Evaluation of Prescription Practices of Domperidone in Parkinson's Disease: A Cross Sectional Study Among French Neurologists

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Abstract (247/250 words)

Background– Domperidone is used to treat gastrointestinal symptoms in patients with Parkinson's disease (PD). Due to increased risk of cardiac adverse events, the European Medicines Agency (EMA) has issued recommendations restricting its use mainly in terms of age and dose and treatment duration.

Objective– The aim of this study was to investigate nowadays prescription practices of domperidone in PD among French neurologists.

Methods– A cross sectional study based on a questionnaire was conducted among French neurologists from Parkinson Expert Centers from the French NS-Park/FCRIN network, general hospitals and private practice.

Results– Among the 253 neurologists who completed the questionnaire, 86 (34%) were physicians from Expert Centers and 167 (66%) from other healthcare settings; 209 (83%) were aware of recommendations restricting domperidone use. The majority of neurologists (92%) declared prescribing domperidone regardless of the age of the patients. Neurologists were 61% to prescribed domperidone beyond 7 days in newly diagnosed patients, 33% in patients with orthostatic hypotension and 79% in patients under continuous apomorphine. They did not follow the recommendation on posology in newly diagnosed patients (7% of neurologists), patients with orthostatic hypotension (10%) and patients under continuous apomorphine therapy (25%). Finally, 58% of neurologists declared taking specific precautions before prescribing domperidone.

Conclusions– These findings underline most French neurologists who responded do not fully follow the restrictions on domperidone use, particularly in terms of treatment duration, and in

patients with continuous apomorphine. This may reflects unmet needs to prevent nausea in PD patients treated with dopaminergic drugs, particularly continuous apomorphine.

key points

- The European Medicines Agency has issued recommendations restricting domperidone use to patients younger than 60 years-old, at doses below 30 mg/day and for a short period only; making it challenging for neurologists to prescribe domperidone for patients with Parkinson's disease.
- Our results underline most French neurologists who responded do not fully follow the restrictions on domperidone use and specific precautions are not always taken before prescribing this medicine to Parkinson disease patients.
- This study highlights the unmet needs to prevent nausea in Parkinson disease patients treated with dopaminergic drugs.

1. Introduction

Parkinson disease (PD) is the second most frequent neurodegenerative disease after Alzheimer disease and affects 1% of the population over 60 years of age [1]. As a consequence of population aging and life expectancy improvement, the number of PD patients is predicted to grow substantially in future years and should affect 260,000 persons in France in 2030[2]. The treatment of PD is based on dopamine replacement therapies (DRT). Nausea is the most frequent adverse event of DRT, occurring in 30-40% of patients at initiation of treatment [3-7]. Domperidone is an "old" antiemetic drug supposed to work by blocking dopamine D2 receptors in the gut and the area postrema controlling vomiting [8]. As compared to other antiemetic drugs, domperidone does not readily cross the blood-brain barrier and can thus be used in Parkinson's disease despite its dopamine receptor antagonist properties. Domperidone has indeed shown efficacy in preventing nausea related with dopaminergic medication in PD [9]. Domperidone is also used in PD to treat orthostatic hypotension, another adverse effect of dopaminergic drugs [10].

Arrhythmias, sudden death and cardiac arrest were reported with high intravenous domperidone doses [11, 12], this alert has led to the withdrawal of the parenteral form of the drug in 1984. More recently, two case control studies found an increased risk of sudden death associated with oral domperidone use. In these studies, the increased risk was depending on age, dose, and the use of domperidone in combination with CYP3A4 inhibitors [13, 14]. Following this alert, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has issued recommendations restricting domperidone use to patients younger than 60 years-old, at doses below 30 mg/day and for a short period only (up to 7 days)[15].

Because alternative antiemetic drugs are limited in PD because of their dopaminergic antagonist properties (other benzamides), or because of their similar safety profile (prolonged QT), domperidone has been prescribed as a preventive therapy in PD patients in several countries, including France. In this population, usually older than 60 years, doses of 60 or 80 mg/day were commonly prescribed [9], for at least the first two months of the DRT escalating dose period or longer. In addition, a particular "niche" of domperidone use are patients treated with continuous subcutaneous administration of apomorphine, a second line therapy in PD, inducing severe and prolonged nausea in many patients.

Little is known about domperidone use in PD in France in clinical practice since EMA recommendations have restricted its use. Nevertheless, due to PD patients' characteristics and use of domperidone in PD, complying with the recommended restrictions on age, dose and duration of treatment, may be challenging for neurologists. Therefore, the aim of this study was to investigate the prescription practices of French neurologists regarding domperidone in PD, after the EMA recommendations restricting its use.

2. Methods

2.1. Study design, study setting and participants

This sudy is the first part of a global project named "DUMP" (Domperidone use and misuse in Parkinson Disease") registered with an ENCEPP seal EUPAS26319 (http://www.encepp.eu/encepp/viewResource.htm?id=33284) and funded by the French agency for drugs (Agence Nationale de Sécurité du Médicament). We conducted an observational cross sectional study based on an anonymous paper or web-based questionnaire completed by neurologists between June 2018 and February 2019 across France. To ensure the representativeness of diverse practices, neurologists were recruited from PD Expert Centers[16] (France Parkinson Expert Centers list available at www.franceparkinson.fr/la-maladie/prise-en-charge/centres-experts-parkinson/), public (university and general hospitals) and private practices.

French neurologists were identified and contacted to participate to the survey by different ways and several emails sent by (1) the French Society of Neurology (www.sf-neuro.org/) that is the national society for French neurologists (four emails from July to October 2018) and (2) the French clinical research network for PD and movement disorders (NS-Park/FCRIN network, https://parkinson.network/) gathering the 25 French Parkinson Expert Centers (three emails from October 2018 to January 2019). In addition, in order to recruit private practice neurologists, questionnaires were distributed for completion during the congress of the Association des Neurologues Libéraux de Langue Française (French liberal neurologists association, http://anllf.org/) and an online version of the questionnaire was also available on the website of this association.

In each setting, neurologists received a training note detailing how to answer the questionnaire.

The study aimed at describing physician self-reported usual practices and did not involve any patient. All data were collected anonymously. In accordance to French law, no ethics committee advice was needed.

2.2. Questionnaire and measurements

The questionnaire was conceived by a multidisciplinary team of neurologists, pharmacologists and epidemiologists (Supplemental file).

The first part of the questionnaire collected data on the respondent: age, sex, duration of practice in years, practice location and profiles of PD patients in the practice. Then, data on domperidone prescribing practices (indication, dosage, duration, evaluation of contraindications and precaution for use) were collected according to patients' profile. The questionnaire ended with questions about awareness of the revised recommendations endorsed by the EMA to restrict the use of domperidone, whether or not neurologists had changed their prescribing practice since then; whether or not they encountered difficulties to treat the symptoms (e.g. nausea and orthostatic hypotension) due to the prescription restrictions of domperidone and which therapeutic alternatives to domperidone were being used.

2.3. Statistical methods

Categorical variables were reported as counts and percentages and quantitative variables as mean and standard deviation. For the question about "clinical situations for prescribing domperidone in patients with Parkinson's disease", neurologists had the option of multiple responses; percentages were calculated according to all marked responses.

Shapiro-Wilk (if $n>50$) or Anderson and Darling (if $n<50$) tests were used to evaluate each variable for normality. Comparisons of qualitative variables were performed with Fisher's Exact or Pearson's Chi-squared test, as appropriate, while those on quantitative variables were performed with the Wilcoxon rank sum test. The level of significance was set at $p<0.05$. All analyses were performed with the R software (Version 1.1.419).

3. Results

3.1. Participants

Overall, 253 neurologists participated in the study; 86 (34%) were physicians from PD expert centers and 167 (66%) from other healthcare settings (Public hospitals, private practices or clinics). According to the Conseil de l'Ordre National des Médecins (French National Medical Council, www.conseil-national.medecin.fr/lordre-medecins/conseil-national-lordre/international-relations) 2,362 neurologists were registered in France in 2016, of those 92 belonged to expert centers. Therefore, the participation rate was 94% (N=86/92) among PD expert centers, and 7% (N=167/2270) among non-expert centers.

Among participating neurologists, mean age was 51.8 years, a majority of participants were men (N=149, 59%) and the average duration of practice was 22.5 years (Table 1). Physicians from PD expert centers were younger (mean age 46.5 vs 54.6 years old, $p<0.001$) and consequently with fewer years of practice (mean duration 17.3 vs 25.1 years, $p<0.001$).

The median number of PD patients followed by neurologists per year was 400 in PD expert centers and 140 in non-expert centers respectively. Patient population differed according to the type of practice (i.e. expert or non-expert centers); more patients newly diagnosed (median number 30 vs 18.5, $p<0.001$), with severe diagnosis (median number 200 vs 30, $p<0.001$) or under continuous apomorphine therapy (median number 20 vs 4, $p<0.001$) were seen in PD expert centers annually (table 1).

3.2. Clinical situations for prescribing domperidone

The main clinical situation for prescribing domperidone to PD patients was nausea at treatment initiation with dopamine agonists (N=176, 35%) followed by nausea under continuous apomorphine infusion (N=91, 18%) and all patients under continuous apomorphine infusion (whether they had nausea or not) (N=86, 17%) (Figure 1). Orthostatic hypotension represented 12.45% (N=63) of the clinical situations for prescribing domperidone.

There was no difference in the frequency of indications for domperidone between neurologists in expert or non-expert centers except that there were more neurologists who completely stopped prescribing domperidone in expert centers (6% vs 1%, p=0.013).

3.3. Use and misuse of domperidone among neurologists

Among participants, 83% (N= 209) were aware of the recommendations endorsed by the EMA to restrict the use of domperidone (93% in PD expert centers vs 78% non-expert centers; p=0.003).

Overall, 74.1% (N=186) of the participants acknowledged having changed their prescribing habits since the safety alerts and the revision of recommendations regarding the use of domperidone; with no significant difference between expert and non-expert centers (77% vs 73%, p=0.49).

Only 6% (N=14) of the respondents complied with the EMA recommendation to limit the prescription of domperidone to patients below the age of 60 (figure 2, Panel a). The great majority of neurologists (92%, N=223) declared prescribing domperidone to all patients regardless of their age.

Neurologists reporting prescribing domperidone in newly diagnosed patients at higher dose than recommended by the EMA (i.e. above 30mg/per day) were 7% (N=17). They were 10% (N=25) prescribing it in patients with orthostatic hypotension and 25% (N=61) in patients under continuous apomorphine therapy (Figure 2, Panel c).

Regarding treatment duration, the proportion of neurologists who prescribed domperidone for more than 7 days was 61% (N=152) in newly diagnosed patients, 33% (N=82) in patients with orthostatic hypotension and 79% (N=163) in patients under continuous apomorphine therapy (Figure 2, Panel d).

3.4. Precaution for use

Among the 253 neurologists, 144 (58%) declared taking special precautions before prescribing domperidone to PD patients (Figure 2, panel b). Among them, the most frequent precaution was “searching for concomitant use of contraindicated anti-arrhythmic” (N=119, 83%), followed by “searching for a personal or family history of cardiovascular diseases” (N=116, 81%) and “asking for a consultation with a cardiologist whenever in doubt” (N=72, 50%) (Table 2).

In expert centers, neurologists were more likely to perform or having performed an ECG before domperidone initiation than neurologists from non-expert centers (74% vs 33%, $p<0.001$).

3.5. Alternative therapeutics

Overall, 41% (N=120) of the neurologists reported continuing to prescribe domperidone to PD patients in the absence of a suitable alternative, despite of the EMA recommendations. Some of the neurologists declared prescribing ondansetron (N=20, 7%) or metoclopramide (N=10, 3%) as an alternative, and only 3% (N=17) completely stopped prescribing domperidone. One third (34%, N=86) of the participants declared having difficulties to treat nausea or orthostatic hypotension in PD patients.

4. Discussion

To our knowledge, this is the first survey on clinical practice for the use of domperidone. Our results highlight that many French neurologists are still prescribing domperidone in PD without strictly respecting the EMA recommendations, and without taking specific precautions in more than 40% of them. This occurs despite the fact that 83% are aware of these recommendations. However, 74% declare having changed their prescribing habits. The main reasons for using domperidone were to prevent or treat nausea at dopaminergic therapy initiation in de novo patients (35%) or in patients treated with continuous apomorphine (18%). Prescription of domperidone to all patients starting dopaminergic treatment was however not systematic, representing only 11% of neurologists. Domperidone was also prescribed for orthostatic hypotension by 13% of the respondents, a relatively low rate considering the prevalence of orthostatic hypotension estimated to be ranging from 30% to 65% in PD[22-24]. Age restriction was the least followed recommendation, with 92% neurologists prescribing domperidone regardless of age. Patients for which the neurologists were more prone to prescribe domperidone out of EMA restrictions were those treated with continuous subcutaneous apomorphine infusion, 25% of the neurologists prescribing domperidone at a higher dose (i.e. >30 mg) and 79% for a longer period (i.e. beyond 7 days) than recommended.

The benefit-risk ratio of domperidone use is currently not adequately assessed in PD and should be at least moderate due to the lack of therapeutic alternatives to treat adverse effects of DRT. Efficacy of domperidone was assessed in “old” clinical trials with small sample size, and a methodology that do not comply with the current gold standards [9, 10]. The evidence of efficacy is thus considered as low for nausea and orthostatic hypotension in PD and the drug is not approved in certain countries such as in the US. However, because extrapyramidal

adverse effects are minimal with domperidone, off-label prescriptions in PD are understandable, particularly in the context of apomorphine concomitant prescription [25]. Domperidone was systematically proposed in clinical trials testing subcutaneous apomorphine infusion, before and after treatment initiation (30-60 mg per day, 48 hours before and 2 weeks after treatment initiation) [26], although lower doses were proposed in more recent trials (30 mg/day starting 3 days before apomorphine infusion)[27].

On the other hand, domperidone was associated with an increased risk of mortality in the general population, recently confirmed in the PD population, the current use of domperidone being associated with a 2-fold increase mortality, increasing to 3-fold in the month following initiation [28]. The cause of this higher mortality in PD is not known and the increased risk in this study concerned all causes of mortality. However, the higher mortality associated with domperidone has been suggested to be related the propensy of domperidone to prolong QT and has been associated with sudden death in the general population [28]. In our study, less than 60% of the neurologists declared taking special precaution regarding this risk, and among all respondents, only a quarter of neurologists declared performing an ECG before initiating domperidone or requesting a consultation with a cardiologist. These findings highlight the need to secure domperidone prescriptions outside of safety restrictions for patients with PD, by systematically recommending consultation with a cardiologist and/or an ECG before initiating treatment.

Alternatives to domperidone are very limited in PD. In our study, alternative anti-emetic drugs were prescribed by 3-7% of neurologists only, and 30% of them declared having difficulties in treating nausea and orthostatic hypotension. Indeed, other benzamides or neuroleptics are not accurate alternatives in PD because they cross the blood brain barrier and worsen parkinsonian symptoms by blocking dopamine receptors in the central nervous system. Trimethobenzamide is the only drug that has shown efficacy in treating nausea in PD,

but is only available in the US[29]. More importantly, all antiemetic drugs, including benzamides (of which trimethobenzamide), and setrons, are associated with an increased risk of prolonged QT similarly to domperidone. Further studies would be needed to compare the safety profile of these potential alternatives to domperidone in the PD population. Non-pharmacological intervention such as hypnosis for preventing or treating nausea may also be evaluated in PD, but they are probably not appropriate for chronic and long-term treatment like continuous infusion of apomorphine.

The strength of our study is the relatively large number and the different varieties of neurologists from private or public practice who responded to the questionnaire. Some limitations have also to be acknowledged. Although the participation rate of neurologists from expert centers was high and probably representative of PD specialists, the participation rate among non-expert centers was low and probably less representative. Neurologists from expert centers are more often exposed to the management of more severe patients or patient under continuous apomorphine therapy, and therefore, their opinions were particularly important in this study as they could encounter daily dilemma regarding domperidone restriction or prescription[16]. However, neurologists from non-expert centers who responded followed a relatively high number of PD patients, and their responses were globally concordant with expert centers, the differences being mainly due to differences in patients profile rather than differences in clinical practice and prescribing habits. Another limitation is related to the design of this observational study based on self-reported questionnaires known to overestimate acceptable answers. In our case, anonymity should have reduced the social desirability bias.

4.1. Conclusion

French neurologists treating PD patients encounter difficulties in complying with EMA recommendations, given the characteristics of these patients and the lack of therapeutic alternatives. However, precautions are not sufficiently taken when introducing the domperidone treatment, probably due to the lack of specific recommendations for this population of patients. These findings underline the unmet needs to prevent nausea in PD patients treated with dopaminergic drugs, particularly continuous apomorphine.

5. Legends and captions

5.1. Tables

Table 1: Characteristics of questionnaire respondents and patient population by center status.

Table 2: Precautions taken by neurologists before prescribing domperidone in patients with Parkinson's disease.

Legend: Percentages were calculated as the ratio of the number of neurologists using a precaution over the total number of neurologists who answered YES to the question "Do you take any precautions before prescribing domperidone in patients with Parkinson's disease? (N=144/253)

5.2. Figures

Figure 1: Clinical situations for prescribing domperidone in patients with Parkinson's disease

Legend: For this question, neurologists had the option of multiple responses. Percentages were calculated according to all marked responses (N=506).

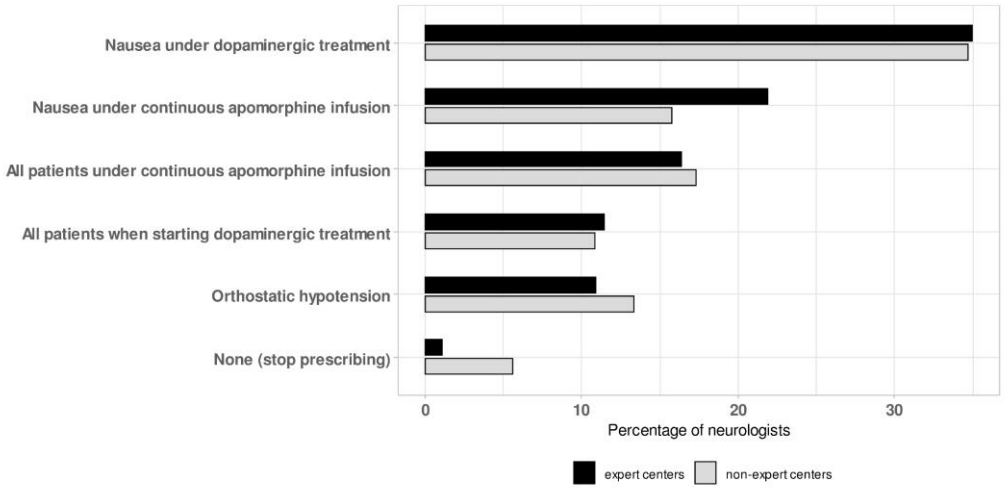
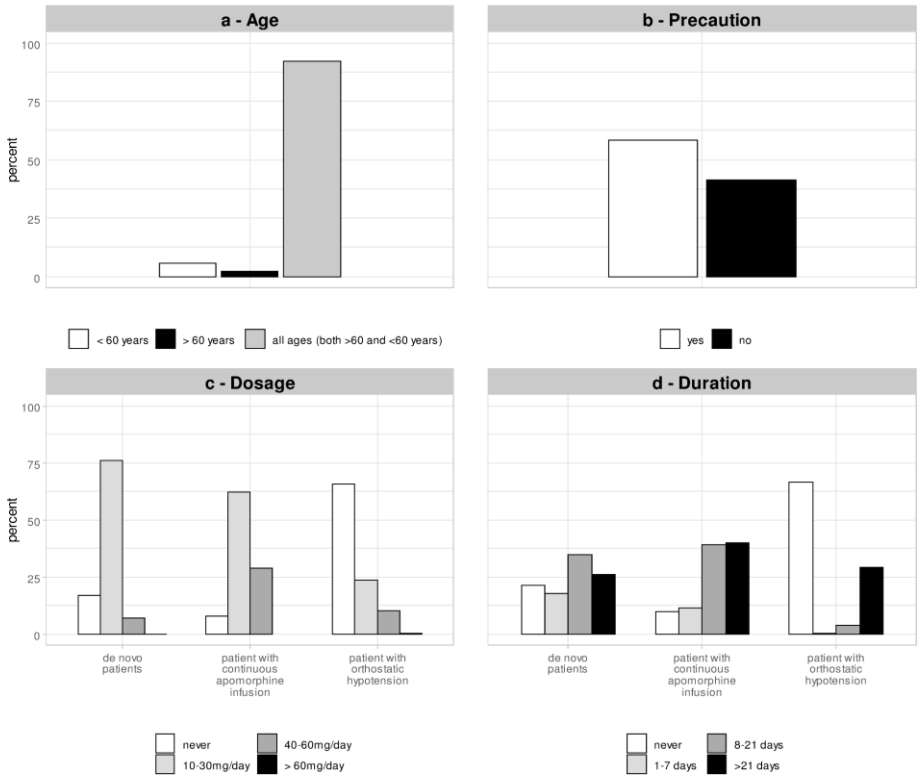


Figure 2: Habits of domperidone prescription by neurologists in Parkinson disease patients: patient's age, precaution for use, dosage and duration of treatment



Supplemental File: members of the NS-PARK/F-CRIN network

6. Declarations

6.1. Funding

This study was funded by the ANSM (Agence National de Sécurité du Médicament). The « DUMP » is registered under the reference EUPAS26319 and received and ENCePP Seal that recognises studies following the ENCePP principles of standards, transparency and independence.

6.2. Conflicts of interest/Competing interests

The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Competing financial interests unrelated to the present work:

L.L. MARIANI received research support grants from INSERM, JNLF, The L'Oreal Foundation; speech honoraria from CSL, Sanofi-Genzyme, Lundbeck, Teva; consultant for Alzprotect, Bionure, Digitsole and received travel funding from the Movement Disorders Society, ANAINF, Merck, Merz, Medtronic, Teva and AbbVie, outside the submitted work.

O. RASCOL served as a member of advisory boards for AbbVie, Adamas, Acorda, Addex, AlzProtect, Apopharma, Astrazeneca, Bial, Biogen, Britannia, Buckwang, Clevexel, INC Reasearch, Lundbeck, Lupin, Merck, MundiPharma, Neuratris, Neuroderm, Novartis, ONO Pharma, Orion Pharma, Osmotica, Oxford Biomedica, Parexel, Pfizer, Prexton Therapeutics, Quintiles, Sanofi, Servier, Sunovion, Théranexus, Takeda, Teva, UCB, Watermark, Research, XenoPort, XO, Zambon and received grant from Agence Nationale de la Recherche (ANR), CHU de Toulouse, France-Parkinson, INSERM-DHOS Recherche Clinique Translationnelle, MJFox Foundation, Programme Hospitalier de Recherche Clinique, European Commission (FP7, H2020) as well as a grant to participate in a symposium and contribute to the review of an article IPMDS, outside the submitted work.

J.D. Turc received honorarium from Abbvie for a symposium outside the submitted work.

J.C. CORVOL served as a member of advisory boards for UCB, Biogen, Prevail Therapeutic, Idorsia, Sanofi, Ever Pharma, Denali, BrainEver, Theranexus, and received unrestricted grant from the Michael J Fox Foundation outside the present work.

F. TUBACH is head of the Centre de Pharmacoépidémiologie (Cephepi) of the Assistance Publique – Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière hospital, both these structures have received research funding, grants and fees for consultant activities from a large number of pharmaceutical companies that have contributed indiscriminately to the salaries of its employees. Florence Tubach didn't receive any personal remuneration from these companies.

6.3. Authors' contributions

Louise-Laure Mariani, Olivier Rascol, Jean-Denis Turc, Maryse Lapeyre-Mestre, Jean-Christophe Corvol, Florence Tubach contributed to the study conception and design. Analysis were performed by Hala Alfaisal and Diane Lastennet. The first draft of the manuscript was

written by Diane Lastennet and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

6.4. Ethics approval

This is an observational study that did not involve any patient. All data were collected anonymously. In accordance to French law, no ethical approval is required.

6.5. Consent to participate – Not applicable

6.6. Consent for publication– Not applicable

6.7. Availability of data and material

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

6.8. Code availability – Not applicable

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