

Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

Serum acetaminophen concentrations after acute overdose are not altered by opioid co-ingestion

Waring WS, Benhalim S. *J Toxicol Sci* 2008; 33: 549-53.

Abstract

Serum acetaminophen concentrations are of critical importance in determining the need for acetylcysteine therapy after acute acetaminophen overdose. Limited data suggest opioid co-ingestion might alter acetaminophen pharmacokinetics. The present study was designed to examine serum acetaminophen concentrations after acute overdose, and to compare between patients that co-ingested an opioid and those that did not.

A prospective study of consecutive patients that presented to hospital within 16 hr of acute acetaminophen overdose. Equivalent 4-hr acetaminophen concentrations were calculated using the serum acetaminophen concentration at a fixed interval 3 to 16 hr after ingestion. Groups were compared using Mann Whitney tests. There were 990 patients; 295 (29.8%) had co-ingested an opioid, and 695 had not. The median (interquartile range) stated dose was 10 g (6-16 g) vs. 10 g (7-16 g) respectively ($P = 0.94$), interval between ingestion and acetaminophen determination was 4.5 hr (4.0-6.0 hr) vs. 4.5 hr (4.0-5.5 hr) respectively ($P = 0.41$), and serum acetaminophen concentration was 56 mg/l (24-105 mg/l) vs. 60 mg/l (23-129 mg/l) respectively ($P = 0.25$).

A positive relationship was noted between stated dose and equivalent 4-hr serum acetaminophen concentration, but did not differ between groups. The acetaminophen dose-concentration relationship was similar in patients that did and did not co-ingest an opioid. Therefore, early serum acetaminophen concentrations can be used to determine the extent of drug exposure, irrespective of whether an opioid has been co-ingested.

Coma and impaired consciousness in the emergency room: characteristics of poisoning versus other causes

Forsberg S, Höjer J, Enander C, Ludwigs U. *Emerg Med J* 2009; 26: 100-2.

Objectives

Unconscious patients represent a diagnostic challenge in the emergency room (ER), but studies on their characteristics are limited. The aim of this study was to investigate the frequency, characteristics and prognosis of different coma aetiologies with special focus on poisoning.

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Design

An observational study of consecutive adults admitted to the non-surgical ER, with a Glasgow coma scale (GCS) score of 10 or below. The GCS score on admission was prospectively entered into a study protocol, which was complemented with data from the medical record within one month.

Results

938 patients were enrolled. Poisoning caused unconsciousness in 352 cases (38%). In the remaining 586 cases (non-poisoning group) the underlying cause was a focal neurological lesion in 24%, a metabolic or diffuse cerebral disturbance in 21%, epileptogenic in 12%, psychogenic in 1% and was still not clarified at hospital discharge in 4%. Among patients below the age of 40 years, the coma was caused by poisoning in 80%, but among those over 60 years, poisoning was the cause in only 11%. The median GCS score on admission was identical in the two study groups. Hospital mortality rates were 2.8% and 39% in the two groups, respectively.

Conclusion

Poisoning was the most common cause of coma and young age was a strong predictor of this condition. The prognosis was favourable among poisoned patients but poor in the rest of the study population as a group.

Unintentional child poisonings treated in United States hospital emergency departments: national estimates of incident cases, population-based poisoning rates, and product involvement

Franklin RL, Rodgers GB. Pediatrics 2008; 122: 1244-51.

Objectives

The goals were to develop national estimates of unintentional child poisoning cases treated in US hospital emergency departments, to determine population-based poisoning rates, and to evaluate characteristics of the victims and the products involved.

Methods

Cases reported through the US Consumer Product Safety Commission National Electronic Injury Surveillance System, involving a national probability sample of US hospital emergency departments, were used as a basis for developing national estimates of product-related poisonings involving children <5 years of age treated in US hospital emergency departments in 2004.

Results

There were an estimated 86194 child poisoning incidents treated in US hospital emergency departments in 2004, amounting to 429.4 poisonings per 100000 children. Approximately 70% of the poisonings involved children 1 or 2 years of age, slightly more than one half involved boys, and 13.3% resulted in hospital admission. Approximately 59.5% of the poisonings involved oral prescription drugs, oral nonprescription drugs, or supplements. Other major product categories resulting in poisonings included cleaning products (13.2%), drugs and ointment preparations intended for external use (4.9%), and personal care products (4.7%). Approximately 54.7% of the poisonings involved products already subject to child-resistant packaging requirements under the Poison Prevention Packaging Act.

Conclusions

Despite advances in recent years, unintentional child poisonings remain an important public health concern. The circumstances surrounding poisonings need to be evaluated further, and intervention strategies need to be developed.

Treatment for amphetamine psychosis

Shoptaw SJ, Kao U, Ling WW. Cochrane Database Syst Rev 2008; 4: CD003026.

Background

Chronic amphetamine users may have experience of paranoia and hallucination. It has long been believed that dopamine antagonists, such as chlorpromazine, haloperidol, and thioridazine, are effective for the treatment of amphetamine psychosis.

Objectives

To evaluate risks, benefits, costs of treatments for amphetamine psychosis.

Search strategy

MEDLINE (1966-2007), EMBASE (1980-2007), CINAHL (1982-2007), PsychINFO (1806-2007), CENTRAL (Cochrane Library 2008 issue 1), references of obtained articles.

Selection criteria

All randomised controlled and clinical trials (RCTs, CCTs) evaluating treatments (alone or combined) for people with amphetamine psychosis.

Data collection and analysis

Two authors evaluated and extracted the data independently. Dichotomous data were extracted on an intention-to-treat basis in which the dropouts were assigned as participants with the worst outcomes. The Relative Risk (RR) with the 95% confidence interval (95% CI) was used to assess the dichotomous data. The Weighted Mean Difference (WMD) with 95% CI was used to assess the continuous data.

Main results

The comprehensive searches found one randomised controlled trial of treatment for amphetamine psychosis meeting the criteria for considering studies. The study involved 58 participants and compared the efficacy and tolerability of two antipsychotic drugs, olanzapine (a newer antipsychotic) and haloperidol (a commonly used antipsychotic medication used as a control condition), in treating amphetamine-induced psychosis. The results show that both olanzapine and haloperidol at clinically relevant doses were efficacious in resolving psychotic symptoms, with the olanzapine condition showing significantly greater safety and tolerability than the haloperidol control as measured by frequency and severity of extrapyramidal symptoms.

Authors' conclusions

Only one RCT of treatment for amphetamine psychosis has been published. Outcomes from this trial indicate that antipsychotic medications effectively reduce symptoms of amphetamine psychosis, the newer generation and more expensive antipsychotic medication, olanzapine, demonstrates significantly better tolerability than the more affordable and commonly used medication, haloperidol. There are other two studies that did not meet the inclusion criteria for this review. The results of these two studies show that agitation and some psychotic symptoms may be abated within an hour after antipsychotic injection. Whether this limited evidence can be applied for amphetamine psychotic patients is not yet known. The medications that should be further investigate are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and the prevalence of relapse to psychosis in the presence of amphetamine, are also crucial for advising the development of study designs appropriate for further treatment studies of amphetamine psychosis.

Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study

Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. Clin Pharmacol Ther 2009; 85: 31-5.

Abstract

A large number of women receive codeine for obstetric pain while breastfeeding. Following a case

of fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultrarapid metabolizer (UM), we examined characteristics of mothers and infants with or without signs of central nervous system (CNS) depression following codeine exposure while breastfeeding in a case-control study.

Mothers of symptomatic infants (n = 17) consumed a mean 59% higher codeine dose than mothers of asymptomatic infants (n = 55) (1.62 (0.79) mg/kg/day vs. 1.02 (0.54) mg/kg/day; P = 0.004). There was 71% concordance between maternal and neonatal CNS depression. Two mothers whose infants exhibited severe neonatal toxicity were CYP2D6 UMs and of the UGT2B7*2/*2 genotype.

There may be a dose-response relationship between maternal codeine use and neonatal toxicity, and strong concordance between maternal-infant CNS depressive symptoms. Breastfed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.

Melamine-contaminated powdered formula and urolithiasis in young children

Guan N, Fan Q, Ding J, Zhao Y, Lu J, Ai Y, Xu G, Zhu S, Yao C, Jiang L, Miao J, Zhang H, Zhao D, Liu X, Yao Y. N Engl J Med 2009; online early: doi: 10.1056/NEJMoa0809550: 1-8.

Background

A recent epidemic of melamine contamination of baby formula in China has been associated with the development of urinary tract stones, though the clinical manifestations and predisposing factors are incompletely delineated.

Methods

We administered a questionnaire to the parents of children 36 months of age or younger who were being screened for a history of exposure to melamine and symptoms of, and possible predisposing factors for, urinary tract stones. In addition, we performed urinalysis, renal-function and liver-function tests, urinary tests for biochemical markers and the calcium:creatinine ratio, and ultrasonography. Powdered-milk infant formulas were classified as having a high melamine content (>500 ppm), a moderate melamine content (<150 ppm), or no melamine (0 ppm); no formulas contained between 150 and 500 ppm of melamine.

Results

Contaminated formula was ingested by 421 of 589 children. Fifty had urinary stones, including 8 who had not received melamine-contaminated formula; 112 were suspected to have stones; and 427 had no stones. Among children with stones, 5.9% had hematuria and 2.9% had leukocyturia, percentages that did not differ significantly from those among children who were suspected to have stones or those who did not have stones. Serum creatinine, urea nitrogen, and alanine aminotransferase levels were normal in the 22 children with stones who were tested. Four of the 41 children (9.8%) who had stones and in whom urinary markers of glomerular function were measured had evidence of abnormalities; none had tubular dysfunction. Children exposed to high-melamine formula were 7.0 times as likely to have stones as those exposed to no-melamine formula. Preterm infants were 4.5 times as likely to have stones as term infants.

Conclusions

Prematurity and exposure to melamine-contaminated formula were associated with urinary stones. Affected children lacked typical signs and symptoms of urolithiasis.

Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis

Mink PJ, Alexander DD, Barraj LM, Kelsh MA, Tsuji JS. Regul Toxicol Pharmacol 2008; 52: 299-310.

Abstract

Although exposure to high levels of arsenic in drinking water is associated with excess cancer risk (e.g., skin, bladder, and lung), lower exposures (e.g., <100-200 µg/L) generally are not. Lack of significant associations at lower exposures may be attributed to methodologic issues (e.g., inadequate statistical power, exposure misclassification), or to differences in the dose-response relationship at high versus low exposures. The objectives of this review and meta-analysis were to evaluate associations, examine heterogeneity across studies, address study design and sample size issues, and improve the precision of estimates.

Eight studies of bladder cancer and low-level arsenic exposure met our inclusion criteria. Meta-analyses of never smokers produced summary relative risk estimates (SRREs) below 1.0 (highest versus lowest exposure). The SRRE for never and ever smokers combined was elevated slightly, but not significantly (1.11; 95% CI: 0.95-1.30). The SRRE was somewhat elevated among ever smokers (1.24; 95% CI: 0.99-1.56), and statistical significance was observed in some subgroup analyses; however, heterogeneity across studies was commonly present.

Although uncertainties remain, low-level arsenic exposure alone did not appear to be a significant independent risk factor for bladder cancer. More studies with detailed smoking history will help resolve whether smoking is an effect modifier.

Epidemiological, clinical characteristics and outcome of severe scorpion envenomation in South Tunisia: multivariate analysis of 951 cases

Bouaziz M, Bahloul M, Kallel H, Samet M, Ksibi H, Dammak H, Ahmed MNB, Chtara K, Chelly H, Hamida CB, Rekik N. Toxicol 2008; 52: 918-26.

Abstract

The aim of this retrospective descriptive study was to describe both epidemiologically and clinically manifestations following severe scorpion envenomation and to define simple predictive factors which can be used in routine practice in general Intensive Care Units (ICU) as an indicator of poor prognosis.

Cases were collected from hospital patients' files during 13-year (1990-2002) period in the medical Intensive Care Unit of a university hospital (Sfax, Tunisia). The diagnosis of scorpion envenomation was based on a history of scorpion sting. Nine hundred fifty-one patients, who were admitted for a scorpion sting, were analyzed. There were 769 patients (80.8%) in the grade III group (with cardiogenic shock and/or pulmonary edema or severe neurological manifestation (coma and/or convulsion)) and 182 patients (19.2%) in the grade II group (with systemic manifestations). Scorpion envenomation is more frequent in summer; indeed 82.3% of our patients were admitted between June and September. The mean age (\pm SD) was 14.7 \pm 17.4 years, ranging from 0.5 to 90 years. In this study 739 patients (77.8%) had neuromuscular signs, 700 patients (73.6%) had gastrointestinal signs and 585 patients (61.5%) had a pulmonary edema, while 195 patients (20.5%) had a cardiogenic shock. The mean blood sugar on admission was at 11.32 \pm 5.66 mmol/l, a high blood sugar level (>11 mmol/l) was observed in 39% of cases. The mean blood urea was at 7.1 \pm 3.2 mmol/l, it was above 10 mmol/l in 10.7% of cases. The mean of leucocytes was at 17418 \pm 7833 cells/mm³, it was above 11 000/mm³ in 80% of cases. In the end of the stay in ICU, evolution was marked by the improvement of 879 patients (92.5%) while 72 patients (7.5%) died.

A multivariate analysis found the following factors to be correlated with a poor outcome: age < 5 years (OR = 2.27), fever >38.5°C (OR = 2.79), coma with Glasgow coma score \leq 8/15 (OR = 9.87), pulmonary edema (OR = 8.46), leucocytes >25000 cells/mm³ (OR = 2.35) and blood urea >8 mmol/l

(OR = 4.02). Moreover, in children group, a significant association was found between PRISM score and mortality rate, this model had a high discriminative power with an area under the ROC curve at 0.93. In the adult patients a significant association was found between SAPS II score and mortality rate, this model had a high discriminative power with an area under the ROC curve at 0.82.

In summary, in severe scorpion envenomation, age less than 5 years, fever $>38.5^{\circ}\text{C}$, coma with Glasgow coma score $\leq 8/15$, pulmonary edema, leucocytes >25000 cells/ mm^3 and blood urea >8 mmol/l were associated with a poor outcome.

The role of prednisolone in reducing limb oedema in children bitten by green pit vipers: a randomized, controlled trial

Nuchprayoon I, Pongpan C, Sripaiboonkij N. Ann Trop Med Parasitol 2008; 102: 643-9.

Abstract

When green pit vipers (GPV), which are common venomous snakes in Thailand, bite humans they cause coagulopathy as well as local tissue oedema. The use of steroids to reduce such oedema is controversial. The role of low, oral doses of prednisolone in the treatment of GPV bites in children has therefore now been assessed, in a randomized, double-blinded, placebo-controlled, clinical trial in Bangkok.

Overall, 43 children aged 3-15 years, each with a recent GPV bite to one limb, were randomly assigned to receive oral prednisolone (1 mg/kg.day) or placebo for 3 days, without antivenom or prophylactic antibiotics. The degree of limb oedema was assessed, immediately before the first dose and then daily, by measuring the limb circumference around the fang marks.

By 72 h post-bite, both treatment groups showed significant decreases in the level of their limb oedema. Since, at each time-point, the patients in the two groups showed similar levels of limb oedema (and of reduction in such oedema), there appeared to be no benefit from the use of the prednisolone.

Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases

Teschke R, Schwarzenboeck A, Hennermann K-H. Eur J Gastroenterol Hepatol 2008; 20: 1182-93.

Background/aims Hepatotoxicity has been previously suspected by national regulatory agencies in 26 patients in causal relationship with the treatment by kava extracts commonly used as herbal anxiolytic drugs.

Methods A quantitative causality assessment was undertaken using the system of the Council for International Organizations of Medical Sciences, scale of objective probability scoring.

Results Causality was unassessable, unrelated, or excluded in 16 patients owing to lack of temporal association and causes independent of kava or comedicated drugs. Low Council for International Organizations of Medical Sciences scores additionally resulted in excluded or unlikely causality assessments ($n = 2$), leaving a total of eight patients with various degrees of causality for kava \pm comedicated drugs. Only one out of these eight patients adhered to the regulatory recommendations regarding both daily dose (≤ 120 mg kavapyrones) and duration of therapy (≤ 3 months) and experienced toxic liver injury with a probable causality for kava. In six cases with kava overdose and/or increased duration of kava treatment causality for kava was possible ($n = 3$) and for kava together with the comedicated drug(s) possible ($n = 2$) or probable ($n = 1$).

Conclusion Kava taken as recommended is associated with rare hepatotoxicity, whereas overdose, prolonged treatment and comedication may carry an increased risk.

TOXICOLOGY

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