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ARTÍCULO ORIGINAL

Epidemiological profile of patients intoxicated with acetaminophen for suicidal purposes

Perfil epidemiológico de pacientes intoxicados con acetaminofén con intenciones suicidas / Perfil epidemiológico de pacientes intoxicados com acetaminofen (Paracetamol) com intenções suicidas

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ABSTRACT

Objective: this study aims to describe patients with overdose intake of acetaminophen between 2019 and 2020 at a reference center for liver transplantation in Colombia.

Methodology: study derived from a secondary analysis of the clinical records between January 1st, 2019, to December 31st, 2020. Inclusion criteria were individuals with voluntary acute ingestion of toxic doses of acetaminophen (>4 g/day).

Results: sixty-three cases, 68% women, 67% <18-year-old, and 54% students. 60% had personal history of psychiatric illness and 35% reported at least one previous suicide attempt. The median dose of acetaminophen was 15g, 46% referred to co-ingestion with other substances and 13% were under the effect of any psychoactive substance. 57% had a clear intention of suicide. 81% vomited before the arrival to the emergency room, 22% received decontamination intervention with gastric lavage or activated charcoal, and 10% did not receive any dose of N-Acetylcysteine. Fifteen individuals developed an acute liver injury, nine with severity criteria.

Conclusions: the population was predominantly young, the personal history of psychiatric disease was highly prevalent, and most of the cases referred a vital event that explains the impulsive behavior in acetaminophen consumption. None developed criteria for liver transplantation, and this could be explained by the young age of the individuals, the episodes of early vomiting, and the absence of chronic liver disease or hepatotoxic substance consumption.

Key words: acetaminophen; drug induced liver disease; attempted suicide; acetylcysteine.

RESUMEN

Objetivo: este estudio busca describir los individuos evaluados por sobredosis de acetaminofén entre 2019 y 2020 en un centro de referencia de trasplante hepático en Colombia.

Metodología: estudio derivado del análisis secundario de historias clínicas entre el 1.º de enero de 2019 y el 31 de diciembre de 2020. Los criterios de inclusión abarcan individuos con ingestión aguda y voluntaria de dosis tóxicas de acetaminofén (>4 g/día).

Resultados: sesenta y tres casos, 68% mujeres, 67% menores de 18 años y 54% estudiantes. Reportó historia personal de enfermedad psiquiátrica el 60% y el 35% al menos un intento de suicidio previo. La mediana de dosis de acetaminofén fue 15g, 46% refirieron co-ingesta de otras sustancias y 13% estaba bajo efecto de sustancias psicoactivas. El 57% tenía la intención clara de suicidarse, así como 81% vomitó antes de acudir al servicio de urgencias, 22% recibió medidas de descontaminación y 10% no recibió N - acetilcisteína. Quince individuos desarrollaron lesión hepática aguda, nueve con criterios de severidad.

Conclusiones: la población era predominantemente joven, la historia de enfermedad psiquiátrica fue muy prevalente y la mayoría refirieron un evento vital que explicara el

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comportamiento impulsivo de consumo. Ninguno desarrolló criterios para trasplante hepático, lo cual podría explicarse por la edad de los individuos, los episodios de vómito temprano, y la ausencia de enfermedad hepática crónica o de consumo de sustancias hepatotóxicas.
Palabras clave: acetaminofén; enfermedad hepática inducida por sustancias y drogas; intento de suicidio; acetilcisteína.

RESUMO
Objetivo: este estudo busca descrever os indivíduos avaliados por sobredose de acetaminofen entre 2019 e 2020 num centro de referência de transplante hepático na Colômbia.
Metodologia: estudo derivado da análise secundário de histórias clínicas entre o dia 1.º de janeiro de 2019 e 31 de dezembro de 2020. Os critérios de inclusão abrangem indivíduos com ingestão aguda e voluntária de dose tóxicas de acetaminofen (>4 g/dia).
Resultados: sessenta e três casos, 68% mulheres, 67% menores de 18 anos e 54% estudantes. Reportou história pessoal de doença psiquiátrica, 60% e 35% pelo menos uma tentativa de suicídio prévio. A média de dose de acetaminofen foi de 15g, 46% referiram com ingestão de outras sustâncias e 13% estava sob efeito de sustâncias psicoativas. 57% tinham a intenção clara de suicidar-se, assim como 81% vomitou antes de acudir ao serviço de urgências, 22% receberam medidas de descontaminação e 10% não recebeu N - acetilcisteína. Quinze indivíduos desenvolveram lesão hepática aguda, nove com critérios de severidade.
Conclusões: a população era predominantemente jovem, a história de doença psiquiátrica foi muito prevalente e a maioria referiram um evento vital que explicasse o comportamento impulsivo de consumo. Nenhum desenvolveu critérios para transplante hepático, o qual se poderia explicar pela idade dos indivíduos, os episódios de vómito precoce, e a ausência de doença hepática crónica ou de consumo de sustâncias hepatotóxicas.
Palavras chave: acetaminofen; doença hepática induzida por sustâncias e drogas; tentativa de suicídio; acetilcisteína.

INTRODUCTION

Acetaminophen is an extendedly available drug and the most widely used analgesic in the world[1]. However, its associated adverse effects are not trivial. The clinical use of acetaminophen was initially approved in the 1950s, but associated hepatotoxicity and liver failure were not recognized until the first case reported in the mid-1990s[2].

The mechanism of toxicity has been typically attributed to the formation of N-acetyl-p-benzoquinoneimine (NAPQI) by a minor fraction of oxidative metabolism of CYP450. The accumulation of NAPQI by the saturation of conjugative pathway and depletion of glutathione (GSH) stores[3–6], brings a mitochondrial dysfunction by covalent binding to mitochondrial proteins[7,8]. All the changes derived from this cascade could result in hepatic and brain dysfunction[2]

Each year, close to 800 000 people die due to suicide and suicide is considered the third cause of death for people between 15 and 19 years-age across the world[9].

In Colombia around 5.5% of men and 7.6% of women had suicide thoughts[10]4.5-6.7 and 2 580 cases of medicament poisoning were reported in 2019, but there is a lack of information about the intentionality of those events[11].

The information about acetaminophen overdose and toxicity in Colombia is limited. However, the report of poisonings with chemical substances in Bogotá in the second semester of 2019 informed that acetaminophen was the drug most frequently associated with intoxication for women (23%) while benzodiazepines were the most common in men (24%)[12].

This study aims to describe clinical, social, and demographic characteristics of all the patients being attended in the emergency room after an acetaminophen overdose intake, between 2019 and 2020, at a reference center for liver transplantation in Colombia.

METHODOLOGY

Study design and settings

This is a retrospective cohort study derived from data of the clinical records of patients hospitalized for acute acetaminophen overtake.

All variables of interest were obtained from the clinical records of the Hospital San Vicente Fundación (HSVF) Rionegro, and participants were identified with the CIE-10 code registered in the institutional database.

The follow-up time was limited between the first clinical record in the emergency room of HSVF and the discharge from the same institution. Those data from previous health institutions, or information related with the event, registered in the clinical records were included.

All clinical records from January 1st of 2019 to December 31st of 2020 were included in the search. Inclusion criteria were all those individuals that presented in the emergency room (autonomously or remitted from a lower complexity medical center) of the HSVF Rionegro after voluntary acute ingestion of toxic doses of acetaminophen (more than 4 g/day). No exclusion criteria were considered.

This study was approved by the ethics committee of the Hospital San Vicente Fundación (HSVF) and the institution gave the aval to extract the information from clinical records.

Variables and measurement

Our variables of interest were extracted using a structured instrument and divided by subgroups following the primary goal of this study. We evaluated age, sex, education as high school completed, marital status, and occupation as sociodemographic variables. About clinical variables we evaluated any personal history of psychiatric and non-psychiatric disease, and relevant outcomes like development of encephalopathy, drug-induced liver injury, acute kidney injury, and death. We assessed alanine transaminase (ALT) 24, 48 and 72 hours after the event, and total bilirubin levels (TBL) and international normalized ratio (INR) 24 and 48 hours after. We did not include phosphatase alkaline levels, gamma-glutamyl transferase (GGT) nor TBL or INR 72 hours after the event due the high missingness of information.

For the variables related with acetaminophen poisoning, we defined acute liver injury as the evidence of ALT higher than 200 IU/L (five times upper normal limit or ULN) or ALT values higher than 120 IU/L (three times ULN) with TBL higher than 2mg/dL. An INR higher than 1.5 was considered as severity criteria[13–15]the definitions and terminology related to the clinical phenotypes of DILI must be harmonized. For this purpose, an international DILI Expert Working Group of clinicians and scientists reviewed current DILI terminology and diagnostic criteria so as to develop more uniform criteria that would define and characterize the spectrum of clinical syndromes that constitute DILI. Consensus was established with respect to the threshold criteria for definition of a case as being DILI, the pattern of liver injury, causality assessment, severity, and chronicity. Consensus was also reached on approaches to characterizing DILI in the setting of chronic liver diseases, including autoimmune hepatitis (AIH.

We defined as variables of interest for suicidal attempt the acetaminophen dose and other ingested substances, being under the effect of any psychoactive substance, the planning and suicidal ideation related with the event, any previous suicidal attempt, and the persistence of suicidal ideation at the time of the first psychiatric assessment.

Context of the study

The HSVF Rionegro is a high-complexity health institution that is a national reference center of liver transplant. There, when a patient consults for suicide attempt is always assessed by a psychiatrist and the SAD PERSON scale is used routinely in the firs assessment in the emergency room because it is part of the hospital protocol, as a clinical tool for suicide risk assessment. The higher the SAD PERSON SCORE the higher the suicide risk in a 0-10 scale.

Data analysis

Data extraction was performed by a medical intern trained in the instrument for data recollection, in MICROSOFT EXCEL®. Then, those registries with missing data were reviewed in a second step and the missing information that was actually available was included. The rest of items without the required information are presented as missing values in the results.

A descriptive analysis of the data was performed with RStudio (version 1.2.5019). We did not perform any inferential procedure.

RESULTS

From January 1st, 2019, to December 31st, 2020, 63 cases of suicidal intents with acetaminophen overdose were identified. A total of 43 (68%) patients were women, 67% had less than 18-year-age, and 34 (54%) were students. Also, 13 (21%) and 38 (60%) of the cases

reported any personal history of non-psychiatric and psychiatric illness respectively, while 22 (35%) reported at least one previous suicide attempt or "autolytic" conduct in their life (Table 1).

Of those who referred any personal history of psychiatric disease illness, seven (11%) presented substance abuse, 20 (32%) a mood disorder, 10 (16%) a personality disorder, and five (8%) a history of childhood sexual abuse.

About the suicide attempt, the median dose of acetaminophen was 15g (IQR: 11.5g) being 5g and 50g the minimum and the maximum dose reported respectively. Twenty-nine individuals (46%) referred co-ingestion of other substances and eight (13%) were under the effect of any psychoactive substance. Also, 51 (81%) cases had vomited before the arrival to the emergency room, 14 (22%) received decontamination intervention with gastric lavage or activated charcoal, and six (10%) did not receive N-Acetylcysteine (NAC) (Table 2).

The assessment of the suicidal risk using the SAD PERSON scale showed that 28 subjects (44%) had a score between 0 and 2, 24 (38%) scores between 3 and 4, nine (14%) between 5 and 6, and two individuals (3%) received a score of 7 as the maximum obtained value. About the availability and intentionality, 36 (57%) referred a clear intention to suicide, 18 (29%) had ambivalent ideas in the discourse, and nine (14%) did not wanted to die. Also, 47 individuals (75%) did not have a structured plan and those had the acetaminophen available at home (Table 2).

Anyone died, developed encephalopathy or needed liver transplantation during the hospitalization. One patient presented acute kidney injury, and 15 developed acute liver injury, 9 with criteria of severity. At the initial assessment by the psychiatrist, eight patients (13%) persisted with the suicide idea, 12 (19%) were ambivalent, and 40 (68%) did not have suicidal ideation. Also, after being treated, 13 (21%) patients needed a remission to a psychiatric center due to a persisting mental state requiring further management (Table 2). We did not evidence any variable between those with acute liver injury with severity criteria or acute kidney

Table 1. Sociodemographic characterization and personal history of psychiatric and non-psychiatric disease.

	Woman (N=43)*	Man (N=20)*	Overall (N=63)*
Age, median [min, max]	18.0 [14, 41]	20.0 [14, 43]	18.0 [14, 43]
Adult (18 or more years old)	16 (37)	5 (25)	21 (33)
Highschool completed	12 (28)	9 (45)	21 (33)
Marital status			
Single	32 (74)	16 (80)	48 (76)
Married or consensual union	9 (21)	2 (10)	11 (18)
Divorced	1 (2)	2 (10)	3 (5)
Widower/Widow	1 (2)	0 (0)	1 (2)
Occupation			
Currently working	7 (16)	5 (25)	12 (19)
Unemployed	6 (14)	3 (15)	9 (14)
Student	23 (54)	11 (55)	34 (54)
Housewife	6 (14)	0 (0)	6 (10)
Unschooling	1 (2)	1 (5)	2 (3)
Personal history of non-psychiatric disease	8 (19)	5 (25)	13 (21)
Personal history of psychiatric disease	26 (61)	12 (60)	38 (60)
Previous suicide attempt	17 (40)	5 (25)	22 (35)

All values are presented as n (%) unless otherwise specified. Other referred substances includes ibuprofen, ethanol, ciprofloxacin, carbamazepina, methocarbamol, cocaine, marihuana, benzodiazepines, metronidazol, trimebutine, naproxen, hyoscine, omeprazole, ranitidine, sertraline, thiamine, esomeprazole, levothyroxine, nimesulide, acyclovir, amoxicillin, cephalexin, melatonin, pregabalin, tramadol, escitalopram, dipyrone, zopiclone, loratadine, diclofenac, salbutamol.

Table 2. Characterization of the suicidal attempt.

	Woman (N=43)	Man (N=20)	Overall (N=63)
Acetaminophen dose, median [min, max]	15 [5, 50]	18.8 [5, 40]	15 [5, 50]
Other substances	18 (42%)	11 (55%)	29 (46%)
Vomit before admission	35 (81%)	16 (80%)	51 (81%)
Treated with NAC	37 (86%)	18 (90%)	55 (87%)
Any acute adverse effect to NAC	4 (9%)	3 (15%)	7 (11%)
Attended to HSVF first	8 (19%)	2 (10%)	10 (16%)
Decontamination (gastric lavage/ activated charcoal)	10 (23%)	4 (20%)	14 (22%)
Needed admission to psychiatry	9 (21%)	4 (20%)	13 (21%)
SAD-PERSON score			
0 - 2	24 (56%)	4 (20%)	28 (44%)
3 - 4	13 (30%)	11 (55%)	24 (38%)
5 - 6	6 (14%)	3 (15%)	9 (14%)
7 - 10	0 (0%)	2 (10%)	2 (3%)
Access to acetaminophen			
Bought for the event	9 (21%)	3 (15%)	12 (19%)
Available at home	34 (79%)	17 (85%)	51 (81%)
Drug-induced Liver Injury			
Acute liver injury with severity criteria	6 (14%)	3 (15%)	9 (14%)
Acute liver injury without severity criteria	3 (7%)	3 (15%)	6 (10%)
Suicide intentionality			
With intention	26 (61%)	10 (50%)	36 (57%)
Ambivalent	11 (26%)	7 (35%)	18 (29%)
Structured plan	10 (23%)	6 (30%)	16 (25%)
Any vital/acute event attributed	32 (74%)	12 (60%)	44 (70%)
Suicide intent under any psychoactive subtance effect	2 (5%)	6 (30%)	8 (13%)

Of those under the effect of any psychoactive substance at the suicide intent, two (3%) cases consumed cocaine, 4 (6%) tetrahydrocannabinol, 1 (2%) consumed benzodiazepines, and 6 (10%) alcohol.

injury that could explain a higher risk to these outcomes (Supplementary Table 1).

Considering the time to medical attention, the median of time between the event and the arrival to the emergency room was five hours (interquartile range, IQR: 10) and 24 hours (IQR: 22.5) to a highly complex hospital. 14 (22%) cases arrived first at a highly complex hospital specialized in liver disease while for the rest the median of time from the first attention to the remission was 14 hours (IQR: 15.4). Finally, 50% were discharged four days or less after the event (IQR: 4), with a minimum value of one day and a maximum value of 35 (Table 3).

DISCUSSION

Exposure to analgesics has been reported as the first cause of exposure to poisoning substances as well as the first cause of drug-induced liver injury[16,17]. Since acetaminophen poisoning is considered as the first cause of drug-induced acute liver failure in developed countries, some studies have reported that those cases associated with a chronic intake and unintentional overdose largely related with opioid-acetaminophen combination represent around 50% of the cases[18].

Some studies characterizing the population that uses the acetaminophen for suicidal attempt have

Table 3. Times reported from the event to different stages of medical attendance.

	Woman (N=43)	Man (N=20)	Overall (N=63)
Time event-attention, median (IQR)	4.55 (10.0)	5.00 (9.0)	4.78 (10.0)
Time from low-complexity hospital to remission, median (IQR)	14.6 (13.3)	12.9 (16.2)	14.3 (15.4)
Time to HSVF (high-complex), median (IQR)	23.8 (22.3)	24.5 (35.1)	24.4 (22.5)
Time from event to discharge, median (IQR)	4.00 (2.50)	5.00 (5.25)	4.00 (4.00)

IQR: Interquartile range. HSVF: Hospital San Vicente Fundación.

similar results as those obtained in our study, showing that suicidal attempts with acetaminophen ingestion is more common among younger individuals and related with impulsivity[19–21]measures of depression and suicidal intent, information collected through the Oxford Monitoring System for Attempted Suicide, and the results of liver function tests. Results Acute liver dysfunction (25 patients. However, the current knowledge about their psychiatric profiles and about the suicidal attempt itself is limited and this result represents a matter of interest in the study of acetaminophen poisoning, psychiatry, and hepatology.

Our study shows heterogeneity in the acetaminophen dose. This could be explained at least in part by the availability of the substance at home. Also, some of those patients that referred to have premeditation and planning the suicidal attempt, referred that they searched in the internet information like the lethal dose. In this respect, studies in London after the 1998 legislation restricting to 36 the maximum number of tablets that could be purchased impulsively in pharmacies[22] have shown a reduction of 30% of the liver unit admissions for acetaminophen hepatotoxicity in four years and a reduction of 20% of the number of admissions for acetaminophen overdose[8]. A study with a 11-years follow-up after the legislation demonstrated a reduction of the 40% in mortality from paracetamol overdose but no similar reduction in liver transplant rates. Moreover, a study in Ireland after a similar legislation reducing the maximum pack sizes to 24 tablets in pharmacies showed no overall difference in the size of overdose between countries. Due to the heterogeneity in this topic, some systematic reviews and meta-analysis have shown a lack of enough studies to present a firm conclusion while the results among countries tend to have important differences[23].

Current guidelines recommend the use of the Rumack-Matthew nomogram to establish the likelihood of hepatic injury due acetaminophen toxicity and the necessity of treatment with NAC[24]. Since in Colombia plasma acetaminophen concentration is not measured routinely, some studies have suggested the reported ingested dose as a good predictor of outcome, however, the benefit or indication of it in these cases are less well defined[24,25]irrespective of reported dose. Objective. To determine if reported dose predicts the need for N-acetylcysteine (NAC.

The SAD PERSON score has been reported as a helpful tool for the assessment of suicide potential by non-psychiatrists, recommending that between 0 and 2 is reasonable to send home the patient with a follow-up; between 3 and 4 a close follow-up could be a better option, and between 5 and 10 the hospitalization is recommended[26]. Although this score is frequently used in the emergency room, some characteristics evidenced in our population shows that the score tends to be low even when the suicidal risk determined by a semi-structured interview at the time of the psychiatric assessment is high. Other studies have shown that there is not enough evidence to support the use of this tool in the emergency room[27]and a priority requirement is accurately identifying high-risk individuals. The SAD PERSONS suicide risk assessment scale is widely implemented in clinical settings despite limited supporting evidence. This article aims to determine the ability of the SAD PERSONS scale (SPS.

Regarding the time to the emergency room, most cases consult for medical attention after the first gastrointestinal symptoms (phase 1 of toxicity), delaying the access to specialized medical attention and diminishing the chances of early decontamination strategies[28].

While acetaminophen overdose is considered the major cause of hepatic failure in some countries such as the United States and England[29], none of our patients fulfilled any of the King's College Criteria for Liver

Transplantation in acetaminophen toxicity or MELD score to predict progression to encephalopathy or death. As mentioned before, the Rumack–Matthew nomogram could not be assessed because acetaminophen plasma levels are not measured routinely in Colombia[30]; as a response of this situation, NAC is applied as earlier as possible to every case of acute acetaminophen overdose that presents to the emergency room. Considering different therapeutic schemes, the limited evidence, and recommendations for the start of NAC therapy without plasmatic concentrations of acetaminophen, and the risks of developing adverse effects such as flushing or more severe, anaphylactoid reactions, more studies are needed in this situation[31–35].

This benign response of our patients could be explained by several factors. First, our population was predominantly young while the development of severe liver injury with acetaminophen doses as low as 2-4 g per day has been reported in long-term alcoholism[34]. Importantly, while the chronic consumption of alcohol is associated with chronic liver disease that predispose to the acetaminophen poisoning, the acute consumption of alcohol has been associated with a protective effect against this due the competitive utilization of CYP2E1 substrates, diminishing NAPQI concentration[35]. Other aspects increasing hepatotoxicity after acetaminophen overdose are higher doses, some herbal medication, advanced age, impaired glucuronidation due to genetic variants, malnutrition, chronic liver diseases, pregnancy, prolonged fasting or chronic use of isoniazid[36–39]. Secondly, it is important to note that spontaneous vomit before admission was common while some of the clinical records registered the evidence of the tablets in the vomit (not shown). When the vomit occurs early enough to expel part of the substances before absorption it could reduce the poisoning risk.

Regarding those that developed acute hepatitis or acute kidney disease, we cannot identify any specific risk factor or any difference with the rest of the subjects that explain this evolution with the taken dose. This evolution could be attributed to any genetic variant in CYP, but we have no data to confirm that[18].

Although drug-induced liver disease is common and benign in most cases, it is important to understand that baseline liver disease and some other factors of susceptibility, such as chronic exposure of some substances and genetic susceptibility, may promote a worst outcome in patients with this type of lesions[28]. Since the diagnosis of drug induced liver injury (DILI) is highly suggestive by clinical presentation and a temporal link, and previous studies have described the use of instruments for the assessment and diagnosis of DILI due to some specific drugs, acetaminophen is not that case and no standardized tool has been used[40]diagnostic scales, such as the Councils for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM.

The high prevalence of a vital event referred by the patient as trigger of the suicidal attempt supports in part the diathesis-stress model[41]. However, while some people manifest an impulsive behavior associated with the ingestion of the first drugs available, others indicate a persistent suicidal ideation that let them to plan the suicidal attempt, search on the internet about the lethal dose, and in other cases buy enough medication.

Our study has several limitations. Since the number of registries are relatively small, we considered that performing an inference analysis will not give any more information than the presented here. The retrospectively nature of this research and the clinical records as a source of information restricts the availability of some information as well as the availability of some lab tests performed in other institutions before the admission. Finally, this study cannot present an hypothesis that allows for any change in clinical practice; however, it is very valuable since the studies in this field are limited.

In conclusion, our study presented a characterization of a group of individuals that attended the emergency room of a highly complex health institution and reference center for liver transplantation in Colombia after an overdose intake of acetaminophen in a 2-years time-lapse. The results show that the population was predominantly young, the personal history of psychiatric disease was highly prevalent, and most of the cases reported a vital event that explain the impulsive behavior of acetaminophen consumption. This study evidence the need for larger and prospective population studies that examine the psychiatric profile in the suicidal attempt with acetaminophen and its implications for posterior outcomes.

Conflict of interests statement

None of the authors have conflicts of interest in relation to this study.

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