CASE REPORT

Assessing risk of liver toxicity in acute paracetamol intoxication when basing treatment on a Rumack-Matthew toxicity nomogram is not feasible

Jordi PUIGURIGUER FERRANDO[1], Bernardí BARCELÓ MARTÍN[2], Tomeu CASTANYER PUIG[2,3], Santiago NOGUÉ XARAU[4]

[1]Servicio de Urgencias. [2]Servicio de Análisis Clínicos. [3]Unidad de Toxicología. Hospital Universitario Son Dureta. Palma de Mallorca, Spain. [4]Sección de Toxicología Clínica. Área de Urgencias. Hospital Clínic. Barcelona, Spain.

Correspondence:
Dr. Jordi Puiguriguer
Servicio de Urgencias
Hospital Universitario Son Dureta
Andrea Doria, 55
07014 Palma de Mallorca,
Spain
E-mail: jordi.puiguriguer@ssib.es

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The Rumack-Matthew nomogram is used to guide treatment with N-acetylcysteine (NAC) as an antidote for paracetamol intoxication, but this approach has limitations. The elimination half-life of paracetamol increases to over 4 hours in the presence of hepatic toxicity. The aim of this study is to describe the characteristics of a series of cases of paracetamol toxicity in which a nomogram could not be used; the patient's risk was assessed by means of the elimination half-life. Patients with paracetamol intoxication from a single or cumulative overdose who came to Hospital de Son Dureta de Palma de Mallorca and Hospital Clínic de Barcelona over a 5-year period (July 2005-July 2010) were included if the findings of at least 2 immunoassays for paracetamol concentration were available. Half-life was estimated by means of the ratio between 2 consecutive concentrations determined 2 hours apart. Of 11 patients with paracetamol intoxication for whom a Rumack-Matthew nomogram was not used, 3 had liver toxicity. Two of them were accidental intoxications caused by ingesting several doses of the drug. The third was an attempted suicide. In all cases, the elimination half-life exceeded 4 hours. We suggest that in cases of paracetamol intoxication the Rumack-Matthew nomogram be complemented by calculation of the elimination half-life, which will provide an indication of possible liver toxicity in these patients. This approach should be chosen at least when there are doubts about when paracetamol ingestion occurred or if intoxication is the result of several doses. [Emergencias 2010;22:365-368]

Key words: Paracetamol. Elimination half-life. Toxicity, liver.

Introduction

Paracetamol (PCT) is an over-the-counter drug used as an analgesic and antipyretic. Wide availability means that PCT poisoning is common. The target organ poisoned by PCT is the liver, but damage to other organs and systems is also possible. Despite extensive clinical experience with PCT poisoning and advances in understanding its toxicity, little is known about the toxico-dynamic mechanisms which would allow differentiating between individuals who are most likely to develop severe hepatotoxicity or even multiorgan failure and those who are most likely to remain asymptomatic or show only moderate, transient transaminase elevation. Only certain predictive risk factors for toxicity have been identified[1], although recent studies point to new influential factors such as the state of the intestinal flora (p-cresol)[2].

The concentration of plasma PCT is known to correlate with the probability of liver damage. This fact has resulted in the so-called Rumack nomogram, which is used to indicate when to use antidote treatment with N-acetylcysteine (NAC) in patients at risk of hepatotoxicity[3]. But this nomogram has several constraints, among which is the inability to use it when the time lapse from PCT intake is unknown or if the dose of PCT has been fractionated.

The elimination half-life (t1/2) of PCT is about two hours with therapeutic doses in normal patients, but increases to more than four hours in cases of hepatotoxicity[4,5]. The correlation between prolonged t1/2 and drug toxicity is not exclusive to PCT; the underlying cause is saturation of the

mechanisms of drug elimination[6]. This pharmacokinetic parameter can be used as an effective tool for predicting hepatotoxicity when it is not possible to apply the Rumack nomogram, in both pediatric and adult patients. However, to obtain the value of t1/2, a series of complex mathematical calculations is required, which hinders its application in routine clinical practice. Therefore, as presented in previous studies, we have developed and validated a simple method to estimate whether t1/2 is greater or lower than four hours simply by calculating the ratio between two plasma concentrations of PCT. We perform this calculation for all patients suspected of PCT poisoning, regardless of whether the Rumack nomogram can be applied or not[7,8].

The aim of this paper is to describe the characteristics of PCT-poisoned patients where application of the Rumack nomogram was impossible and to show how the estimated t1/2 allowed predicting the appearance of hepatotoxicity in these cases.

Method

The study included patients with an overdose of PCT who attended the Hospital Son Dureta Palma de Mallorca and the Hospital Clínic of Barcelona during a period of 5 years (July 2005-July 2010), selected on the basis of lack of information necessary for Rumack nomogram application and where at least 2 determinations of PCT were available. We collected the following data: gender, age (over 15 years in both the participating hospital emergency departments), day of the intake, type of intake (single or fractionated), amount ingested (when possible to calculate), reason for intake, PCT taken simultaneously with ethyl alcohol, illicit drugs or other intoxicants, and blood test results for PCT and signs and symptoms of intoxication. We also took into account relevant data from the medical history, including: HIV or hepatitis virus infection, chronic liver disease, pancreatopathy, nephropathy, chronic diabetes mellitus. Standard laboratory data were obtained: blood count, biochemistry profile of the liver and kidney, and hemostasis at admission, during hospitalization and at discharge. We also recorded treatment administered and clinical evolution. The two participating hospitals followed the same criteria for patient assessment and treatment decisions[9]. Hepatotoxicity was defined as an elevation of transaminases (ALT and/or AST) greater than 1000 IU/L[10].

The value of t1/2 was estimated by dividing the first concentration (C1) of PCT measured on admission by the second concentration (C2) of PCT obtained after a fixed interval of time. C2 was always obtained for exact periods (60-minute intervals as from 2 hours to 12 hours with respect to C1). To facilitate data recording we developed a table containing the limits for this ratio indicating potential hepatotoxicity (Table 1). When the ratio C1/C2 was at or below this value for each time period between measurements, it was considered positive and indicated a t1/2 > 4 h and therefore high probability of liver damage. Conversely, when the ratio C1/C2 indicated a t1/2 value of < 4 h, it was considered negative and thus predicted a low probability of liver damage. The calculation of t1/2 was made considering that PCT metabolism follows first order kinetics[11]. Analytical determinations of PCT were performed using fluorescence polarization immunoassay (FPIA) with a TDX/FLX analyzer by Abbott Diagnostics®, with analytic sensitivity of 1 mg/L.

Results

Eleven patients with PCT overdose were included in the study, none with sufficient information on the episode to allow application of the Rumack nomogram. The epidemiologic, clinical and laboratory data are shown in Table 2. Three patients developed hepatotoxicity: two were cases of accidental poisoning by fractionated PCT intake seeking analgesic effect, while the third was PCT overdose with suicidal intent. In the latter case the time of intake could not be established, nor whether the dose was single or fractionated. The evolution of all three patients was eventually good, but the latter required liver transplantion.

In the three patients who developed hepatotoxicity, the C1/C2 ratio showed that t1/2 showed that the t1/2 value was greater than 4 hours. The exact values calculated subsequently were 8.5, 8.7 and15 hours respectively.

In the 8 patients who did not develop hepatotoxicity, the estimated t1/2 in all cases was less than four hours and therefore not predictive of hepatotoxicity. The median t1/2 value in this group of patients was 2.2 (1.2 to 3.8) hours.

Specific antidote treatment with NAC infusion was administered in 9 cases: the 3 patients with t1/2 greater than 4 hours and 6 patients with t1/2 values less than 4 hours.

Table 1. C1/C2 ratio values for time intervals between the analytic results. Values between 2 and 12 hours*

Time interval (in hours) between laboratory tests	t1/2 > 4 hours if ratio ≤ than
2	1.4
3	1.7
4	2
5	2.4
6	2.8
7	3.7
8	4
9	4.7
10	5.6
11	6.7
12	8

*It is imperative that the second blood sample (C2) be extracted every 60 minutes exactly, at least 2 hours after C1.

Discussion

Rumack nomogram is the tool of choice for predicting the risk of hepatotoxicity in acute poisoning by PCT. However, its application requires that three conditions be met: a) a single intake, b) time elapsed since intake must be known and c) time elapsed since intake must be at least four hours, except in children aged 1 to 5 years with liquid PCT overdose where this is reduced to 2 hours[12,13].

It is known that in the absence of other risk factors, patients with fractionated intake run a greater risk of hepatotoxicity[14,15]. This type of poisoning is often accidental, due to dosage error or greater analgesic effect, as occurred in the first two of the three patients who developed hepatotoxicity. Not uncommonly, patients with suicidal intent and PCT overdose consult the emergency services after a prolonged and imprecise period of time. The time elapsed from intake to consultation is often a rough estimate provided by the patient him/herself or by others, and thus cannot be verified. Taking into account the fact that most adult cases of PCT poisoning are voluntary[16], as in 64% of the present series, these preliminary considerations are accentuated[17]. Also, the patient may present a decreased level of consciousness, making it even more difficult to obtain reliable information about the episode[18]. In all cases, the plasma concentration of the drug obtained from one blood sample provides undoubtedly important information, but that only allows an approximate prognosis in cases of very high values (> 200 mg/L) or very low values (< 10 mg/L). In cases of unknown or doubtful quantity and time lapse due to the clinical state (coma) or patient age (children under 2 years), urine PCT concentration has been shown to provide reliable qualitative information[19], to confirm or rule out its presence in order to avoid blood extractions[20].

Table 2. Demographic and clinical variables of the 11 patients studied

Variable	Value
Age (years, mean and range)	38 (17-94)
Male [n (%)]	7 (64)
Reason for intake [n (%)]	
Autolysis	7 (64)
Accidental	3 (27)
Unknown	1 (9)
Amount ingested, g (N: 9) (mean and range) provided by the patient and/or family	13 (9-40)
Amount ingested, mg/kg (N: 6) (mean and range)	280 (109-666)
Concomitant with ethyl alcohol [n (%)]	5 (45)
Concomitant with illicit drugs [n (%)]	1 (10) cannabis
Concomitant with other toxic substances or drugs [n (%)]	5 (45)**
Risk factors for hepatotoxicity [n (%)]	
HIV carrier	0 (0)
Hepatitis virus	0 (0)
Chronic liver disease	0 (0)
Pancreatopathy	1 (0)
Chronic kidney disease	0 (0)
Diabetes mellitus	1 (9)
Symptoms [n (%)]	
Gastrointestinal	3 (27)
Neurological	5(46)
Asymptomatic	3 (27)
Plasma concentration (C1) of paracetamol on admission (mg/L) (mean ± SD)	81.9 ± 72.5
Creatinine (mg/dL)* (mean and range)	0.86 (0.7 to 4.2)
GOT or AST (U/L)* (mean and range)	53 (11-8331)
ALT or AST (U/L)* (mean and range)	16 (55-4854)
Total bilirubin (mg/Dl)* (mean and range)	1.3 (0.3 to 18.6)
Prothrombin time (%)* (mean and range)	78 (900-100)
Leukocytes (/mL)* (mean and range)	7850 (4600-29700)
Administration of activated charcoal [n (%)]	1 (9)
NAC administration [n (%)]	9 (82)
Clinical outcome [n (%)]	
Survival	11 (100)
Liver Transplantation	1 (9)
Hospital stay (hours) (mean and range)	25 (16-2160)

N: Number of patients for whom data were collected. NAC: N-acetylcysteine. no.: Number of patients for whom the data collected were positive. *The biochemical and hematologic results correspond to the worst results. Concomitant drugs**: etumina, ibuprofen, metoclopramide, norfloxacin.

Finally, although the Rumack nomogram is now a key tool in therapeutic decision-making for the administration of antidotes in PCT poisoning, we propose it should be complemented with an estimate of t1/2 in all cases, or at least when there are doubts about time elapsed and the type of dose (single or fractionated). Our policy of estimating t1/2 in all cases prevented unnecessary antidote administration in two of our patients and, secondarily, resulted in less time spent in the emergency department. Performing the additional determination in all cases, whether adult or pediatric, increases the value of prognosis, since it allows the clinician to verify whether the patient presents the same level of risk as that indicated by the Rumack nomogram, thus facilitating a more accurate prognosis.

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Valoración del riesgo de hepatotoxicidad en la intoxicación aguda por paracetamol cuando no es posible aplicar el nomograma de Rumack-Matthew

Puiguriguer Ferrando J, Barceló Martín B, Castanyer Puig T, Nogué Xarau S

El nomograma de Rumack se utiliza para indicar el tratamiento antidótico con N-acetil-cisteína (NAC) en la intoxicación por paracetamol (PCT), pero tiene varias limitaciones de uso. La semivida de eliminación (t1/2) del PCT se incrementa a más de cuatro horas en caso de hepatotoxicidad. El objetivo de este trabajo es describir las características de los pacientes intoxicados por PCT de una serie en los que la aplicación del nomograma de Rumack nunca fuera posible y valorar su riesgo de hepatotoxicidad a través de la estimación de la t1/2. Se incluyeron los pacientes con una sobredosificación o intoxicación por PCT que acudieron al Hospital de Son Dureta de Palma de Mallorca y al Hospital Clínic de Barcelona durante un periodo de 5 años (julio 2005-julio 2010) en los que se dispusiera de al menos 2 determinaciones de PCT. La estimación de la t1/2 se realizó mediante un cociente entre dos determinaciones consecutivas separadas por un intervalo de tiempo de 2 o más horas. De 11 pacientes intoxicados por PCT a los que no se les pudo aplicar el nomograma de Rumack, tres desarrollaron hepatotoxicidad, dos de ellos fueron intoxicaciones accidentales producidas por ingesta fraccionada del fármaco y el tercero una intoxicación con intencionalidad suicida. En todos ellos la estimación del cálculo de la t1/2 puso de manifiesto que era superior a 4 horas. Proponemos que se complemente al nomograma de Rumack con la estimación de la t1/2 en los casos de intoxicación por PCT, y que esta estimación de la t1/2 sea la que aporte la información sobre la posible hepatotoxicidad de la intoxicación. Esto debe hacerse al menos en los casos en que existan dudas o se desconozca el tiempo transcurrido de la ingesta, o la misma haya sido fraccionada. [Emergencias 2010;22:365-368]

Palabras clave: Paracetamol. Semivida de eliminación. Hepatotoxicidad.