

Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

2008 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th annual report

Bronstein AC, Spyker DA, Cantilena LR, Jr., Green JL, Rumack BH, Giffin SL. Clin Toxicol 2009; 47: 911-1084.

Background

This is the 26th Annual Report of the American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org>) National Poison Data System (NPDS). During 2008, 60 of the nation's 61 US poison centers uploaded case data automatically. The median upload time was 24 [7.2, 112] (median [25%, 75%]) minutes creating a real-time national exposure and information database and surveillance system.

Methodology

We analyzed the case data tabulating specific indices from NPDS. The methodology was similar to that of previous years. Where changes were introduced, the differences are identified. Poison center cases with medical outcomes of death were evaluated by a team of 28 medical and clinical toxicologist reviewers using an ordinal scale of 1-6 to determine Relative Contribution to Fatality (RCF) from the exposure to the death.

Results

In 2008, 4,333,012 calls were captured by NPDS: 2,491,049 closed human exposure cases, 130,495 animal exposures, 1,703,762 information calls, 7336 human confirmed nonexposures, and 370 animal confirmed nonexposures. The top five substances most frequently involved in all human exposures were analgesics (13.3%), cosmetics/personal care products (9.0%), household cleaning substances (8.6%), sedatives/hypnotics/antipsychotics (6.6%), and foreign bodies/ toys/ miscellaneous (5.2%). The top five most common exposures in children age 5 or less were cosmetics/personal care products (13.5%), analgesics (9.7%), household cleaning substances (9.7%), foreign bodies/toys/miscellaneous (7.5%), and topical preparations (6.9%). Drug identification requests comprised 66.8% of all information calls. NPDS documented 1756 human exposures resulting in death with 1315 human fatalities deemed related with an RCF of at least contributory (1, 2, or 3).

Conclusions

Poisoning continues to be a significant cause of morbidity and mortality in the US. The near real-time, always current status of NPDS represents a national resource to collect and monitor US

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poisoning exposure cases and information calls. NPDS continues its mission as one of the few real-time national surveillance systems in existence, providing a model public health surveillance system for all types of exposures, public health event identification, resilience response and situational awareness tracking.

The effect of decontamination procedures on the pharmacokinetics of venlafaxine in overdose

Kumar VV, Oscarsson S, Friberg LE, Isbister GK, Hackett LP, Duffull SB. Clin Pharmacol Ther 2009; 86: 403-10.

Abstract

The aim of this work was to investigate the pharmacokinetics (PK) of venlafaxine in overdose and the effects of single-dose activated charcoal (SDAC) and whole-bowel irrigation (WBI), alone or in combination, as methods of decontamination.

The data included 339 concentration-time points from 76 venlafaxine overdose events (median dose 2625 (150-13,500 mg)); 69 were slow-release doses. SDAC, WBI, a combination of both, or no decontamination were administered to patients as decided by the treating clinician. The data were modeled using WinBUGS (Windows Bayesian Inference Using Gibbs Sampling).

A one-compartment model with first-order input and elimination provided an adequate description of the data. SDAC increased clearance (CL) of venlafaxine by 35%, and SDAC and WBI combined reduced the fraction absorbed by 29%. However, the latter produced a greater reduction in maximum plasma concentration (C_{max}) for a similar drop in area under the plasma concentration-time curve (AUC).

Both SDAC alone, and a combination of SDAC and WBI, decreased the AUC after venlafaxine overdose, but the combination may be more beneficial because it reduces peak concentrations to a greater extent.

Hydroxocobalamin and sodium thiosulfate versus sodium nitrite and sodium thiosulfate in the treatment of acute cyanide toxicity in a swine (*Sus scrofa*) model

Bebarta VS, Tanen DA, Lairet J, Dixon PS, Valtier S, Bush A. Ann Emerg Med 2009; online early: doi:10.1016/j.annemergmed.2009.09.020: 1-7.

Study objective

Cyanide can cause severe hypotension with acute toxicity. To our knowledge, no study has directly compared hydroxocobalamin and sodium nitrite with sodium thiosulfate in an acute cyanide toxicity model. Our objective is to compare the return to baseline of mean arterial blood pressure between 2 groups of swine with acute cyanide toxicity and treated with hydroxocobalamin with sodium thiosulfate or sodium nitrite with sodium thiosulfate.

Methods

Twenty-four swine were intubated, anesthetized, and instrumented (continuous arterial and cardiac output monitoring) and then intoxicated with a continuous cyanide infusion until severe hypotension. The animals were divided into 2 arms of 12 each and then randomly assigned to intravenous hydroxocobalamin (150 mg/kg)+sodium thiosulfate (413 mg/kg) or sodium nitrite (10 mg/kg)+sodium thiosulfate (413 mg/kg) and monitored for 40 minutes after start of antidotal infusion. Twenty animals were needed for 80% power to detect a significant difference in outcomes (alpha 0.05). Repeated measures of analysis of covariance and post hoc t test were used for determining significance.

Results

Baseline mean weights, time to hypotension (31 min 3 s vs 28 min 6 s), and cyanide dose at

hypotension (5.6 vs 5.9 mg/kg) were similar. One animal in the hydroxocobalamin group and 2 animals in the sodium nitrite group died during antidote infusion and were excluded from analysis. Hydroxocobalamin resulted in a faster return to baseline mean arterial pressure, with improvement beginning at 5 min and lasting through the conclusion of the study ($P < 0.05$). No statistically significant difference was detected between groups for cardiac output, pulse rate, systemic vascular resistance, or mortality at 40 min postintoxication. Mean cyanide blood levels (4.03 vs 4.05 $\mu\text{g/mL}$) and lactate levels (peak 7.9 vs 8.1 mmol/L) at hypotension were similar. Lactate levels (5.1 vs 4.48 mmol/L), pH (7.40 vs 7.37), and base excess (-0.75 vs 1.27) at 40 min were also similar.

Conclusion

Hydroxocobalamin with sodium thiosulfate led to a faster return to baseline mean arterial pressure compared with sodium nitrite with sodium thiosulfate; however, there was no difference between the antidote combinations in mortality, serum acidosis, or serum lactate.

Interpretation of clinical guidelines for poisoned patients: positive and negative effects of standard phrases used in TOXBASE

Waring WS, McDonald SH, Good AM, Gordon LD, Bateman DN. Eur J Clin Pharmacol 2009; 65: 1007-12.

Introduction

Electronic information sources are increasingly relied upon for clinical management advice. TOXBASE is a standardised online resource that offers clinical advice on the management of poisoned patients and is the first point of contact between clinicians and the National Poisons Information Service in the United Kingdom. Advice is delivered using a series of standard phrases. The present study examined how healthcare professionals interpret the phrases and studied their impact on clinical decision-making.

Methods

A structured prospective written questionnaire was offered to healthcare staff in the Lothian region, and an electronic questionnaire issued to TOXBASE users across the United Kingdom. Participants were asked to respond to a variety of scenarios representing acutely poisoned patients. Clinical management advice was offered via TOXBASE using a variety of standard phrases, and participants were asked to express the likelihood that they would then administer gut decontamination treatment.

Results

There were 70 respondents to written questionnaires, and 119 respondents to the electronic version. Phrases that included didactic instructions, for example 'give', 'contraindicated', 'do' and 'perform' were associated with strongly positive or strongly negative responses. In contrast, advice that consisted of open phrases such as 'consider', 'benefit uncertain', and 'few data' were associated with inconsistent responses.

Conclusion

Didactic words and phrases are associated with more consistent interpretation and response than open-ended words and phrases. The choice of words and phrases used in electronic systems can have an independent impact on clinical decision-making and require further consideration.

Sudden death in patients receiving drugs tending to prolong the QT interval

Jolly K, Gammage MD, Cheng KK, Bradburn P, Banting MV, Langman MJS. Br J Clin Pharmacol 2009; 68: 743-51.

Aims

To examine risks of sudden death in the community associated with drugs grouped by their risk of

causing torsades de pointes (TdP) and to explore the risks for individual drugs.

Methods

Case-control study comparing prior drug intakes and morbidities, using the Arizona classification of drugs causing TdP. Participants included 1010 patients dying suddenly where post-mortem examination did not identify a clear cause of death, and 3030 matched living controls from primary care.

Results

Noncardiac drug risk was posed by antipsychotics and antidepressants. Significantly raised odds ratios (ORs) were found for takers of typical and atypical antipsychotics, ORs [95% confidence interval] 3.94 (2.05, 7.55) and 4.36 (2.54, 7.51), and of selective serotonin reuptake inhibitors [SSRIs] rather than tricyclic antidepressants, ORs 2.21 (1.61, 3.05) and 1.44 (0.96, 2.13). No significant risk was associated with other, noncardiac or psychiatric drugs, OR 1.09 (0.85, 1.41). Arizona classified drugs considered to raise risk of TdP were associated with raised risk of sudden death, as were those only weakly associated with TdP and not considered to pose a risk in normal use, ORs 2.08 (1.45, 3.00) and 1.74 (1.33, 2.28), respectively.

Conclusions

Atypical and typical antipsychotic drug use were both strongly associated with raised risks, as were SSRIs. Tricyclic antidepressants were not associated with raised risks. The Arizona classification of risk of TdP was a poor predictor of likelihood of noncardiac drug-associated sudden death.

Snake bite

Warrell DA. Lancet, 2010; 375: 77-88.

Summary

Snake bite is a common and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. Its public health importance has been largely ignored by medical science.

Snake venoms are rich in protein and peptide toxins that have specificity for a wide range of tissue receptors, making them clinically challenging and scientifically fascinating, especially for drug design. Although the full burden of human suffering attributable to snake bite remains obscure, hundreds of thousands of people are known to be envenomed and tens of thousands are killed or maimed by snakes every year.

Preventive efforts should be aimed towards education of affected communities to use proper footwear and to reduce the risk of contact with snakes to a minimum through understanding of snakes' behaviour. To treat envenoming, the production and clinical use of antivenom must be improved. Increased collaboration between clinicians, epidemiologists, and laboratory toxinologists should enhance the understanding and treatment of envenoming.

Lipid resuscitation for local anesthetic toxicity: is it really lifesaving?

Leskiw U, Weinberg GL. Curr Opin Anaesthesiol 2009; 22: 667-71.

Purpose of review

Laboratory studies and clinical reports have led to the acceptance of lipid emulsion as an effective treatment of local anesthetic-induced cardiac arrest. This review discusses subsequent clinical reports, relevant laboratory studies and topics for further research.

Recent findings

Case reports have confirmed the efficacy of lipid resuscitation for local anesthetic systemic toxicity. Furthermore, lipid emulsion has been used with apparent success early in the spectrum of

local anesthetic systemic toxicity to preempt cardiac arrest. The role of lipid emulsion has expanded to treatment of cardiac toxicity due to other lipophilic drugs. This appears to have an acceptable safety profile, although elevated amylase has been reported. Laboratory investigations in animals suggest that concomitant hypoxemia hinders resuscitation attempts, and that epinephrine and vasopressin are more likely to be associated with poor outcomes than lipid.

Summary

Lipid emulsion infusion appears to be an effective treatment for cardiac toxicity induced by lipophilic medications. Given the difficulties of performing clinical trials, further laboratory investigation and clinical correlation are needed to better define its role in resuscitation.

Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data

Stoove MA, Dietze PM, Jolley D. Drug Alcohol Rev 2009; 28: 347-52.

Introduction and aims

Experiencing previous non-fatal overdoses have been identified as a predictor of subsequent non-fatal overdoses; however, few studies have investigated the association between previous non-fatal overdose experiences and overdose mortality. We examined overdose mortality among injecting drug users who had previously been attended by an ambulance for a non-fatal heroin overdose.

Design and methods

Using a retrospective cohort design, we linked data on non-fatal heroin overdose cases obtained from ambulance attendance records in Melbourne, Australia over a 5-year period (2000-2005) with a national death register.

Results

4884 people who were attended by ambulance for a non-fatal heroin overdose were identified. One hundred and sixty-four overdose deaths occurred among this cohort, with an average overdose mortality rate of 1.20 per 100 person-years (95% CI, 1.03-1.40). Mortality rate decreased 10-fold after 2000 coinciding with widely reported declines in heroin availability. Being male, of older age (>35 years) and having been attended multiple times for previous non-fatal overdoses were associated with increased mortality risk.

Discussion and conclusions

As the first to show a direct association between non-fatal overdose and subsequent overdose mortality, this study has important implications for the prevention of overdose mortality. This study also shows the profound effect of macro-level heroin market dynamics on overdose mortality.

Long-term ocular consequences of sulfur mustard in seriously eye-injured war veterans

Ghasemi H, Ghazanfari T, Ghassemi-Broumand M, Javadi MA, Babaei M, Soroush MR, Yaraee R, Faghihzadeh S, Poorfarzam S, Owlia P, Naghizadeh MM, Etezzad-Razavi M, Jadidi K, Naderi M, Hassan ZM. Cutan Ocul Toxicol 2009; 28: 71-7.

Introduction

Sulfur mustard (SM) has been used as a dangerous chemical warfare agent since the early 20th century. Although many descriptive studies about SM-induced ocular injuries are present in the medical literature, few of them have been conducted over a large group with serious ocular involvement.

Materials and methods

This descriptive study was conducted on 149 severe SM-intoxicated war veterans. Ocular history,

anterior and posterior segment findings using a slit lamp, and direct and indirect ophthalmoscopic findings were recorded. Severity of the disease was also recorded based on a chart of the Foundation of Martyrs and Veterans Affairs.

Results

Ocular complaints included photophobia (73.2%), sense of decreased vision (72.5%), dry eye sensation (66.4%), foreign body sensation (61.1%), tearing (46.3%), and pain (43.0%). Slit lamp findings were meibomian gland dysfunction (MGD; 96%), blepharitis, punctal closure, trichiasis, tear break-up time, and tear meniscus layer abnormality (80% to 90%). Conjunctival disturbances included vascular abnormality, ischemia, hyperemia, subconjunctival fibrosis, and pterygium. Limbal changes were abnormal vessels, limbal tissue loss and pigment loss, and pannus formation. Corneal problems included epithelial and stromal disturbances, calcium deposition, and melting. The most frequent previous surgeries were punctal closure, lamellar keratoplasty (LK), and stem cell allograft. Severity of intoxication included mild (17%), moderate (25%), and severe (57%).

Conclusion

Chronic blepharitis and decreased tear secretion are the 2 most important and influencing factors in progression of ocular problems in SM injuries. The more severe the initial exposure, percentage of disability, and duration of ocular involvement, the higher the likelihood of mustard gas keratopathy.

Pattern of oseltamivir ingestions reported to Texas poison centers

Forrester MB. Hum Exp Toxicol 2009; online early: doi: 10.1177/0960327109357219: 1-4.

Abstract

During serious influenza outbreaks, the number of oseltamivir exposures reported to poison centers might be expected to increase. This investigation describes the pattern of oseltamivir ingestions reported to Texas poison centers during 2000-2008.

Of 298 total ingestions, 91.9% occurred in December-March, 76.8% involved patients aged 0-19 years, 72.5% resulted from therapeutic error, 90.0% were managed on-site, and 80.0% had no effect. The most frequently reported adverse clinical effects were vomiting (7.5%), nausea (3.8%), and abdominal pain (3.8%).

Oseltamivir ingestions were reported to Texas poison centers primarily during periods of influenza outbreak. Most involved children, resulted from therapeutic error, and were managed on-site without serious outcome.

The cost-effective implementation of an electronic document management system at a poison information center to improve preparedness for a terrorism incident

Pummer TL, Wisniewski CS, Krenzelok EP. J Homeland Secur Emerg Manage 2009; 6: 84.

Abstract

Access to evidence-based literature in a timely and efficient manner is critical in a situation involving a terrorism incident. The purpose of this project was to develop a method that provides rapid access to key biological, chemical, and radiological terrorism literature for poison information specialists, working in either the poison center or as remote agents, during a terrorism incident.

Various electronic document management systems were evaluated and compared based on the cost of implementation and maintenance, ease of use, capabilities, and efficiency. After a thorough evaluation of these systems, it was determined that Adobe Acrobat Professional

software met the needs of the center, with minimal expense. The implementation process involved scanning selected biological, chemical, and radiological terrorism literature via an HP Digital Sender 9250c scanner. The Adobe Acrobat Professional software was used to enter the author, title, and assigned keywords for searching.

Total cost of implementation was approximately \$4500. The full software version was necessary for a minimal number of users, while the searching component for specialists in poison information was available through Adobe Acrobat Reader. A majority of the staff was satisfied with the new system and felt it was user friendly.

The described system allows specialists rapid access to key papers, whether they are working in the center or remotely. This improves efficiency when surge capacity is compromised, which can occur during a terrorism incident.

New views on the hypothesis of respiratory cancer risk from soluble nickel exposure; and reconsideration of this risk's historical sources in nickel refineries

Heller JG, Thornhill PG, Conard BR. J Occup Med Toxicol 2009; 4:

Introduction

While epidemiological methods have grown in sophistication during the 20th century, their application in historical occupational (and environmental) health research has also led to a corresponding growth in uncertainty in the validity and reliability of the attribution of risk in the resulting studies, particularly where study periods extend back in time to the immediate postwar era (1945-70) when exposure measurements were sporadic, unsystematically collected and primitive in technique; and, more so, to the pre-WWII era (when exposure data were essentially non-existent). These uncertainties propagate with animal studies that are designed to confirm the carcinogenicity by inhalation exposure of a chemical putatively responsible for historical workplace cancers since exact exposure conditions were never well characterized. In this report, we present a weight of scientific evidence examination of the human and toxicological evidence to show that soluble nickel is not carcinogenic; and, furthermore, that the carcinogenic potencies previously assigned by regulators to sulphidic and oxidic nickel compounds for the purposes of developing occupational exposure limits have likely been overestimated.

Methods

Published, file and archival evidence covering the pertinent epidemiology, biostatistics, confounding factors, toxicology, industrial hygiene and exposure factors, and other risky exposures were examined to evaluate the soluble nickel carcinogenicity hypothesis; and the likely contribution of a competing workplace carcinogen (arsenic) on sulphidic and oxidic nickel risk estimates.

Findings

Sharp contrasts in available land area and topography, and consequent intensity of production and refinery process layouts, likely account for differences in nickel species exposures in the Kristiansand (KNR) and Port Colborne (PCNR) refineries. These differences indicate mixed sulphidic and oxidic nickel and arsenic exposures in KNR's historical electrolysis department that were previously overlooked in favour of only soluble nickel exposure; and the absence of comparable insoluble nickel exposures in PCNR's tankhouse, a finding that is consistent with the absence of respiratory cancer risk there. The most recent KNR evidence linking soluble nickel with lung cancer risk arose in a reconfiguration of KNR's historical exposures. But the resulting job exposure matrix lacks an objective, protocol-driven rationale that could provide a valid and reliable basis for analyzing the relationship of KNR lung cancer risk with any nickel species. Evidence of significant arsenic exposure during the processing step in the Clydach refinery's hydrometallurgy department in the 1902-1934 time period likely accounts for most of the elevated respiratory cancer risk observed at that time. An

understanding of the mechanism for nickel carcinogenicity remains an elusive goal of toxicological research; as does its capacity to confirm the human health evidence on this subject with animal studies.

Concluding remarks

Epidemiological methods have failed to accurately identify the source(s) of observed lung cancer risk in at least one nickel refinery (KNR). This failure, together with the negative long-term animal inhalation studies on soluble nickel and other toxicological evidence, strongly suggest that the designation of soluble nickel as carcinogenic should be reconsidered, and that the true causes of historical lung cancer risk at certain nickel refineries lie in other exposures, including insoluble nickel compounds, arsenic, sulphuric acid mists and smoking.

Paralytic shellfish poisoning: seafood safety and human health perspectives

Etheridge SM. *Toxicon* 2009; online early: doi: 10.1016/j.toxicon.2009.12.013:

Abstract

Paralytic shellfish poisoning (PSP) is the foodborne illness associated with the consumption of seafood products contaminated with the neurotoxins known collectively as saxitoxins (STXs).

This family of neurotoxins binds to voltage-gated sodium channels, thereby attenuating action potentials by preventing the passage of sodium ions across the membrane. Symptoms include tingling, numbness, headaches, weakness and difficulty breathing. Medical treatment is to provide respiratory support, without which the prognosis can be fatal. To protect human health, seafood harvesting bans are in effect when toxins exceed a safe action level (typically 80 µg STX eq 100 g⁻¹ tissue).

Though worldwide fatalities have occurred, successful management and monitoring programs have minimized PSP cases and associated deaths. Much is known about the toxin sources, primarily certain dinoflagellate species, and there is extensive information on toxin transfer to traditional vectors - filter-feeding molluscan bivalves. Non-traditional vectors, such as puffer fish and lobster, may also pose a risk. Rapid and reliable detection methods are critical for toxin monitoring in a wide range of matrices, and these methods must be appropriately validated for regulatory purposes.

This paper highlights PSP seafood safety concerns, documented human cases, applied detection methods as well as monitoring and management strategies for preventing PSP-contaminated seafood products from entering the food supply.

Azaspiracid poisoning (AZP) toxins in shellfish: toxicological and health considerations

Furey A, O'Doherty S, O'Callaghan K, Lehane M, James KJ. *Toxicon* 2009; online early: doi: 10.1016/j.toxicon.2009.09.009: 1.

Abstract

It has been almost a decade since a previously unknown human toxic syndrome, azaspiracid poisoning (AZP), emerged as the cause of severe gastrointestinal illness in humans after the consumption of mussels (*Mytilus edulis*).

Structural studies indicated that these toxins, azaspiracids, were of a new unprecedented class containing novel structural features. It is now known that the prevalent azaspiracids in mussels are AZA1, AZA2 and AZA3, which differ from each other in their degree of methylation. Several hydroxylated and carboxylated analogues of the main azaspiracids have also been identified, presumed to be metabolites of the main toxins. Since its first discovery in Irish mussels, the development of facile sensitive and selective LC-MS/MS methods has resulted in its discovery in other

countries and in other species. Mice studies indicate that this toxin class can cause serious tissue injury, especially to the small intestine, and chronic exposure may increase the likelihood of the development of lung tumours. Studies also show that tissue recovery is very slow following exposure.

These observations suggest that AZA is more dangerous than the other known classes of shellfish toxins. Consequently, in order to protect human consumers, proper risk assessment and regulatory control of shellfish and other affected species is of the utmost importance.

Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations

Matok I, Gorodischer R, Koren G, Landau D, Wiznitzer A, Levy A. Br J Clin Pharmacol 2009; 68: 956-62.

What is already known about this subject

Previous studies have suggested a tendency of antifolate drugs to be associated with higher rates of neural tube defects.

What this study adds

This study makes use of the data on abortuses, which is missed in many other studies. In this case, the abortion data were critical. The study documents that clinicians should avoid, as much as possible, the use of folic acid antagonists during the first trimester of pregnancy, when embryogenesis takes place.

Aim

To investigate the safety of folic acid antagonists during the first trimester of pregnancy in a large cohort.

Methods

Computerized databases for medications dispensed from 1998 to 2007 to women registered in 'Clalit' HMO, Israel southern district, was linked with maternal and infant hospitalization records, and to therapeutics abortions data. The risk for adverse pregnancy outcomes of folic acid antagonists exposure was assessed by adjusting for known confounders.

Results

Eighty-four thousand, eight hundred and twenty-three infants were born and 998 therapeutic abortions took place; 571 fetuses and infants were exposed to one or more folic acid antagonists in the first trimester of pregnancy. Exposure was associated with an overall increased risk of congenital malformations [odds ratio (OR) 2.43, 95% confidence interval (CI) 1.92, 3.08], due mainly to increased risk for neural tube (adjusted OR 6.5, 95% CI 4.34, 9.15) and cardiovascular defects (OR 1.76, CI 1.05, 2.95).

Conclusion

First-trimester exposure to folic acid antagonists is associated with increased risk of congenital malformations.

Parental occupational exposure to organic solvents and anencephaly in Mexico

Aguilar-Garduño C, Lacasaña M, Blanco-Muñoz J, Borja-Aburto VH, García AM. Occup Environ Med 2010; 67: 32-7.

Objective

To assess the relationship between parental occupational exposure to organic solvents, and the risk of anencephaly in Mexico.

Methods

A case-control study was conducted based on the registers of the Epidemiological Surveillance System for Neural Tube Defects in Mexico; 151 cases of anencephaly of ≥ 20 weeks' gestation

were included. A control, born alive and without any apparent congenital malformations at birth, was selected for each case in the same maternity service in which the case was born. Information on occupational exposures, lifestyle habits, reproductive history, use of medicines, supplementation with multivitamins and folic acid, was obtained by a general questionnaire; a food frequency questionnaire was also applied to obtain information of daily intake of folate and other B vitamins. Occupational exposure to organic solvents was based on job title as a proxy for exposure and analysed considering two critical periods around conception.

Results

In logistic regression analysis, the odds of having a child with anencephaly was higher if the mother or the father was occupationally exposed to organic solvents during the periconceptional period, or when both parents or at least one of them were occupationally exposed during this period with an adjusted odds ratio of 2.97 (95% CI 1.36 to 6.52).

Conclusions

The results support the hypothesis that both maternal and paternal occupational exposure to organic solvents can increase the probability of having a child with anencephaly.

Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight

Konishi K, Sasaki S, Kato S, Ban S, Washino N, Kajiwara J, Todaka T, Hirakawa H, Hori T, Yasutake D, Kishi R. *Environ Res* 2009; 109: 906-13.

Abstract

Several human studies have shown that low-level exposure to environmental contaminants, such as polychlorinated biphenyls (PCBs) and organochlorine pesticides, negatively influences birth outcomes. However, the effects of low-level exposure to polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs (DL-PCBs) on birth outcomes have not been clarified in human studies.

A prospective cohort study was established to investigate the possible adverse effects of PCDDs/PCDFs and DL-PCBs on fetal growth and neurodevelopment. We recruited 514 pregnant women between July 2002 and October 2005 in Sapporo, Japan. We measured 29 congener levels of PCDDs/PCDFs and DL-PCBs in maternal blood.

Using multiple linear regression analysis of the association between birth weight and the levels of PCDDs/PCDFs and DL-PCBs with full adjustments for potential confounders, a significant adverse effect was observed regarding total PCDDs toxic equivalents (TEQ) levels (adjusted beta = -231.5 g, 95% CI: -417.4 to -45.6) and total PCDFs TEQ levels (adjusted beta = -258.8 g, 95% CI: -445.7 to -71.8). Among male infants, significant adverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among female infants, these significant adverse associations were not found. With regard to individual congeners of PCDDs/PCDFs and DL-PCBs, we found significantly negative association with the levels of 2,3,4,7,8-PeCDF (adjusted beta = -24.5 g, 95% CI: -387.4 to -61.5).

Our findings suggest that prenatal low-level exposure to PCDDs and PCDFs, especially 2,3,4,7,8-PeCDF, may accumulate in the placenta and retard important placental functions, which result in lower birth weight

Maternal blood lead levels and the risk of pregnancy-induced hypertension: the EDEN cohort study

Yazbeck C, Thiebaugeorges O, Moreau T, Goua V, Debotte G, Sahuquillo J, Forhan A, Foliguet B, Magnin G, Slama R, Charles M-A, Huel G. *Environ Health Perspect* 2009; 117: 1526-30.

Background

Prior studies revealed associations of environmental lead exposure with risks of hypertension and elevated blood pressure.

Objective

We examined the effect of blood lead levels on blood pressure and the incidence of pregnancy-induced hypertension (PIH) in the second and third trimesters of pregnancy.

Methods

One thousand seventeen pregnant women were enrolled in two French municipalities between 2003 and 2005 for the EDEN (Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant) cohort study. Blood lead concentrations were measured by atomic absorption spectrometry in mothers between 24 and 28 weeks of gestation.

Results

PIH was diagnosed in 106 subjects (10.9%). Age, parity, weight gain, alcohol, smoking habits, and calcium supplementation were comparable between hypertensive and nonhypertensive women. Lead levels were significantly higher in PIH cases (mean \pm SD, 2.2 ± 1.4 $\mu\text{g/dL}$) than in normotensive patients (1.9 ± 1.2 $\mu\text{g/dL}$; $p = 0.02$). Adjustment for potential confounder effects slightly attenuated but did not eliminate the significant association between blood lead levels and the risk of PIH (adjusted odds ratio of PIH = 3.3; 95% confidence interval, 1.1-9.7). We also observed geographic differences in lead exposure and in the incidence of PIH and found significant correlations between blood lead levels and unadjusted as well as adjusted systolic and diastolic blood pressures after 24 weeks of gestation.

Conclusions

These findings confirm the relationship between blood lead levels at mid-pregnancy and blood pressure and suggest that environmental lead exposure may play an etiologic role in PIH.

Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery

Ochoa-Acuna H, Frankenberger J, Hahn L, Carbajo C. *Environ Health Perspect* 2009; 117: 1619-24.

Background

Atrazine and other corn herbicides are routinely detected in drinking water. Two studies on potential association of atrazine with small-for-gestational-age (SGA) and preterm birth prevalence found inconsistent results. Moreover, these studies did not control for individual-level potential confounders.

Objectives

Our retrospective cohort study evaluated whether atrazine in drinking water is associated with increased prevalence of SGA and preterm birth.

Methods

We developed atrazine concentration time series for 19 water systems in Indiana from 1993 to 2007 and selected all births ($n = 24,154$) based on geocoded mother's residences. Log-binomial models were used to estimate prevalence ratios (PRs) for SGA and preterm delivery in relation to atrazine concentrations during various periods of the pregnancy. Models controlled for maternal

demographic characteristics, prenatal care and reproductive history, and behavioral risk factors (smoking, drinking, drug use).

Results

Atrazine in drinking water during the third trimester and the entire pregnancy was associated with a significant increase in the prevalence of SGA. Atrazine in drinking water $> 0.1 \mu\text{g/L}$ during the third trimester resulted in a 17-19% increase in the prevalence of SGA compared with the control group ($< 0.1 \mu\text{g/L}$). Mean atrazine concentrations over the entire pregnancy $> 0.644 \mu\text{g/L}$ were associated with higher SGA prevalence than in the control group (adjusted PR = 1.14; 95% confidence interval, 1.03-1.24). No significant association was found for preterm delivery.

Conclusions

We found that atrazine, and perhaps other co-occurring herbicides in drinking water, is associated with an increased prevalence of SGA, but not preterm delivery.

A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure

Wigle DT, Turner MC, Krewski D. Environ Health Perspect 2009; 117: 1505-13.

Objectives

We conducted a systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure.

Data sources

Searches of MEDLINE (1950-2009) and other electronic databases yielded 31 included studies.

Data extraction

Two authors independently abstracted data and assessed the quality of each study.

Data synthesis

Random effects models were used to obtain summary odds ratios (ORs) and 95% confidence intervals (CIs). There was no overall association between childhood leukemia and any paternal occupational pesticide exposure (OR = 1.09; 95% CI, 0.88-1.34); there were slightly elevated risks in subgroups of studies with low total-quality scores (OR = 1.39; 95% CI, 0.99-1.95), ill-defined exposure time windows (OR = 1.36; 95% CI, 1.00-1.85), and exposure information collected after offspring leukemia diagnosis (OR = 1.34; 95% CI, 1.05-1.70). Childhood leukemia was associated with prenatal maternal occupational pesticide exposure (OR = 2.09; 95% CI, 1.51-2.88); this association was slightly stronger for studies with high exposure-measurement-quality scores (OR = 2.45; 95% CI, 1.68-3.58), higher confounder control scores (OR = 2.38; 95% CI, 1.56-3.62), and farm-related exposures (OR = 2.44; 95% CI, 1.53-3.89). Childhood leukemia risk was also elevated for prenatal maternal occupational exposure to insecticides (OR = 2.72; 95% CI, 1.47-5.04) and herbicides (OR = 3.62; 95% CI, 1.28-10.3).

Conclusions

Childhood leukemia was associated with prenatal maternal occupational pesticide exposure in analyses of all studies combined and in several subgroups. Associations with paternal occupational pesticide exposure were weaker and less consistent. Research needs include improved pesticide exposure indices, continued follow-up of existing cohorts, genetic susceptibility assessment, and basic research on childhood leukemia initiation and progression.

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CHEMICAL INCIDENTS AND POLLUTION

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