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Comparison of expired carbon monoxide and plasma cotinine as markers of cigarette abstinence

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Abstract

The clinical pharmacology of biochemical measures of nicotine exposure has been thoroughly reviewed with regard to usefulness and limitations in detecting abstinence from cigarette smoking. While plasma nicotine concentration measures only acute nicotine exposure, plasma, salivary, and urine cotinine concentrations reflect exposure over an extended period of time. Although, expired carbon monoxide (CO) is frequently used to confirm self reports, it has a relatively short half life, calling into question whether this measure might provide misleading information by exaggerating smoking cessation success rates. To examine this question, we analyzed expired CO, plasma cotinine and self report data collected in a clinical trial in which subjects ($N = 207$) were randomly assigned to gain- or loss-framed messages for smoking cessation in combination with open label sustained-release bupropion (300 mg/day). In examining measurements collected at 6 weeks, 3 and 6 months, results showed that CO significantly overestimated abstinence rates as compared with cotinine, although the discrepancy was less at the later time points. These data suggest that while expired CO is a useful and well-established marker in certain contexts, when testing extended abstinence from smoking with non-nicotine medications, cotinine measurements should be preferred.

Keywords: Carbon monoxide (CO); Plasma cotinine; Self report; Smoking; Tobacco; Abstinence

1. Introduction

The clinical pharmacology of the several biochemical measures of nicotine exposure, including their usefulness and limitations as markers of abstinence, has been thoroughly reviewed (SRNT Subcommittee on Biochemical Verification, 2002). Plasma nicotine concentration is a measure only of acute nicotine exposure (or abstinence) consequent to its very rapid disposition (short half life). On the other hand, plasma, salivary and urine cotinine concentrations provide an approximation of average nicotine exposure over a more extended period of time (SRNT Subcommittee on Biochemical Verification, 2002). Expired carbon monoxide (CO) is a well characterized marker of cigarette smoking, but with its short half life, CO only indicates relatively recent exposure (about 6–9 h) or documents acute abstinence. In contrast, cotinine, by virtue of its longer half life, offers a window of 5–7 days for detection of nicotine exposure. Despite this limitation, because it is non-invasive, inexpensive and provides information in real time, expired CO measurements are understandably attractive and have been used to document abstinence in the majority of large scale smoking cessation clinical trials with both nicotine (e.g., nicotine patch, gum, and lozenge; Hays et al., 1999; Hughes et al., 1999; Jamrozik et al., 1984; O'Malley et al., 2006; Shiffman et al., 2002) and non-nicotine medications (e.g., bupropion and varenicline; Ahluwalia et al., 2002; Hurt et al., 1997; Gonzales et al., 2006; Jorenby et al., 1999, 2006).

Reliable biochemical markers of nicotine exposure are an important adjunct to self reports for the objective evaluation of new approaches to achieving smoking cessation. In the smoking cessation clinical trials literature, the majority of studies with non-nicotine containing medications or behavioral treatments

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use CO as the sole method for biochemical verification with a cut off of 9 or 10 ppm (e.g., Williams et al., 2007; Gonzales et al., 2006, 2001; Jorenby et al., 2006; Nakamura et al., 2007; Nides et al., 2006; Oncken et al., 2006; Tonstad et al., 2006, 2003; Tsai et al., 2007; Hays et al., 2001; Hurt et al., 1997; Spring et al., 2004; Aubin et al., 2004; Dalsgarð et al., 2004; Tashkin et al., 2001; Tønnesen et al., 2003; Cox et al., 2004). We were concerned that short term, or unsustained abstinence that occurs only hours prior to evaluation might provide misleading information, and exaggerate treatment success rates, if expired CO rather than cotinine measurements are used to verify patient self reports. Even though other investigators have raised this concern (Gariti et al., 2002), it appears that the field is consistently still only using CO as the method of biochemical verification, even for newer non-nicotine medications (e.g., varenicline; Gonzales et al., 2006; Jorenby et al., 2006), and few, if any, clinical trials have systematically compared breath CO to plasma cotinine as measures of abstinence. Our investigation was designed to address this issue by using data from a randomized controlled smoking cessation study utilizing bupropion.

2. Method

2.1. Participants and procedure

We report an analysis of data collected in a prior clinical trial that investigated varying messages to assist smoking cessation with open label sustained-release (SR) bupropion (Toll et al., 2007). All participants received 150 mg of bupropion SR once per day for 3 days, then twice per day for the duration of the 7-week treatment period (1 week pre- and 6 weeks post-quit; Ahluwalia et al., 2002; Hurt et al., 1997). The message framing intervention included framed video and print messages encouraging smoking abstinence (i.e., 2 short videos, print matter, and a water bottle and air freshener with printed slogans on them). For example, a typical gain-framed message was "In addition to the physical benefits of quitting smoking, it can also have a positive impact on one's social life" and a typical loss-framed message was "In addition to the negative physical effects of smoking, it can have a negative impact on one's social life" (see Toll et al., 2007 for additional examples).

Smoking was assessed using Timeline Followback (TLFB) methodology at each weekly appointment utilizing procedures outlined by Sobell and Sobell (1992, 2003). Specifically, participants were asked to indicate the number of cigarettes they consumed each day at baseline (for the 30 days prior to the screening session) and at all weekly or bi-weekly appointments (for the preceding weeks; Brandon et al., 1995; Brown et al., 1998). As the message framing intervention was provided via video and print messages, the research assistant that administered the TLFB did not provide the framed messages.

Assays were performed during clinic visits at 6 weeks, and 3 and 6 months after the targeted quit date. Self-reported abstinence from smoking was verified at each clinic visit using an exhaled CO level less than or equal to 10 ppm (Toll et al., 2007). Although a cut off of 10 ppm is commonly used in clinical trials, we also reanalyzed the data using cut offs values of 8, 6 and 4 ppm.

At week 6 (i.e., end of treatment), 3-month follow-up, and 6-month follow-up appointments, blood samples were also obtained and used for determining plasma cotinine concentrations utilizing a modified HPLC procedure (Hariharan et al., 1988).

A concentration of less than 25 ng/mL was considered to be in accordance with abstinence. Lack of interferences from bupropion and/or its several serum metabolites was verified by the absence of any peaks that co-eluted with cotinine or the internal standard in patients on bupropion who were abstinent (cotinine free). There were slightly fewer plasma cotinine samples (week 6 = 13 fewer; 3 months = 9 fewer; 6 months = 4 fewer) obtained than CO samples due to the fact that obtaining plasma cotinine requires a blood draw, and it is easier to obtain a breath sample than a blood sample (e.g., sometimes the phlebotomist cannot find a participant's vein). Of those subjects who provided self reports and expired CO measurements, cotinine concentrations were obtained on 92%, 92% and 94% of subjects at 6 weeks, 3 and 6 months, respectively.

The average age of participants ($N = 207$; 48.8% Men; 82.9% White) was 42.2 (S.D. = 11.18), and the mean number of cigarettes smoked per day was 22.7 (S.D. = 9.45). On average, participants reported having smoked for 25.0 years (S.D. = 11.12), and the mean score on the Fagerström Test for Nicotine Dependence (FTND) scale was 5.37 (S.D. = 2.06). Participants exhibited an average expired CO level of 22.7 ppm (S.D. = 10.06,) and a mean baseline plasma cotinine level of 282.8 ng/mL (S.D. = 126.42) consistent with levels expected for pack a day or greater smokers. This study was approved by the Institutional Review Board (IRB) of the Yale University School of Medicine.

2.2. Data analysis plan

We compared self reports of point prevalence (i.e., the preceding 7 days) abstinence with the biochemical markers expired CO and plasma cotinine at the end of the study treatment (6 weeks post-quit) and at the 3- and 6-month follow-ups. We chose to use point prevalence abstinence as our measure of self-reported abstinence because this is the most common measure used in smoking cessation clinical trials (Fiore et al., 2000; Hughes et al., 2003). We compared abstinence rates using the following methods: self reports vs. CO, self reports vs. cotinine, CO vs. cotinine, and self report + CO vs. self report + cotinine. Comparisons were presented numerically in tabular format and analyzed statistically using chi-square tests. It should be noted that for the purposes of these analyses, we focused on an "as treated" study sample (i.e., participants that came in to the clinic for appointments) instead of an "intention to treat" sample (i.e., all participants) because we only wanted to compare self reports, CO and cotinine samples for subjects who actually made reports and provided samples.

3. Results

The results of self report, cotinine, and CO measurements at 6 weeks and 3 and 6 months following the "quit date" are displayed in Tables 1–4. As presented in Tables 2–4, all comparisons were

Table 1
Abstinence by self report, cotinine, and CO at week 6, 3 months, and 6 months

	Abstinent	Smoking	Total
Week 6			
Self report	107 (62.6%)	64 (37.4%)	171
Serum cotinine	77 (48.7%)	81 (51.3%)	158
Expired CO			
10 ppm	146 (85.4%)	25 (14.6%)	171
8 ppm	141 (82.5%)	30 (17.5%)	171
6 ppm	132 (77.2%)	39 (22.8%)	171
4 ppm	116 (67.8%)	55 (32.2%)	171
3 months			
Self report	57 (50.9%)	55 (49.1%)	112
Serum cotinine	55 (53.4%)	48 (46.6%)	103
Expired CO			
10 ppm	78 (69.6%)	34 (30.4%)	112
8 ppm	73 (65.2%)	39 (34.8%)	112
6 ppm	68 (60.7%)	44 (39.3%)	112
4 ppm	59 (52.7%)	53 (47.3%)	112
6 months			
Self report	34 (47.2%)	38 (52.8%)	72
Serum cotinine	32 (47.1%)	36 (52.9%)	68
Expired CO			
10 ppm	42 (58.3%)	30 (41.7%)	72
8 ppm	34 (47.2%)	38 (52.8%)	72
6 ppm	39 (54.2%)	33 (45.8%)	72
4 ppm	31 (43.1%)	41 (56.9%)	72