ABSTRACTS

baseline of 66 μg/mL, and clobazam 367 ng/mL (normal range 30–300 ng/mL).

Conclusion: Cannabidiol contained in hemp oil extract inhibits CYP3A4 and CYP2C19, the primary isoenzymes involved in the metabolism of clobazam, and inhibits UDP-glucuronyl transferase, which is involved in the metabolism of lamotrigine and valproic acid. Symptomatic elevations in valproic acid and clobazam have been reported following the addition of cannabidiol to antiepileptic therapeutic regimens. Several studies have reported the efficacy of cannabidiol as an adjuvant therapy for refractory epilepsy, however evidence suggests that hemp extract may cause elevations of serum concentrations of various AEDs. Clinicians should be aware that the use of hemp extract in combination with AEDs requires caution and careful monitoring of serum AED concentrations.

219. Paracetamol-induced renal failure: an underestimated consequence of delayed managed overdoses

Bastien Domangé, Corinne Schmitt, Romain Torrents, Audrey Boulamery, Nicolas Simon and Luc De Haro
Marseille Poison Centre, Marseille, France

Objective: Paracetamol poisoning is one of the most frequent drug intoxications with well-known risk of liver toxicity. However the direct renal toxicity of this painkiller is still mysterious and much less studied. In Southern France, paracetamol overdose is an everyday problem but observations with proven renal damage seem to be rare. In order to illustrate this notion, 9 cases of renal failure during paracetamol overdose managed in the Marseille Poison Centre are detailed.

Case series: Nine cases (6 suicide attempts, 3 self-medications) were studied, concerning 6 women and 3 men between 13 to 70 years old. In 7 cases there was acute poisoning after a massive quantity of paracetamol and 2 cases involved repeated high doses over 3 to 5 days. A classic hepatic cytolysis was observed in 7 cases but for 2 patients there was no liver impact. The acute kidney injury scores (Acute Kidney Impairment Network) were two grade I, two grade II and five grade III. Hemodialysis was required for 4 patients with grade III kidney impairment; all of them had delayed medical management. Oliguria/anuria was present for 3 to 14 days. For 2 patients a kidney biopsy was performed and showed a toxic acute tubular necrosis. All patients recovered.

Conclusion: Direct paracetamol toxicity on the kidneys seems to be a rare but serious event. This kind of toxicity is only reported when an oliguria or anuria is present; however in our everyday practice we do not evaluate the renal impact during a common paracetamol overdose. The kidney toxicity of paracetamol is certainly underestimated and should be studied more seriously. An important recent study [1] examined the correlation between the severity of the hepatic failure and the development of kidney disturbances, the possible efficient therapeutic activity of the acetylcysteine on the renal toxicity of the paracetamol, and the higher risk of renal failure when the medical management is delayed.

Reference


220. Mechanistic biomarkers stratify patients after paracetamol overdose with high sensitivity and specificity

James W. Deara, Joanna I. Clarkeb, Ben Francisb, Lowri Philipsea, Jonathan Wraithe, Paul I. Darganc, David M. Woodd, Jamie Cooperf, Simon H. L. Thomase, Andrea Jorgensena, Munir Pirmohamedb, B. Kevin Parkb and Daniel J. Antoinef

*aUniversity of Edinburgh, Edinburgh, UK; bUniversity of Liverpool, Liverpool, UK; cGuy’s and St. Thomas’ NHS Foundation Trust, London, UK; dAberdeen Royal Infirmary, Aberdeen, UK; eNewcastle University, Newcastle, UK

Objective: Paracetamol (acetaminophen) overdose is the most common cause of liver toxicity in the Western world but patient stratification is sub-optimal. A number of new biomarkers that have improved hepatic expression (miR-122) or provide mechanistic insights (keratin-18 [K18], High Mobility Group Box-1 [HMGB1]), have been proposed to have higher specificity and sensitivity than currently used tests. The objective of this study was to prospectively explore the ability of these biomarkers to stratify patients by risk of subsequent liver injury in 2 paracetamol overdose patient cohorts that faithfully represented the spectrum of clinical presentations requiring treatment with acetylcycteine.

Methods: Patients who needed acetylcysteine treatment for paracetamol overdose were recruited. Independent derivation (Markers and Paracetamol Poisoning, 8 UK hospitals) and validation (Biomarkers of Paracetamol Hepatotoxicity, 10 UK hospitals) studies prospectively recruited 985 and 202 patients, respectively. Circulating biomarkers were measured at hospital presentation. The primary endpoint was acute liver injury (ALI), defined as peak alanine transaminase activity (ALT) >100 IU/L. Secondary endpoints included ALT >1000 IU/L and liver synthetic dysfunction (INR >1.5). Receiver Operator Characteristic Area Under the Curve (ROC-AUC) and Multivariate Net Reclassification Index (NRI) analyses were utilised to determine the ability of these novel biomarkers to stratify patients by liver injury risk.

Results: In the derivation and validation cohorts, ALI was predicted at presentation to hospital with high sensitivity and specificity by miR-122, HMGB1 and full length-K18 (FL-K18) (ROC-AUC values: 0.97 [0.95–0.98], 0.95 [0.93–0.98] and 0.95 [0.92–0.97], respectively). High predictive accuracy was maintained when the cohorts were censored by normal presentation ALT, time from overdose and overdose type (acute or staggered). For prediction of INR elevation, HMGB1 had the maximal prognostic ability in acute and staggered overdoses in both the derivation and validation cohorts (ROC-AUC: 0.94 [0.88–1.00] compared with ALT (0.55 [0.39–0.72]).

Conclusion: In these two multi-centre prospective studies, we have demonstrated that a panel of mechanistic circulating biomarkers can predict subsequent liver injury and dysfunction with high accuracy despite treatment with acetylcysteine. Using these biomarkers, a precision medicine approach to patient stratification and management can be applied at hospital presentation. This study has directly contributed to the regulatory (Food and Drug Administration [FDA] and European Medicines Agency [EMEA]) letters of support for the further qualification of these biomarkers across the spectrum of drug-induced liver injury.