

Library Watch

substance use
medical aspects

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fall 2010

A delayed methadone encephalopathy: Clinical and neuroradiological findings.

Zanin A; Masiero S; Severino MS; Calderone M; Da Dalt L; Laverda AM. *Journal of Child Neurology* 25(6): 748-751, 2010. (15 refs.)

Several studies on opiates demonstrated that selected brain areas as cerebellum and limbic system have the greatest density of opioid receptors. Recently, few cases of severe cerebellitis following methadone poisoning have been reported in children. We present the case of a 30-month-old girl who developed a delayed encephalopathy after methadone intoxication. She was admitted to our emergency department in coma, and after naloxone infusion, she completely recovered. Five days after intoxication, she developed psychomotor agitation, slurred speech, abnormal movements, and ataxia despite a negative neuroimaging finding. A repeat magnetic resonance imaging (MRI) performed 19 days after the intoxication for persistent symptoms showed signal abnormalities in the temporomesial regions, basal ganglia, and substantia nigra. To our knowledge, this is the first report of these delayed MRI findings associated with synthetic opioid intoxication. Copyright 2010, Sage Publications.

A fatality involving an unusual route of fentanyl delivery: Chewing and aspirating the transdermal patch.

Carson HJ; Knight LD; Dudley MH; Garg U. *Legal Medicine* 12(3): 157-159, 2010. (19 refs.)

We recently encountered a subject who died from an uncommon misuse of a fentanyl transdermal patch, chewing, followed by complications of aspiration of the patch. We report this case to alert medical examiners to the troubling trend of increased fentanyl patch abuse and its expanding range of misuses and associated morbidities. The decedent was a 28-year-old white male with a past medical history of prescription drug abuse who was pronounced dead in the emergency department shortly after arrival. An autopsy was completed and a tough but stretchy beige foreign body was identified lodged in a mainstem bronchus. Toxicological analysis of femoral blood showed methamphetamine, fentanyl and norfentanyl

concentrations of 1456, 8.6 and 1.4 ng/mL, respectively. Individuals who abuse prescription medications often modify the route of administration of the drug from the intended method. As this case demonstrates, this choice can be fatal. The novel findings include a chewed patch, aspiration of a drug patch, and combination with an illicit drug at potentially lethal blood levels for both methamphetamine and fentanyl in a novice user. Copyright 2010, Japanese Society of Legal Medicine.

An analysis of the 'legal high' mephedrone.

Gibbons S; Zloh M. *Bioorganic & Medicinal Chemistry Letters* 20(14): 4135-4139, 2010. (21 refs.)

'Legal highs' are compounds, plant or fungal material which can be readily bought from the internet without legal restriction and the single chemicals may be structurally related to illegal drugs of abuse such as the amphetamines. Several recent deaths in the UK have been attributed to these legal highs and unfortunately there is little chemical or biological literature on these materials or certified standards. Here, we detail the analysis of the widely consumed synthetic N-methyl-cathinone analogue known as mephedrone ((1) 2-aminomethyl-1-tolyl-propan-1-one (4'-methylmethcathinone)) and report its spectral data and molecular properties. Material was purchased from an internet site and examined by extensive one- and two-dimensional NMR studies, high-resolution mass spectrometry, elemental analysis and optical rotation, which demonstrated the sample to be of high purity and racemic in nature. Additionally, we report the molecular modelling properties of methyl-cathinones and compare them to their corresponding methyl-amphetamine series. This indicated that the methyl-cathinones are considerably more hydrophilic than the methyl-amphetamines which may account for the higher doses that are needed to demonstrate similar effects. The presence of a ketone in the side chain introduces a far more planar quality to the methyl-cathinones which is absent in the methyl-amphetamine series, and this planarity may contribute to toxicity. Copyright 2010, Elsevier Science.

Biomarkers of alcohol abuse. Part II. New biomarkers and their interpretation.

Waszkiewicz N; Poplawska R; Konarzewska B; Szajda SD; Galinska B; Rutkowski P et al. *Psychiatria Polska* 44(1): 137-146, 2010. (34 refs.)

An increasing number of new biomarkers of alcohol abuse appear in the literature. The most commonly used biomarkers (5-hydroxy-tryptophol, fatty acid ethyl esters, ethyl glucuronide, phosphatidyl ethanol, ethyl sulphate, mitochondrial aspartate aminotransferase, carbohydrate deficient transferrin, acetaldehyde adducts, beta-hexosaminidase, and sialic acid) were described. Then other known and less known biomarkers associated with alcohol abuse were described in brief (e.g. acetaldehyde, acetate, methanol, alpha-amino-n-butyric acid, dolichol, proteomics). Their sensitivity and specificity is generally higher than that of traditional biomarkers. The time of detection in biological fluids occur from one day to few months after alcohol consumption. Hence, their usefulness in clinical practice as well as in experimental studies is increasing. Copyright 2010, Wydawniczy Towarzystwa.

Dipstick tests for secondhand smoke exposure.

Best D; Green EM; Smith JH; Perry DC. *Nicotine & Tobacco Research* 12(6): 551-556, 2010. (21 refs.)

We tested TobacAlert and NicAlert immunochromatographic strips for use as indicators of secondhand smoke (SHS) exposure. Urine samples collected from SHS-unexposed volunteers were spiked with cotinine to concentrations of 5, 8, 13, and 23 ng cotinine/ml urine. One sample was not spiked and used as a control. According to manufacturer's instructions, 45 NicAlert and 45 TobacAlert dipsticks were prepared. The exercise was repeated once. Cotinine levels in urine samples were measured using liquid chromatography/mass spectrometry (LC/MS). STATA was used for statistical analyses. Ninety NicAlert and 90 TobacAlert dipsticks were tested. Each strip was read by 3 different readers, for 270 NicAlert and 270 TobacAlert readings; 98/270 (36%) NicAlert and 104/270 (39%) TobacAlert readings agreed with the readings predicted by LC/MS-determined cotinine levels. Spearman's rho for the NicAlert strips was .13 and for the TobacAlert strips .23. Both were statistically significant. Using a dichotomous scheme to interpret any strip reading ≥ 1 as "positive," indicating SHS exposure, NicAlert strips were 94% sensitive and 31% specific, while TobacAlert strips were 89% sensitive and 60% specific. NicAlert and TobacAlert strips performed poorly at low cotinine levels. While the strips could be used to prescreen samples prior to more accurate

testing, their use in the clinical or research setting to indicate SHS exposure should be restricted to carefully selected scenarios. Copyright 2010, Oxford University Press.

Disposition of smoked cannabis with high Delta(9)-tetrahydrocannabinol content: A kinetic model.

Hunault CC; van Eijkeren JCH; Mensinga TT; de Vries I; Leenders MEC; Meulenbelt J. *Toxicology and Applied Pharmacology* 246(3): 148-153, 2010. (26 refs.)

Introduction: No model exists to describe the disposition and kinetics of Inhaled cannabis containing a high THC dose. We aimed to develop a kinetic model providing estimates of the THC serum concentrations after smoking cannabis cigarettes containing high THC doses (up to 69 mg THC). Methods. Twenty-four male non-daily cannabis users smoked cannabis cigarettes containing 293 mg, 49.1 mg, and 69.4 mg THC. Blood samples were collected over a period of 0-8 h and serum THC concentrations were measured. A two-compartment open model was fitted on the individual observed data. Results: Large inter-individual variability was observed in the pharmacokinetic parameters. The median pharmacokinetic parameters generated by the model were C-max = 175 ng/mL, T-max = 14 min, and AUC(0-8h) = 8150 ng x min/mL for the 69.4 mg THC dose. Median model results show an almost linear dose response relation for C-max/Dose = 2.8×10^{-6} /mL and AUC(0-8h)/Dose = 136×10^{-6} min/mL. However, for increasing dose level, there was a clear decreasing trend C-max/Dose = 3.4, 2.6 and 2.5 x 10^{-6} /mL and AUC(0-8h)/Dose = 157, 133 and 117 x 10^{-6} min/mL for the 29.3, 49.1 and 69.4 mg dose, respectively. Within the restriction of 8 h of observation, the apparent terminal half life of THC was 150 min. Conclusion: The model offers insight into the pharmacokinetics of THC in recreational cannabis users smoking cannabis containing high doses of THC mixed with tobacco. The model is an objective method for providing serum THC concentrations up to 8 h after smoking cannabis with a high THC content (up to 23%). Copyright 2010, Academic Press/Elsevier Science.

First-trimester fetal heart rate in mothers with opioid addiction.

Schmid M; Kuessel L; Klein K; Metz V; Fischer G; Krampfl-Bettelheim E. *Addiction* 105(7): 1265-1268, 2010. (27 refs.)

Aim: To investigate the difference in fetal heart rate of opioid-dependent mothers compared to non-dependent mothers in the first trimester of pregnancy. Design:

The data of 74 consecutive singleton pregnancies of mothers enrolled in a maintenance programme for opioid-dependent women was matched to 74 non-exposed singleton pregnancies by maternal age, crown-rump length, smoking status, ethnic background and mode of conception. Measurement: Fetal heart rate measured as part of first-trimester screening by Doppler ultrasound between 11+0 and 13+6 gestational weeks was compared retrospectively. Findings: The mean fetal heart rate in opioid-dependent mothers was 156.0 beats per minute (standard deviation 7.3) compared to 159.6 (6.5) in controls. The difference in fetal heart rate was significant ($P = 0.02$). There was a significant difference in mean maternal body mass index ($P = 0.01$) but not in mean nuchal translucency ($P = 0.3$), gestational age (0.5), fetal gender ($P = 0.3$) and parity ($P = 0.3$) between both groups. Fifty-five per cent (41 of 74) of cases were taking methadone, 30% (22 of 74) buprenorphine and 15% (11 of 74) were taking slow-release morphines throughout the pregnancy. Conclusions: In fetuses of opioid-dependent mothers a decreased fetal heart rate can already be observed between 11+0 and 13+6 gestational weeks. The effect of opioid intake needs to be taken into consideration when interpreting fetal heart rate in opioid-dependent mothers at first-trimester screening. Copyright 2010, Wiley-Blackwell.

Modeling the effect of high dead-space syringes on the human immunodeficiency virus (HIV) epidemic among injecting drug users.

Bobashev GV; Zule WA. *Addiction* 105(8): 1439-1447, 2010. (50 refs.)

Aims To illustrate the impact of different proportions of injecting drug users (IDUs) sharing high dead-space syringes (HDSS) or low dead-space syringes (LDSS) on the probability of human immunodeficiency virus (HIV) transmission; and thus the impact on injection-related HIV prevalence and incidence. Design A stochastic mathematical model was used to evaluate the impact of HDSS use in high- and low-risk IDU populations. Model parameters were obtained from peer-reviewed publications. Analytical solutions of a simplified deterministic model were obtained to explain the effect of HDSS on HIV endemic states. Findings: Simulation analysis shows that the HIV epidemic could be sustained even when a small percentage of sharing (10%) involved HDSS. The effect is much stronger in high-risk compared with low-risk populations. Steady state HIV prevalence increases with the proportion of HDSS, and for high- and low-risk populations reaches around 80% and 20%, respectively. For low-risk populations, the use of

LDSS could result in the virtual elimination of HIV. These results are dependent upon an evidence-supported assumption of a significant difference in HIV transmission risk associated with HDSS versus LDSS. Conclusions: Our models suggest that injection-related HIV epidemics may not occur when most (e.g. 95% or more) IDUs use LDSS. While these results are based on indirect risk measures and a number of simplifying assumptions, the effect of blood retained in high dead-space syringes on HIV prevalence seems to be very strong, even using relatively conservative assumptions. The findings have potential implications for needle exchange programs and the types of syringes produced and distributed world-wide. Copyright 2010, Wiley-Blackwell.

Oxidative stress contributes to methamphetamine-induced left ventricular dysfunction.

Lord KC; Shenouda SK; McIlwain E; Charalampidis D; Lucchesi PA; Varner KJ. *Cardiovascular Research* 87(1): 111-118, 2010. (34 refs.)

Our aim was to test the hypothesis that the repeated, binge administration of methamphetamine would produce oxidative stress in the myocardium leading to structural remodeling and impaired left ventricular function. Echocardiography and Millar pressure-volume catheters were used to monitor left ventricular structure and function in rats subjected to four methamphetamine binges (3 mg/kg, iv for 4 days, separated by a 10-day drug-free period). Hearts from treated and control rats were used for histological or proteomic analysis. When compared with saline treatment, four methamphetamine binges produced eccentric left ventricular hypertrophy. The drug also significantly impaired systolic function (decreased fractional shortening, ejection fraction, and adjusted maximal power) and produced significant diastolic dysfunction (increased $-dp/dt$ and τ). Dihydroethidium staining showed that methamphetamine significantly increased (285%) the levels of reactive oxygen species in the left ventricle. Treatment with methamphetamine also resulted in the tyrosine nitration of myofilament (desmin, myosin light chain) and mitochondrial (ATP synthase, NADH dehydrogenase, cytochrome c oxidase, prohibitin) proteins. Treatment with the superoxide dismutase mimetic, tempol in the drinking water prevented methamphetamine-induced left ventricular dilation and systolic dysfunction; however, tempol (2.5 mM) did not prevent the diastolic dysfunction. Tempol significantly reduced, but did not eliminate dihydroethidium staining in the left ventricle, nor did it prevent the tyrosine nitration of mitochondrial and

contractile proteins. This study shows that oxidative stress plays a significant role in mediating methamphetamine-induced eccentric left ventricular dilation and systolic dysfunction. Copyright 2010, Oxford University Press.

The effects of alcohol and drug abuse on the skin.

Liu SW; Lien MH; Fenske NA. *Clinics in Dermatology* 28(4): 391-399, 2010. (89 refs.)

Skin changes associated with alcohol and drug abuse can be the earliest clinical manifestation of these disorders. The signs associated with these conditions may be distinctive and easily recognizable. Alcohol abuse can present with jaundice, pruritus, hyperpigmentation, and urticaria. Commonly associated vascular changes include spider telangiectasias, angiomas, caput medusae, flushing, and palmar erythema. Disease states related to alcohol abuse include psoriasis, porphyria cutanea tarda, and nutritional deficiencies. Alcohol abuse may predispose to the development of carcinomas of the skin, oropharynx, liver, pancreas, and breast. Cutaneous signs of drug abuse include skin granulomas, ulcerations, and recurrent infections. Specifically, oral disease and tooth decay are examples of stigmata often associated with methamphetamine abuse, a popular and inexpensive drug now on the scene. By being cognizant of these cutaneous markers of alcohol and drug abuse, dermatologists are often in the unique position of being able to recognize these changes, prompting early diagnosis and intervention, hopefully resulting in a better clinical outcome for these troubled patients and their families. Copyright 2010, Elsevier Science.

Acute physiologic effects of secondhand smoke exposure in children.

Moss DR; Lucht LA; Kip KE; Reis SE. *Nicotine & Tobacco Research* 12(7): 708-714, 2010. (27 refs.)

We investigated the hypothesis that exhaled carbon monoxide (eCO), heart rate (HR), and blood pressure (BP) would increase acutely in exposed but not in unexposed children. In a nonrandomized controlled design, parent-child dyads were assigned to groups based on exposure: child subjects, 7-18 years of age, exposed to smoking daily in the home (exposed) or with no household exposure (unexposed control). HR, BP, and eCO were measured before and after exposure to a parent smoking 1 cigarette (exposed) or a time-lapse equivalent (control). The primary analysis compared mean acute changes in physiological measures following intervention or control procedure.

Forty-one dyads were enrolled. At baseline, no differences in child gender, race, ethnicity, HR, BP, lipids, or fasting glucose were noted between exposure groups. Following experimental or control procedures, the median change in eCO was similar between groups (-0.1 ppm exposed vs. 0.0 ppm unexposed, $p = .27$). Acute hemodynamic changes were also similar between exposed and unexposed children, respectively: (HR change 4.2 vs. 2.6 beats per minute, $p = .62$; systolic blood pressure change 0.08 vs. 0.41 mm Hg, $p = .91$; diastolic blood pressure 0.08 vs. 2.27 mm Hg, $p = .37$). This is the first study to report on acute physiologic changes of secondhand smoke exposure in children in a naturalistic setting. A single acute dose of passive smoke exposure in children did not alter the physiologic variables of HR or BP. Further in-home study using continuous monitoring is needed. Demonstration of acute effects may serve as clinical feedback to motivate parents to quit smoking. Copyright 2010, Oxford University Press.

Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment.

Yuferov V; Levran O; Proudnikov D; Nielsen DA; Kreek MJ. *Annals of the New York Academy of Sciences. Addiction Reviews* 2 1187: 184-207, 2010. (288 refs.)

Addiction to opiates and illicit use of psychostimulants is a chronic, relapsing brain disease that, if left untreated, can cause major medical, social, and economic problems. This article reviews recent progress in studies of association of gene variants with vulnerability to develop opiate and cocaine addictions, focusing primarily on genes of the opioid and monoaminergic systems. In addition, we provide the first evidence of a cis-acting polymorphism and a functional haplotype in the PDYN gene, of significantly higher DNA methylation rate of the OPRMI gene in the lymphocytes of heroin addicts, and significant differences in genotype frequencies of three single-nucleotide polymorphisms of the P-glycoprotein gene (ABCBI) between "higher" and "lower" methadone doses in methadone-maintained patients. In genomewide and multigene association studies, we found association of several new genes and new variants of known genes with heroin addiction. Finally, we describe the development and application of a novel technique: molecular haplotyping for studies in genetics of drug addiction. Copyright 2010, New York Academy of Sciences.