ARTICLES YOU MIGHT HAVE MISSED

Articles You May Have Missed

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Article Title

Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K: Prescription opioids in adolescence and future opioid misuse. *Pediatrics*. 2015; 136(5): e1169–77.

Background

Prescription opioid abuse and overdose are major causes of morbidity and mortality among young adults. Opioids are commonly prescribed to treat pain; however, more information is needed about the relationship between “legitimate” medical use of prescription opioids in adolescents and the risk of future opioid misuse.

Research Question

What is the risk of future opioid misuse among adolescents who have a history of medical use of prescription opioids compared with those that have no history of medical opioid use?

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Methods

Data were derived from the Monitoring the Future study, which surveys a nationally representative sample ($n = \sim 2450$) of high school students annually, and follows some of them after graduation with annual questionnaires. High school seniors who completed a form of the survey that included questions about medical use of prescription opioids between 1990 and 2012 were included. Subjects who reported a history of medical use of prescription opioids were compared with those who did not. The primary outcome was reporting opioid misuse during the prior 12 months on a follow-up survey. Subjects responding that they had taken an opioid not prescribed by a doctor were considered to have opioid misuse. Three different models (based on respondents' baseline risk factors, e.g., drug use behaviors and attitudes, for opioid misuse determined by the initial baseline survey) were used to analyze data in an attempt to replicate a randomized controlled trial from the study's (observational) design. A binomial regression with a log link was used to estimate relative risk (RR).

Results

A total of 6220 adolescents (69 % of those providing a baseline survey) answered questions about opioid misuse on at least one of the first three follow-up surveys. The final number of completed follow-up surveys, analyzed for this study, was 13,542. Overall, receiving an opioid prescription by 12th grade was associated with an increased risk for future opioid misuse of 33 % (RR = 1.33; 95 % CI 1.04–1.7). Subjects were stratified for risk of future opioid misuse based on other risk factors such as attitude towards drugs and use of alcohol and cigarettes. The effect of exposure to prescription opioids was

most pronounced among those with low baseline risk for opioid misuse, increasing the relative risk for future misuse by as much as three times. Although a history of exposure to prescription opioids increased the risk of future opioid misuse overall, it did not increase the risk of frequent opioid misuse (>40 times per year).

Conclusion

Medical use of prescription opioids increased the risk for opioid misuse among adolescents that were otherwise at low risk for opioid misuse.

Critique

As with any observational survey study, the self-report of opioid misuse may be subject to social desirability bias, leading subjects to underreport misuse and, therefore, underestimation of opioid misuse. This study's strengths include the use of a nationally representative sample and prospective data collection. However, this study does not include adolescents who dropped out of school, who may be expected to have higher rates of drug use, limiting its generalizability somewhat. Additionally, the study had a 71 % response rate for follow-up, and it is possible that those who did not follow-up may have been more likely to abuse drugs, introducing bias in the study results.

Implication for Toxicologists

Toxicologists and poison control centers should educate primary care providers, adolescents, and their parents about the risks associated with medical use of prescription opioids.

Article Title

Ronan MV, Herzig SJ. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002–12. *Health Affairs*. 2016; 35(5): 832–837.

Background

Opioid pain reliever and heroin abuse and dependence have increased dramatically in recent years. Although serious infection is a complication of intravenous abuse of these drugs, little is known about the epidemiologic trends of opioid abuse both with and without infections.

Research Question

What are the US national trends in rates of hospitalizations, with and without serious infections, among patients with a history of opioid abuse or dependence? And what are the associated morbidity, mortality, and costs of this care?

Methods

This was a retrospective cohort study using discharge data from the years 2002 and 2012 derived from the Nationwide Inpatient Sample (NIS). NIS is the largest publicly available, all-payer inpatient database in the US, representing 20 % of all inpatient hospitalizations. Exposures were defined using ICD-9 codes for both opioid abuse/dependence and infection. Specific types of serious infections included endocarditis, osteomyelitis, septic arthritis, or epidural abscess. Using this data, the total number of hospitalizations related to “opioid abuse and dependence” and hospitalizations for “opioid dependence with associated infection” was estimated. Total charges for hospitalizations were estimated and corrected for inflation. The study also examined payer distribution and discharge destination. To increase confidence in the accuracy of findings, sensitivity analysis was performed restricting analysis to young patients without other risk factors for serious infection. *Z* test was used to compare hospitalization and charges numbers; chi-squared was used test to compare proportions between the study dates.

Results

The overall number of hospitalizations nationwide was similar in 2002 and 2012, with 36.52 million hospitalizations in 2002 and 36.48 million in 2012. The number of hospitalizations related to opioid abuse/dependence increased from 301,707 in 2002 to 520,275 in 2012. The number of hospitalizations related to opioid abuse/dependence with associated infection increased from 3421 in 2002 to 6535 in 2012. The same trends were noted for each individual type of infection examined. Total inpatient charges for hospitalizations related to opioid abuse/dependence increased from \$4.57 billion in 2002 to \$14.85 billion in 2012. Medicaid was the most common primary payer in both years. Compared to all opioid abuse/dependence-related hospitalizations, patients hospitalized with related infections were more likely to be uninsured, and discharged to a secondary medical facility (rather than to home). Sensitivity analysis of the younger cohort (without other risk factors for serious infection) demonstrated a nearly identical trend to the overall cohort.

Conclusion

Hospitalizations between 2002 and 2012 related to opioid abuse/dependence increased overall, as did those with associated serious infection. Cost of hospitalizations increased out of proportion to the overall number of hospitalizations, and the burden of the cost fell primarily on government-funded agencies.

Critique

This study's strengths include a large cohort size of a nationally representative sample. The sensitivity analysis strengthens confidence that hospitalizations for infection are related primarily to opioid abuse/dependence. However, the retrospective nature of the study and the use of ICD-9 codes may have led to underestimation of the number of hospitalizations. It is possible that the use of ICD-9 codes may have changed between 2002 and 2012 introducing bias. Additionally, the study design did not allow for characterization of the status or severity of opioid abuse/dependence and whether the subjects were using drugs intravenously. In addition, the study only included what the authors considered serious infection (e.g., epidural abscess) and excluded other infections, such as cellulitis, that could have significant morbidity and mortality in this patient population with substantial cost. Additionally, this study does not include post-discharge costs, which may be significant as many patients were discharged to secondary medical facilities.

Implication for Toxicologists

This study reminds toxicologists that the opioid epidemic continues and is associated with significant morbidity and cost.

Article Title

Chen SI, Fox ER, Hall MK, Ross JS, Bucholz EM, Krumholz HM, Venkatesh AK. Despite federal legislation, shortages of drugs used in acute care settings remain persistent and prolonged. *Health Affairs*. 2016; 35(5): 798–804.

Background

Drug shortages continue to plague the healthcare system, with a significant increase noticed over the previous decade. The Food and Drug Administration Safety and Innovation Act (FDASIA) was introduced in 2012 to expand regulatory powers in response to national drug shortages. Despite this, drug

shortages continue to be reported, with evidence suggesting a disproportionate number of shortages in acute care settings. The impact of drug shortages on acute care is significant, potentially contributing to increased medical error rates as healthcare providers struggle to find substitute drugs with which they lack familiarity. Such substitutions can be both challenging and costly to obtain, further enhancing the effect of these shortages.

Research Question

This study compares the trends between 2001 and 2014 in national drug shortages for drugs used in acute care versus those used in non-acute care settings. It also describes the characteristics of these shortages, including frequency, duration, reported cause, and characteristics of the affected drugs. The relationship between any changes seen in drug shortages and the enactment of FDASIA is also examined.

Methods

This was a retrospective observational study using the University of Utah's Drug Information Service (DIS) drug shortage data set from January 1, 2001 to December 31, 2014. This data set is publicly available and includes information on all confirmed national drug shortages via voluntary reports of drug shortages from manufacturers through their website. Each reported drug shortage is confirmed by a clinical pharmacist, who collects information from all manufacturer(s) of the drug regarding the reason behind the shortage and estimated date of resolution. National Drug Codes are also reviewed and confirmed for related shortages. An acute care drug was defined as one used in the Emergency Department (ED) for the diagnosis or management of acute conditions. Specific criteria were created to classify any medication as an acute care drug. These criteria were used by two ED physicians to independently review a list of all drugs with reported shortages and assign each drug a designation as acute care or non-acute care. The inter-rater agreement 91 % with a kappa of 89 (95 % CI: 87–90). A total of 170 (9 %) drugs required adjudication for classification. The number of shortages affecting acute care and non-acute care drugs was reported along with the median duration of the shortage for each group. An end date of December 31, 2014 was used for all drugs with ongoing shortages. A secondary analysis was conducted to determine the number of days of shortage in each calendar year. The etiology for shortages (as reported by the manufacturer) was listed for both groups.

Results

There were 1929 national drug shortages between January 1, 2001 and December 31, 2014 included in the study. The annual average of active drug shortages overall (acute and non-acute drugs) was 271, and there were 138 new shortages each year. Of these, 52 % (1006) were determined to involve acute care drugs. The peak in active drug shortages was seen in 2012 at 489, and the peak in new drug shortages was in 2011 at 268. Overall, the most common classes of drugs to experience shortages were central nervous system (CNS) agents, which included drugs used to treat pain and fever (332); cardiovascular drugs (151); hormones and synthetic substitutes (130); and electrolyte, caloric, and water balance products (129). Most (70 %) drug shortages involved drugs delivered by injection. Manufacturing difficulty was the most common reported reason for drug shortages, accounting for 25 % (484) of cases; although, the cause of the shortage was not reported for 45 % of acute care and 47 % of non-acute care drugs. Among acute care drugs, the most common classes of drugs affected were anti-infectives (208, 21 %); CNS agents (200, 20 %); autonomic drugs (103, 10 %); electrolyte, caloric, and water balance products (82, 8 %); and cardiovascular drugs (81, 8 %). For non-acute care drugs, the most common classes were CNS agents (137, 15 %); cancer drugs (124, 13 %); miscellaneous (77, 8 %); hormones and synthetic substitutes (76, 8 %); and anti-infectives (70, 8 %). There was a statistically significant difference in injectable drug shortages between groups: 69 % of acute care drug shortages compared to 38 % of non-acute care ($p < 0.001$). Between 2001 and 2012 there was a 300 % increase in the number of active annual drug shortages. After 2012 there was a noticeable decrease in the number of non-acute care drug shortages, but no decrease in acute care drug shortages. The overall median duration of drug shortages was 210 days (interquartile range [IQR]: 83 to 531). For non-acute care drugs, the median duration was 173 days (IQR: 69 to 442), which was significantly shorter than 242 days (IQR: 96 to 624) for acute care drugs ($p < 0.001$).

Conclusion

The recent overall decrease in the number of drug shortages, coinciding with the enactment of the FDASIA, has not improved shortages for acute care medications. These data suggest that emergent and critically ill patients remain vulnerable

to shortages in drug supplies. Further interventions are needed to address persistent shortages and maintain drug availability.

Critique

The analyzed dataset relies on voluntary reporting of drug shortages by manufacturers to the DIS website. The data gathered in this study is likely an underestimate of the real scope of the problem. There is also no requirement for manufacturers to provide the reason behind a drug shortage, limiting the usefulness of such information for future policy planning. Some drug shortage durations were truncated by being assigned a shortage completion date of December 31, 2014 despite being active at the study's conclusion.

Implication for Toxicologists

Toxicologist and poison center representatives must be aware of the ongoing shortage of acute care medications, including drugs (e.g., CNS and autonomic agents) that are relevant to our patient population. Medical toxicologists should discuss the availability of reasonable and safe alternatives to ensure providers are not required to use unfamiliar or suboptimal alternatives that may lead to an increased risk of medication error or poor outcome.

Article Title

Garcia J, Costa MV, Carvalho ATP, Silvestre R, Duarte JA, Dourado DFAR, Arbo MD, Baltazar T, Dinis-Oliveira RJ, Baptista P, de Lourdes Bastos M, Carvalho F. A breakthrough on *Amanita phalloides* poisoning: an effective antidotal effect by polymyxin B. Archives of Toxicology. 2015; 89: 2305–2323.

Background

Mushroom forging continues to increase in popularity, and with that grows the number of poisonings due to the misidentification of *Amanita phalloides* as a non-toxic, edible species. Over 90 % of mushroom-related fatalities are due to *A. phalloides* ingestions. These mushrooms contain cyclic octapeptides known as amatoxins, with α -amanitin leading to significant liver and renal injury via RNA-polymerase II (RNAP II) inhibition. With no antidote for *A. phalloides* toxicity, the cornerstone of therapy includes aggressive supportive care, with liver transplantation for those who develop

fulminant hepatic failure. Given the mechanism of action of α -amanitin, an ideal antidote would inhibit its binding to RNAP II and still allow normal transcription.

Research Question

This study aimed to identify an effective antidote for *Amanita* poisoning by identifying drugs, via in silico (computer modeling), that can prevent α -amanitin from binding to RNAP II. Based on initial simulations, can polymyxin B be used to prevent toxicity in a murine model of α -amanitin toxicity? The parameters assessed in the in vivo testing were survival rate, histologic damage, protein carbonylation, NF- κ B nuclear activation, total RNA, and mRNA quantification.

Methods

In Silico Study

The crystal structure of α -amanitin complexed to RNAP II was used to obtain the starting structure for the molecular docking assessment of binding polymyxin B to RNAP II. Ten conformations of polymyxin B in complex with the receptor were ranked based on binding energy to find the best molecular docking solution with overall minimum energy. Molecular dynamic simulations and energy calculations were then performed on the polymyxin-B/RNAP II complexes.

In Vivo Study

Two in vivo studies were performed using a murine model: a short-term study (24 h) and a survival study (30 days). α -amanitin was administered by intraperitoneal (IP) injection at a dose of 0.33 mg/kg, the reported LD50 dose. In the short-term study, animals received three consecutive doses of polymyxin B (2.5 mg/kg) every 4 h starting 4 h after the administration of α -amanitin. Animals were randomly assigned to one of four groups: (1) control—four IP 0.9 % saline injections (0, 4, 8, and 12 h); (2) α -amanitin group (Ama)—one IP dose of α -amanitin at time 0, then three IP 0.9 % saline injections (4, 8, and 12 h); (3) polymyxin B group (Pol)—one IP dose of 0.9 % saline at time 0, then three IP polymyxin B injections (4, 8, and 12 h); and (4) α -amanitin plus polymyxin B group (Ama + Pol)—one IP dose of α -amanitin at time 0, then three IP polymyxin B injections (4, 8, and 12 h). After 24 h, all animals were euthanized, and blood, liver, and kidney samples were collected for histological and immunohistochemistry analysis, RNA quantification by PCR, and protein carbonylation assays.

For the survival study, 20 animals were randomly divided into five groups: (1) control—one IP 0.9 % saline injection at time 0; (2) Ama group—one IP dose of α -amanitin at time 0; (3) Pol group—one IP dose of 0.9 % saline at time 0, then three IP polymyxin B injections (4, 8, and 12 h); (4) Ama + Pol con group—concomitant IP injections of α -amanitin and polymyxin B at time 0; and (5) Ama + Pol group—one IP injection of α -amanitin at time 0, then three IP polymyxin B injections (4, 8, and 12 h). Body weight, motor activity, dyspnea, and overall welfare were observed daily for 30 days. Statistical analysis was performed on all data collected.

Results

The in silico study revealed that the RNAP II binding site for polymyxin B is at the same interface as α -amanitin. From the short-term study it was seen that the 24-h AST and ALT concentrations in the polymyxin B group (68.46 ± 23.92 and 32.70 ± 8.45 U/L, respectively) were significantly lower than the α -amanitin group (359.10 ± 190.40 and 120.20 ± 83.20 U/L, respectively) and similar to the control group (63.80 ± 8.63 and 37.80 ± 6.94 U/L, respectively). The liver weight in the α -amanitin group was significantly less (5.75 ± 0.58 mg/g) than the control (6.77 ± 0.64 mg/g) and polymyxin B treatment (5.94 ± 0.52 mg/g) groups. Treatment with polymyxin B prevented α -amanitin-induced reductions in total kidney RNA (α -amanitin group 0.981 ± 0.645 μ g/mg kidney; polymyxin B group 3.622 ± 1.550 μ g/mg kidney). Polymyxin B prevented the reduction in kidney cellular transcription seen in the α -amanitin group when compared to controls. Polymyxin B was also able to prevent α -amanitin induced hepatic histologic damage and attenuate α -amanitin renal damage.

In the survival study, all mice in the Ama group died within 2–5 days. There was 100 % survival in the Ama + Pol con group; however, this group began to show signs of discomfort at day 5 with involuntary head movements that did not improve over the 30 day observation period. In the Ama + Pol group, there was a 50 % survival rate, with deaths occurring between days 5–7. In the surviving animals, there were no signs of toxicity seen over the 30 days. There were no deaths or signs of toxicity in the control group or the Pol group.

Conclusion

Polymyxin B interacts with RNAP II and prevents α -amanitin toxicity in mice. If these effects can be shown in human studies, polymyxin B should be useful in the treatment of *A. phalloides* toxicity.

Critique

The survival study consisted of four animals per group. The findings fail to reach significance compared to chance due to lack of power. The animals who received concomitant amatoxins and polymyxin B developed “moderate signs of discomfort” (involuntary head movements) that persisted through the end of the study. The repeated polymyxin B treatment group’s survival was only 50 %. Lastly, the ability to translate *in silico* and *in vivo* murine findings to humans is limited. Significant work remains to show safety and efficacy in humans.

Implication for Toxicologists

Treatment with polymyxin-B is not ready for clinical use; however, toxicologists should be aware of this research as they may get called from healthcare providers wanting to add it to their armamentarium for treating *Amanita*-poisoned patients.

Compliance with Ethical Standards

Conflicts of Interest None

Sources of Funding None