BRIEF ORIGINAL

Utility of pediatric urinalysis to screen for paracetamol intake: a preliminary study

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None

Objective: To explore whether urinalysis to screen for paracetamol intake, following the same procedure as is used for blood analysis, would be useful.
Methods: Retrospective cross-sectional, descriptive-analytical study of a random sample of patients for whom urine tests were ordered in an emergency department. The data were classified into 2 groups, according to whether the patients had or had not taken a therapeutic dose of paracetamol during the previous 24 hours. Paracetamol concentration in urine was measured for all patients. We compared the percentages of patients with positive findings between groups and calculated the sensitivity, specificity, and positive and negative predictive values of urinalysis for paracetamol.
Results: A total of 161 children between the ages of 17 days and 17 years were included; 83 had taken paracetamol and 78 had not. Urine tests were positive for all patients in the first group and for 7.7% in the second group. The sensitivity of the test was 100% (95% confidence interval [CI], 95.6%-100%) and the specificity was 92.31% (95% CI, 84.22%-96.43%). No patient who had taken paracetamol had a negative urine test (negative predictive value, 100%; 95% CI, 94.93%-100%).
Conclusions: Urinalysis to screen for paracetamol intake in the previous 24 hours is useful. A negative result would make blood testing unnecessary. This approach to screening would clearly benefit young children who may have taken the medication accidentally or adolescents who may have used it to attempt suicide. [Emergencias 2012;24:372-375]

Key words: Acetaminophen. Paracetamol. Detection. Acute poisoning. Children.

Introduction

Paracetamol (PCM) is the most frequent cause of drug poisoning in hospital pediatric emergency departments (EDs)[1]. The main risk factor for hepatotoxicity is a delay beyond 8 hours in the administration of N-acetylcysteine[2,3]. Indication for use of this antidote is based on serum levels 4 hours after ingestion, applying the Rumack-Matthew nomogram[4] or other more recent nomograms[2,3]. Occasionally ingestion of the drug is uncertain, as when a child is found with the package or when there is intentional poisoning with suicidal purpose, which often involves multiple drugs and the intake of paracetamol must be ruled out[5-7]. According to the National Academy of Clinical Biochemistry, 84% of 300 serum paracetamol determinations obtained in a hospital over 6 months were negative[5]. Studies in adults suggest that the detection of paracetamol in urine (uPCM) has high sensitivity[8-10], which could allow ruling out intake without need for a blood test. In this regard, most hospitals have a quantitative analytical blood test. Using it in urine first could allow ruling out or confirming the presence of PCM without the need for blood extraction or a specific urine test. The aim of this preliminary study was to determine the utility of uPCM to detect intake of the drug in the previous 24 hours in the pediatric population, using the same technique as that used for the blood test.

Method

This cross-sectional, observational, analytical and retrospective study was performed between September 2006 and January 2008 in the ED of a maternal and child tertiary urban hospital which serves an area of 1.3 million inhabitants and annually attends 100,000 pediatric emergencies. We selected a sample of patients whose management required a urine test. The cases included correspond to all urine samples collected in shift work by the researchers (including morning, afternoon and night shifts, every day of the week). The study was approved by the Hospital Research Ethics Committee. After obtaining their consent to be included in the study, patients were questioned on intake of paracetamol in the previous 24 hours, dose and time elapsed since the last intake. Patients were divided into two groups: Group A, who had received at least one therapeutic dose in that period, and group B who had not received the drug. We excluded patients with liver or kidney failure. In all urine samples we determined uPCM levels. For a power of 90% and sensitivity > 95% with a lower confidence interval of 5%, the study required a sample size of 146 subjects. The time limit of 24 hours after intake was set because excretion of a therapeutic dose is completed in that period[12]. The presence of uPCM was determined using TDx/FLx Abbott (USA) fluorescence polarization immunoassay. The detection limit of the test is 1 mg/mL. Results below this value are considered undetectable and equal to zero. Data were stored on a Microsoft Access 2007 (Microsoft Corp., USA) database and analyzed using SPSS 17.0 (SPSS Inc., USA). We compared the proportion of patients with detectable uPCM in the two groups using chi-square test. Significance was defined as p values below 0.05. We also calculated sensitivity, specificity and predictive values.

Results

We included 161 patients, 83 in group A and 78 in group B. None of these patients was subsequently excluded. Mean age was 4.1 years (SD 5.6 years, range 17 days-17 years). No significant differences existed between age groups (median 0.9 versus 1.7 years). Time from last intake in group A was a minimum of 45 minutes and the median was 270 minutes (P25-75 = 189 to 480 minutes).

Table 1 shows the comparison between prior paracetamol intake or not and the resulting positive or negative uPCM test. As expected, the proportion of patients in group A with positive uPCM was significantly higher than that of group B (100% vs 7.7%, p < 0.001). Of the six cases in group B with detectable uPCM, five had levels below 1.5 ug/mL, and one had a value of 4.3 mg/mL. Sensitivity of the test was 100% (95% CI = 95.6 to 100%) and specificity was 92.3% (95% CI = 84.2 to 96.4%). No patient with undetectable uPCM had ingested paracetamol within 24 hours before the test (negative predictive value 100%, 95% CI = 94.9 to 100%). The positive predictive value was 93.3% (95% CI = 86.1 to 96.9%).

Table 1. Comparison between declared prior paracetamol intake or not and positive or negative test results for paracetamol in urine (uPCM)

	uPCM determination		
Prior paracetamol intake	**Positive**	**Negative**	**Total**
Yes	83	0	83
No	6	72	78
Total	**89**	**72**	**161**

Discussion

This work is the first to study the usefulness of uPCM detection in the pediatric population. Previous studies are scarce and all were performed in adults, for whom different qualitative tests were used[8-10]. Moreover, this is the first work to detect uPCM using the same technique as that employed in blood tests; it required no special equipment or laboratory staff training.

Perrone et al[8] compared PCM levels in urine and blood samples of 88 adults with attempted suicide and found no false negatives. Ingram et al[9] evaluated the usefulness of a qualitative test in urine in 191 patients. A positive uPCM test correlated with the presence of PCM in blood with a sensitivity of 100%. MacDaniel et al[10] conducted a prospective study in 29 adult volunteers, comparing PCM detection in urine and blood; uPCM test showed a sensitivity of 100% and a specificity of 97%.

In our series, uPCM detection proved effective at ruling out intake of the drug in the previous 24 hours; we did not find a single case receiving the drug where it was not detected in urine. The sensitivity of the test to therapeutic doses indicates its potential utility for overdose or toxic intake (12 to 20 times higher). A negative uPCM excludes intake and could thus make blood tests unnecessary, reduce costs and ED stay time, as well as avoiding

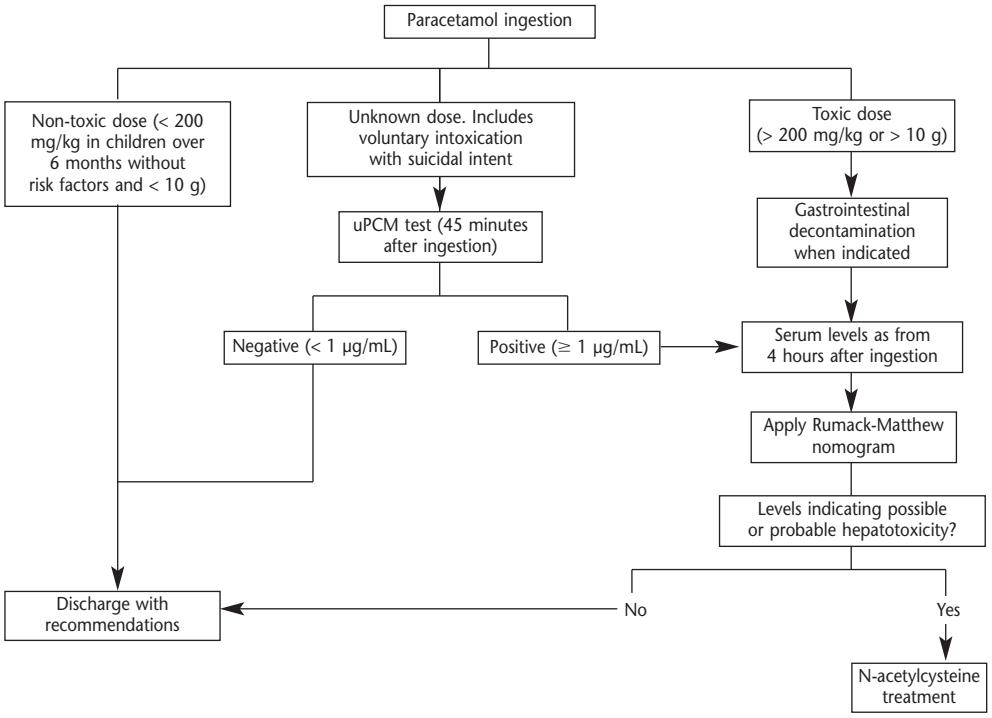

Figure 1. Treatment algorithm for pediatric patients with suspected paracetamol intake.

blood extractions. The urine test could benefit children whose ingestion is uncertain, and adolescents with suicidal poisoning intent. Figure 1 shows a management algorithm for pediatric patients with suspected acute PCM poisoning, and indicates where uPCM might be useful as a screening test. The algorithm shows the doses currently accepted as toxic by international guidelines[2,3,13,14]. A positive result indicates drug intake only, not the level. In cases of known intake of a toxic dose or a positive uPCM result, blood levels must be determined to assess toxicity.

Although false positives were scarce in our study, uPCM was detected in some patients with no known intake. This could be due to interactions with other substances or simply unawareness of drug intake. In any case, the usefulness of the uPCM test as a screening test is based on its sensitivity and negative predictive value, which were optimal.

There are no studies in children showing what levels of PCM in urine become detectable. Given the rapid rate of absorption and renal clearance of 12-13 ml/min[12,15] one would expect to be able to detect 5 ug/ml of PCM at 30 minutes after intake[8]. In our study, the time interval from drug intake to urine collection was at least 45 minutes, which we consider advisable.

Our work does not allow conclusions on the level of uPCM to estimate the amount ingested. This was not an objective of the work and therefore we did not take into account the total amount of drug ingested. This would require studies that control the factors influencing urinary excretion. We would also welcome any studies that corroborate the usefulness of the method in patients with toxic intake and which establish a cutoff point for simple test positivity.

Our study has certain limitations. First, it was a retrospective single-center study. Second, in theory, a false negative result is possible if in addition the accompanying parent or person responsible were unaware of the child's intake of PCM. Since the probability of these two facts occurring simultaneously is very low, we do not consider that the level of sensitivity obtained could be significantly affected. To generalize the use of the technique, further studies are required in which researchers control the administration of the drug and compare the results with those of a validated method for uPCM detection. Our study did not compare uPCM results with blood levels of PCM. Considering that a therapeutic dose would no longer be detectable in blood 10-12 hours after intake[12], such levels would not be adequate for the comparison of sensitivity and specificity.

In conclusion, determining uPCM with the technique used in this study may be useful to rule out PCM intake in the previous 24 hours. Further studies are needed to validate its possible inclu-

sion in the algorithm for suspected acute paracetamol poisoning.

Addendum

The following professionals are Members of the Work Group on Poisoning, Spanish Society of Pediatric Emergency Medicine: A. Barasoain (Fundación Hospital Alcorcón), J.R. Bretón (H. Doctor Peset), C. Campos (H. Servet), E. Crespo (H. Virgen de la Salud), L. del Arco (H. Universitario Cruces), J. Fábrega (H. Universitari Germans Trias i Pujol), P. Fernández (H. Carmen y Severo Ochoa), R. Fernández (H. Cabueñes), M.de la O García (H. General Universitario de Alicante), C. García-Vao (H. Aranjuez), E. García-Vena (C. Hospitalario Jaén), L. Gómez (Complejo Hospitalario de Navarra), J. Humayor (H. Basurto), I.Iturralde (H. Alto Deba), A. Jordá (H. Laredo), J.R. Lasarte (H. Mendaro), J. López (H. Universitario de Salamanca), M.J. López (Hospital de Terrassa), V. López Corominas (H. Universitario Son Espases de Palma de Mallorca), L. Martínez (H. Sant Joan de Deu), M.E. May (Mutua Terrassa), J. Mayordomo-Colunga (H. Universitario Central de Asturias), R. Mendivill (Corporación Sanitaria Parc Taulí), J.C. Molina (H. Niño Jesús), J.A. Muñoz (Complejo Hospitalario Donostia), A. Nuño (H. La Fe), S. Oliva (H. Carlos Haya), A. Palacios (H. Doce de Octubre), A. Pérez (H. de Zumárraga), C. Pérez (H. Universitario Virgen de la Arrixaca), N. Pociello (H. Arnau de Vilanova), M.C. Puente (H. Universitario Puerta de Hierro Majadahonda), R. Rodríguez (H. Universitario Fuenlabrada), R. Sánchez (H. Virgen de las Nieves), M. Tallón (H. Xeral de Vigo), P. Vázquez (H. Gregorio Marañón), R. Velasco (H. Río Ortega), C. Vidal (H. Son Llatzer).

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Estudio preliminar sobre la utilidad de la detección de paracetamol en orina para descartar su ingesta en pacientes pediátricos

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Objetivo: Estudiar en la población pediátrica si la determinación de paracetamol en orina (PCTo) utilizando la misma técnica de análisis en sangre es útil para detectar la ingesta del fármaco.

Método: Estudio transversal, observacional-analítico y retrospectivo realizado en una muestra aleatoria de pacientes a los que por su patología se les realizaba en el servicio de urgencias una analítica de orina. Se dividieron en dos grupos, A y B, según hubieran o no recibido dosis terapéuticas de paracetamol en las 24 horas previas. En todos se determinaron los niveles de PCTo. Se comparó la proporción de pacientes con PCTo detectable en los dos grupos y se calculó sensibilidad, especificidad y valores predictivos.

Resultados: Se incluyeron 161 niños de edades entre 17 días y 17 años (83 del grupo A y 78 del grupo B). La proporción de PCTo positiva fue superior en el grupo A (100%) frente al B (7,7%). La sensibilidad de la prueba fue del 100% (IC 95% = 95,6-100%) y la especificidad del 92,3% (IC 95% = 84,2-96,4%). Ningún paciente con PCTo indetectable había ingerido paracetamol (valor predictivo negativo 100%, IC 95% = 94,9-100%).

Conclusiones: La detección de PCTo es útil para descartar la ingesta del fármaco en las 24 horas previas y su negatividad puede hacer innecesaria la determinación de niveles séricos. Se pueden beneficiar claramente niños con ingesta dudosa y adolescentes con intoxicación con fin suicida. [Emergencias 2012;24:372-375]

Palabras clave: Paracetamol. Detección. Intoxicación aguda. Niños.