, poorer health, or concerned with risk behaviors such as smoking, alcohol, or drugs are less likely to participate in 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.

Conclusions

This 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 a therapeutic dose of paracetamol, whereas they were found in 22.2% of the patients using more than 4 g of paracetamol per day. Clinical symptoms were observed in 40% of the patients who ingested more than 150 $mg.kg^{-1}.24h^{-1}$, 125 $mg.kg^{-1}.24h^{-1}$, or 100 $mg.kg^{-1}.24h^{-1}$ over periods of ingestion of 24, 48, and 72 hours, respectively. Clinical symptoms were mild, unspecific, and resolved without consequences or antidote administration.

Acknowledgments

The authors report no conflicts of interest.

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