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Renal replacement therapy in severe phenobarbital poisoning: Another brick in the wall

Diálisis extracorpórea en el caso de grave fenobarbital envenenamiento: otro ladrillo en la pared

Dear Editor,

The prevalence of severe poisoning with sedatives or hypnotics has been increasing dramatically over the last years.[1] In this setting, barbiturates remain one of the most common classes of drugs associated with fatal poisoning. The current report aims at illustrating the usefulness of renal replacement therapy with intermittent hemodialysis in the acute care of massive phenobarbital poisoning.

A 56-year old woman was addressed to the intensive care unit (ICU) for a massive phenobarbital poisoning (assumed ingested dose: 5.5 g). The estimated maximum delay between phenobarbital ingestion and ICU admission was 6 hours. The patient presented with hypotension (77/44 mmHg), hypothermia (33 °c) and altered mental status (Glasgow Coma Scale: 3) requiring endotracheal intubation, fluid loading with 1000 mL of saline and noradrenalin infusion up to 0.33 μg/kg/min before ICU admission. Her neurological examination revealed bilateral mydriasis with no pupillary response, together with the disappearance of other brainstem reflexes. A trans-thoracic echocardiography showed preserved left ventricle ejection fraction and cardiac output consistent with a vasoplegic shock. In spite of the profound coma and respiratory depression, there was no evidence for aspiration. The diagnosis of massive phenobarbital poisoning was confirmed by high barbiturate plasma levels measured upon admission (273 mg/L).

Initial management of barbiturate poisoning included supportive care of organ failures (*i.e.*, mechanical ventilation and noradrenalin infusion), the administration of activated charcoal (a single 1 g/kg dose) so that to limit the enterohepatic recirculation of barbiturates, together with urinary alkalinization in an attempt to increase their urinary excretion. On day-1, hemodynamic improvement allowed for noradrenalin discontinuation. Yet, the neurological examination was no significantly improved (GCS: 3), except for a spontaneous breathing activity under mechanical ventilation. Multiple-dose activated charcoal (MDAC) was introduced on day-2, with no significant decrease in plasma phenobarbital levels or neurological improvement (Fig. 1). On day-4, because the patient was still deeply comatose, renal replacement therapy (RRT) initiation was decided. Intermittent dialysis was performed using an Artis Physio™ dialysis system (Gambro AB, Meyzieu, France) with a Sureflux™-19E dialyzer (Nipro Europe, Saint Beauzire, France), achieving an estimated average creatinine

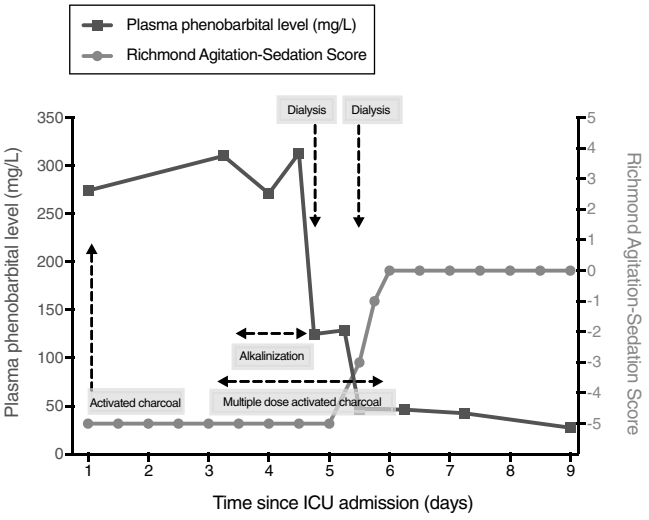

Figure 1 Time course of phenobarbital plasma levels (left *y*-axis) and patient consciousness (Richmond Agitation-Sedation Scale, right *y*-axis). There was a dramatic decrease in phenobarbital plasma levels after two hemodialysis sessions, concomitant with neurological status improvement.

clearance of 188 mL/min. A 4-hour session allowed for dramatically reducing plasma phenobarbital levels from 313 to 125 mg/L. The second dialysis session, performed on day-5, further reduced plasma levels from 129 to 47 mg/L (Fig. 1). The patient awoke twenty-four hours after RRT initiation, as illustrated by an increase in the Richmond Agitation-Sedation Scale from −5 (patient unarousable) to 0 (patient alert and calm) (Fig. 1). The clinical course was eventually favorable, allowing for the patient to be successfully extubated on day-7 and discharged to a psychiatric unit on day-10.

We herein report a case of massive phenobarbital poisoning with a favorable course under intermittent hemodialysis. Medical interventions to enhance phenobarbital elimination (activated charcoal and urinary alkalinization) had failed to improve the neurological status of our patient. Also, this strategy did not significantly alter phenobarbital plasma levels. In a previous study, the administration of repeated doses of activated charcoal enhanced the elimination of barbiturates but had no clear effect on clinical outcome.[2] Furthermore, activated charcoal could hypothetically increase the risk of gastric impaction. This may partially explain the variation in serum concentrations during the initial course (between day-1 and day-4), as phenobarbital is a long-acting barbiturate. Regarding urinary alkalinization, there is to date no clinical evidence of a clinical benefit in barbiturate poisoning, despite its pharmacokinetic rationale.[3]

In the current case, RRT with intermittent hemodialysis dramatically improved the clearance of phenobarbital and, hence, neurological status improved concomitantly. Two 4-hour sessions were sufficient to achieve a dramatic reduction in phenobarbital levels. Hemodialysis was discontinued after neurological status improved, rather than targeting a specific concentration. All barbiturates are inducers of the hepatic cytochrome P450 and hepatic metabolism is the main component of their endogenous clearance. Barbiturates are thus classified according to their pharmacokinetic properties. Long-acting barbiturates (such as phenobarbital) have a smaller volume of distribution, which tends to limit post-dialysis rebound, and are less protein-bound and lipid soluble than short-acting barbiturates. Importantly, up to 20–25% of phenobarbital can be excreted as an active drug in urine. During dialysis, phenobarbital clearance has been shown to vary from 150 to 200 mL/min.[4] For all these reasons, long-acting barbiturates are theoretically dialyzable. A few case studies have reported the effectiveness of both hemoperfusion[5,6] and hemodialysis[7,8] to enhance the clearance of barbiturates. Yet, these two techniques have not been evaluated and compared in randomized control trials. Hemoperfusion is not widely available and requires a specific training. As compared to hemoperfusion, hemodialysis has been shown to be associated with a lower risk of thrombocytopenia or hypocalcemia and seems less costly.[9] The 2015 recommendations of the EXTRIP Workgroup suggest using intermittent hemodialysis to treat long-acting barbiturate poisoning in case of prolonged coma, shock (after initial fluid resuscitation), or persistence of toxicity despite MDAC.[10]

This case provides further support for the early initiation of renal replacement therapy in patients admitted for severe long-acting barbiturates poisoning, especially in those with prolonged coma and/or persistence of toxicity despite multiple-dose activated charcoal.

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Conflict of interests

The authors have no conflicts of interest to declare.

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Utilidad pronóstica de las puntuaciones de fallo multiorgánico y del índice inotrópico en el postoperatorio de trasplante cardiaco en niños

Prognostic utility of the multiorgan failure scores and inotropic index in the postoperative of cardiac transplantation in children

Sr. Editor:

Los pacientes sometidos a un trasplante cardiaco (TC) presentan muchas complicaciones y fallo multiorgánico (FMO) lo que aumenta la morbimortalidad[1,2]. No hay estudios que hayan analizado el FMO tras el TC en niños. Algunos estudios han mostrado el valor predictivo del índice inotrópico (II) en la cirugía cardiaca[3,4] y en el TC en niños[5]. El objetivo de este estudio fue analizar la utilidad pronóstica de las puntuaciones de FMO y del II en el TC en niños en relación a la mortalidad, la duración de ingreso en la unidad de cuidados intensivos pediátricos (UCIP) y la de ventilación mecánica (VM).

Se realizó un estudio observacional retrospectivo unicéntrico, aprobado por el Comité de Ética local, en el que se incluyeron 65 niños (edad mediana de 57 meses) que ingresaron en la UCIP tras un TC entre 2003 y 2014. Se calcularon las peores puntuaciones de gravedad clínica y FMO, *Pediatric Logistic Organ Dysfunction* (PELOD)[6] y *Pediatric Multiple Organ Dysfunction Score* (PMODS)[7], *Pediatric Risk of Mortality* III (PRISM III)[8], *Pediatric Index of Mortality* 2 (PIM2)[9] en las primeras 48 h postrasplante. Se calculó el valor del II = dopamina + dobutamina + 100 × adrenalina + 100 × noradrenalina + 10 × milrinona (todas en μg/kg/min) + 10.000 × vasopresina (mU/kg/min)[3,4]. Se analizó la relación de las puntuaciones con la mortalidad en la UCIP y la duración de ingreso en la UCIP y la de VM. Para el estudio estadístico se utilizaron el test del χ^2 o el test de Fisher, la U de Mann-Whitney y la rho de Spearman. Se consideró significativa una $p < 0,05$.

El 50,8% presentaban una cardiopatía congénita, el 47,7% una miocardiopatía y el 4,6% un tumor miocárdico. La puntuación PRISM III fue del 12,6% (P25-P75: 3,5-25,9), PIM 2 19% (P25-P75: 3,4-27,8), PELOD 11 (P25-P75: 2-13) y PMODS 5 (P25-P75: 3-8). El II fue de 22 (P25-P75: 15-36). Existió una correlación moderada entre el II y las puntuaciones de PRISM III ($r = 0,260$; $p = 0,036$), PELOD ($r = 0,370$; $p = 0,003$), PMODS ($r = 0,300$; $p = 0,002$) pero no con el PIM2 ($r = 0,300$; $p = 0,120$).

Fallecieron 4 pacientes (6,2%) durante el ingreso en la UCIP, solo uno por FMO. No existió relación entre las puntuaciones de FMO y de gravedad clínicas con la mortalidad (tabla 1). El II fue significativamente más elevado en los niños fallecidos (tabla 1). Las diferencias de mortalidad entre los niños con II > 15 (8,1%) y < 15 (0%) no fueron significativas ($p = 0,565$). Los niños que fallecieron precisaron con mayor frecuencia ECMO y técnica de depuración extrarrenal (TDER) que los supervivientes, pero las diferencias solo fueron estadísticamente significativas con la TDER (tabla 1). Existió una correlación moderada entre el II, y las puntuaciones de gravedad y FMO (excepto el PELOD) con la duración del ingreso en la UCIP y de VM (tabla 2). Los pacientes con un II mayor de 15 tras el TC presentaron una mayor duración de ingreso en la UCIP.

Nuestro estudio es el primero que ha estudiado el FMO en el TC en niños. En nuestro estudio las puntuaciones de FMO fueron elevadas, aunque la mortalidad fue baja (6,1%) similar a la referida previamente[2,4,5]. No hemos encontrado una relación significativa entre el FMO y la mortalidad, aunque el hecho de que solo fallecieron 4 pacientes limita la comparación estadística.

En niños tras cirugía cardiaca se ha encontrado relación entre los valores elevados de II y una mayor mortalidad[3,4]. Sanil y Aggarwal encontraron que un II > 15 se asoció con mayor mortalidad en 51 niños tras TC[5]. En nuestro estudio los pacientes que fallecieron tenían un II significativamente más elevado que los supervivientes, y todos los fallecidos