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Detecting biomarkers of secondhand marijuana smoke in young children

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Abstract

Background—The impact of secondhand marijuana smoke exposure on children is unknown. New methods allow detection of secondhand marijuana smoke in children.

Methods—We studied children ages 1 mo to 2 y hospitalized with bronchiolitis in Colorado from 2013 to 2015. Parents completed a survey, and urine samples were analyzed for cotinine using LC/MS/MS (limits of detection 0.03 ng/ml) and marijuana metabolites including COOH-THC (limits of detection 0.015 ng/ml).

Results—A total of 43 subjects had urine samples available for analysis. Most (77%) of the subjects were male, and 52% were less than 1 y of age. COOH-THC was detectable in 16% of the samples analyzed (THC+); the range in COOH-THC concentration was 0.03–1.5 ng/ml. Two subjects had levels >1 ng/ml. Exposure did not differ by gender or age. Non-white children had more exposure than white children (44 vs. 9%; $P < 0.05$). 56% of children with cotinine >2.0 ng/ml were THC+, compared with 7% of those with lower cotinine ($P < 0.01$).

Conclusion—Metabolites of marijuana smoke can be detected in children; in this cohort, 16% were exposed. Detectable COOH-THC is more common in children with tobacco smoke exposure. More research is needed to assess the health impacts of marijuana smoke exposure on children and inform public health policy.

The use of marijuana has been increasing in both acceptability and legality in the past 15 y. Currently 23 states plus Guam allow the legal use of marijuana for medical reasons, and 4 states plus Washington, DC have legalized recreational use. In 2013, 5.7 million persons aged 12 or older used marijuana on a daily or almost daily basis in the previous 12 mo; this

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represents an increase from the 3.1 million daily or almost daily users in 2006 (1). While marijuana can also be aerosolized, or ingested as hash oil or leaf, combusted marijuana is still the most common form of consumption (2). A recent analysis of data from the US National Health and Nutrition Examination Survey (NHANES) finds that daily marijuana users have higher levels of combustion biomarkers (e.g., volatile organic compounds and polycyclic aromatic hydrocarbons) than nonusers (3). Exposure to combustion products likely extends to adjacent nonusers, as has been shown for tobacco smoke (4). Most states with legal marijuana use do not have any restrictions on combustible marijuana use in the presence of children.

While there is clear research on the dangers of secondhand tobacco smoke (4), the impact of secondhand marijuana smoke on children has not yet been studied. There are several studies suggesting that marijuana smoke contains particulate matter known to be harmful when inhaled, in addition to other toxic and carcinogenic chemicals, such as volatile organic compounds, polycyclic aromatic hydrocarbons, and aromatic amines (5,6). A recent study in rats found that brief exposure to secondhand marijuana smoke impaired endothelial function (7). Studies in adults have demonstrated that it is possible to feel the effects of marijuana smoke from intense secondhand marijuana smoke exposure (8). Children could be exposed to secondhand marijuana smoke when parents or other household contacts smoke marijuana indoors, similar to the way children who live with tobacco smokers are exposed to secondhand tobacco smoke (9). Since the co-use of marijuana and tobacco is high (10), there is a significant possibility that children are being exposed to both substances.

Marijuana contains two primary active components: 9-tetrahydrocannabinol (THC), and cannabidiol (CBD) (10). THC is the primary psychoactive chemical in marijuana; CBD is nonpsychoactive, but has other demonstrated effects (11). Currently available analytical methods are not sensitive enough to detect exposure to secondhand marijuana smoke. This is sufficient when testing for active marijuana use. However, in the case of secondhand marijuana smoke, the levels of these chemicals in urine are usually too low to be detected. The Centers for Disease Control and Prevention has recently developed a new high sensitivity assay to monitor trace levels of marijuana biomarkers at levels that might be seen in secondhand marijuana smoke exposure, allowing us to more accurately assess whether children have been exposed (12). The objectives of this study were to (i) document the presence of metabolites of secondhand marijuana smoke exposure in children admitted to a hospital in Colorado for treatment of bronchiolitis, and (ii) to examine the association between secondhand marijuana and tobacco smoke exposure in this population.

Methods

This study was a secondary analysis of urine samples and questionnaire data collected for a study examining the impact of secondhand tobacco smoke exposure on children hospitalized for bronchiolitis.

Participants/Procedures

We recruited previously healthy children ages 1 mo to 2 y who were admitted to Children's Hospital Colorado with a diagnosis of bronchiolitis from 2013 to 2015; Recreational

marijuana use became legal in Colorado on 1 January 2014. We obtained urine samples from the child within 24 h of admission; these were placed in a -80°C freezer. Families were given a \$25 gift card for participation. For this secondary analysis, only samples from children whose parents consented for future research were used, and the data and samples were anonymized prior to analysis. At the time of the secondary analysis, samples were shipped on dry ice to the laboratory at the US Centers for Disease Control and Prevention. The initial study and secondary analysis were both approved by the Colorado Multiple Institutional Review Board; since families had consented for future research we did not need to re-consent.

Measures

After completing informed consent, parents had completed a questionnaire about their child's health, and demographics. Since birth-dates were removed from the secondary dataset to ensure anonymity, we obtained patient age from the family census. Parent report of tobacco smoke exposure was assessed with the question: "Does anyone who lives in your home or who cares for your child smoke tobacco (yes or no)?" Parent report of marijuana smoke exposure was assessed after October 2014 with the question "Does anyone who lives in your home or who cares for your child smoke marijuana (yes or no)".

Analysis of Urinary Marijuana Biomarkers

Analysis for marijuana biomarkers was performed using the method by Wei *et al.*(12) Urine samples were equilibrated with isotopically labeled internal standards, deconjugated by enzymatic and alkaline hydrolysis, and extracted using C18 sorbent. The final extracts were concentrated and 10 μl of each sample was injected into an ultrahigh performance liquid chromatograph and analyzed using tandem mass spectrometry under electrospray ionization mode (ESI-MS/MS). This method has limits of detection of 0.005, 0.015, and 0.009 ng/ml for the three metabolites tested: total urinary THC, COOH-THC, and CBD, respectively.

Analysis of Urinary Tobacco Biomarkers

Urinary cotinine (COT) was analyzed using a modification of the method developed by Bernert *et al.*(13) After adding isotopically labeled internal standards to 200 μl of urine, the samples were hydrolyzed with β -glucuronidase, purified using supported liquid extraction, concentrated, and then taken up in 100 μl water. A 5 μl aliquot of this solution was injected into a ultrahigh performance liquid chromatograph and analyzed using atmospheric pressure chemical ionization tandem mass spectrometry. The limits of detection for COT was 0.030 ng/ml. We used a cutoff of 2.0 ng/ml to identify children with likely household contact exposure, based on Matt *et al.*(8) Laboratory blank and quality control samples were simultaneously processed and analyzed to assure the quality of the analytical results (14).

Data Analysis

Chi square tests were done to assess bivariable differences, and all analyses were done using SAS, (SAS Institute, Cary, NC). For 10 subjects (23%), there was more than one family member under 2, making identification of the subjects' exact age difficult, so we performed

two sensitivity analyses in which we assumed all of the missing participants were (i) in the younger age group and (ii) in the older age group; our results did not change significantly.

Results

Of 180 eligible inpatients in the original study, we enrolled 99 (55%); 86 were able to provide a urine sample. Of these, 43 agreed to the use of the urine for future research and had sufficient sample remained for the current analyses. Most (77%) were male and 52% were less than 1 y of age (Table 1). Patients were predominantly white (79%); 47% were of Hispanic ethnicity. All were residents of the state of Colorado, and 28% lived in multiunit housing. Of those who were screened for contact with marijuana or tobacco users ($N = 25$), 16% reported marijuana use in the home or by a caregiver and 28% reported tobacco use (Table 2). Total urine THC and CBD in all urine samples were below the detection limit; the THC metabolite 11-nor-9-carboxy-THC (COOH-THC) was detected in urine from 16% of patients. The range in COOH-THC concentration was 0.03–1.5 ng/ml, with two patients having levels > 1 ng/ml. Almost one quarter (23%) had urine cotinine levels above 2.0 ng/ml, suggesting household contact exposure.

There was no difference in COOH-THC detection by gender, age, or living in multiunit housing (Table 1). Non-white children were more likely to have detectable COOH-THC (44%) compared to white children (9%; $P = 0.026$); there were no differences by ethnicity. Of those who reported contact with marijuana users, 75% had detectable COOH-THC, compared to 10% of those who reported no exposure ($P < 0.016$). Urinary COOH-THC and cotinine were also positively associated; of those with a urine cotinine of > 2.0 ng/ml, 56% had detectable COOH-THC, compared to 7% of those with lower tobacco smoke exposure ($P < 0.004$). While the prevalence of detectable COOH-THC was higher after legalization (21 vs. 10% prior), this difference was not statistically significant.

Discussion

This is the first study to demonstrate the presence of THC metabolites in children exposed to marijuana smoke. While documenting the presence of metabolites of THC in children does not imply causation of disease, it does suggest that, like tobacco smoke, marijuana smoke is inhaled by children in the presence of adults who are using it. High sensitivity testing will give us the opportunity to study the effects of secondhand marijuana smoke on children's health more effectively, and researchers and funders should prioritize these investigations. National surveys such as NHANES offer opportunities to track trends in secondhand marijuana smoke exposure, as they do for secondhand tobacco smoke. In the interim, parents should be cautioned not to smoke marijuana in the presence of their children.

In our study, there was a relationship between detectable COOH-THC and having a urinary cotinine level > 2.0 ng/ml, indicating that children exposed to marijuana smoke were also more likely to be exposed to tobacco smoke, which increases their risk for cognitive deficits (15) and respiratory illness (4). More study is warranted to investigate if marijuana smoke exposure adds additional risk. This research will help inform appropriate educational

materials and outreach to parents and caregivers who use both marijuana and tobacco in the presence of their children.

Parent report of marijuana exposure was strongly associated with detection of urinary COOH-THC. While we had initially suspected that social desirability bias would lead to underreporting of exposure, this finding suggests that a parent report screening question would be useful for institutions in areas where marijuana is legal. Parents who report household marijuana smoking could then be counseled on safe use around children. It is still possible that the screening question is underestimating use, and further research is needed to understand whether the marijuana use is taking place in the presence of the child, or whether the exposure could represent third-hand exposure.

Limitations

There are several limitations to this study. As we were working with limited samples remaining from a prior study, we have a very small sample size. We had insufficient power to be able to determine additional associations, such as with illness severity, or to complete more quantitative associations, and thus it has limited external validity. Since this was a secondary analysis on previously collected samples, we were unable to assess additional demographic, socioeconomic status, and other factors that may have been associated with marijuana use. Since we could only analyze the samples from those with consent for future research, it is possible that there was bias towards non-marijuana using families in the subsample, and thus the true proportion of exposed children could be higher. We did not assess for medical use of marijuana in these children specifically, but since we enrolled only previously healthy children, medicinal marijuana use would be highly unlikely. We are also unable to assess whether the exposure was from secondhand marijuana smoke vs. neonatal transmission or breastfeeding; however the fact that our exposure rate was similar in the <1-y-old age group as the 1–2-y-old age group would suggest that the detectable COOH-THC is more likely from the secondhand smoke. Finally, this is a sample of children hospitalized for bronchiolitis in Colorado, and the findings may not be generalizable to other populations.

Conclusion

Marijuana metabolites are detectable in young children with exposure to secondhand marijuana smoke. These children are exposed to the psychoactive compounds in marijuana, and are potentially at risk for negative health effects. More than half of children with tobacco smoke exposure were also exposed to marijuana. Understanding the health consequences of marijuana smoke exposure in children is critical for providers, parents, and policymakers to best protect children from harmful exposures.

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Table 1
Comparison of demographics and detectable COOH-THC in urine (n = 43)

	n, %				P value	
	overall (n = 43)	COOH-THC- (n = 36)	COOH-THC+(n = 7)			
Gender					0.173	
Female	10	23.3	10	100.0	0	0.0
Male	33	76.7	26	78.8	7	21.2
Age (years) (n = 33)						0.398
<1	17	51.5	15	88.2	2	11.8
1-2	16	48.5	12	75.0	4	25.0
Race						0.026
White	34	79.1	31	91.2	3	8.8
Not white	9	20.9	5	55.6	4	44.4
Hispanic/Latino ethnicity						0.421
No	23	53.5	18	78.3	5	21.7
Yes	20	46.5	18	90.0	2	10.0
Race/Ethnicity						0.076
White	20	46.5	17	85.0	3	15.0
Hispanic/Latino ethnicity	20	46.5	18	90.0	2	10.0
Other	3	7.0	1	33.3	2	66.7
Multihabit housing						0.378
No	31	72.1	27	87.1	4	12.9
Yes	12	27.9	9	75.0	3	25.0

11-nor-9-carboxy-THC (COOH-THC).

Table 2
Comparison of reported exposure to marijuana and tobacco and detectability of COOH-THC and cotinine in urine (n = 43)

	n, %				P-value	
	Overall (n = 43)	COOH-THC-(n = 36)	COOH-THC+(n = 7)			
Does anyone who lives in your home or who cares for your child smoke marijuana? (n = 25)					0.016	
No	21	84.0	19	90.5	2	9.5
Yes	4	16.0	1	25.0	3	75.0
Does anyone who lives in your home or care for your child use tobacco?						0.081
No	31	72.1	28	90.3	3	9.7
Yes	12	27.9	8	66.7	4	33.3
Dichotomized urinary cotinine using 2.0 ng/ml cutoff (n = 39)						0.004
No	30	76.9	28	93.3	2	6.7
Yes	9	23.1	4	44.4	5	55.6

11-nor-9-carboxy-THC (COOH-THC).