Final report

Study title: Effect of hydrocortisone on desire to smoke and tobacco withdrawal symptoms

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Summary

Objective: There is evidence that cortisol levels drop to subnormal levels during the first days of smoking cessation. This low cortisol is associated with increased desire to smoke, withdrawal symptoms and stress. A decline in cortisol also predicts smoking relapse. We examined whether oral hydrocortisone (HC), relative to placebo, reduces desire to smoke and withdrawal symptoms on the first day of temporary smoking abstinence.

Methods: We recruited 48 male and female smokers (>10 cigarettes a day) to a within-subject cross-over study. Following overnight smoking abstinence, participants received 20mg of HC, 40mg of HC and placebo (double-blind), on separate occasions in random order. They rated desire to smoke and withdrawal symptoms across the morning following overnight abstinence (on waking and 2hrs, 4hrs & 6hrs after waking). Between receiving the treatments participants returned to normal smoking for 3 to 5 days. Ratings for individual symptoms and desire to smoke were compared for the three treatments.

Main results: The recruitment target was met on schedule. No adverse effects of taking hydrocortisone were reported.

There was a statistically significant trend for lower levels of depression and anxiety with higher levels of hydrocortisone. For three withdrawal symptoms (irritability, concentration and stress), significantly lower levels were observed when taking 20mg HC compared with placebo, but there was no further decrease with 40mg HC, and hence no significant dose response effect. There was little apparent effect of treatment on desire to smoke.

Conclusions: Hydrocortisone may be useful for reducing tobacco withdrawal symptoms. A larger trial is needed with smokers attempting to quit smoking, and with smoking cessation as an outcome.

Background

Tobacco withdrawal symptoms and cravings for cigarettes predict smoking relapse and are a serious discomfort to those attempting to stop smoking (West et al 1989, Hughes 2006). Little is known about the biological markers of tobacco withdrawal. Recent research suggests that cortisol may be one such marker. Cortisol is a glucocorticoid which modulates central nervous system activity during stress and its production has been linked to the ability to cope with stress demands (Biondi & Picardi 1999). Cigarettes stimulate cortisol release and therefore smokers tend to have much higher cortisol levels than non-smokers (Steptoe & Ussher 2006). Many smokers experience a pronounced reduction in cortisol levels, to sub-normal levels, during the first days of smoking cessation (Steptoe & Ussher 2006). This phenomenon is likely to be due to a temporary disruption of the feedback mechanism that controls cortisol levels (Benowitz et al 1984, al'Absi et al 2003). While, at the same time, most attempts to quit smoking tend to fail on the first day of abstinence (Hughes et al 2004). It has been found that low levels of cortisol on the first day of smoking abstinence are associated with reports of higher levels of urges to smoke, tobacco withdrawal symptoms and perceived stress and that these associations are observed despite the use of nicotine replacement therapy (Steptoe & Ussher 2006, Ussher et al 2006a). Other work has shown that a greater decline in cortisol following abstinence predicts smoking relapse at one week (al'Absi et al 2004). This phenomenon may be due to increased nicotine receptor sensitivity, as a consequence of sudden decline in cortisol (Steptoe & Ussher 2006, Pomerleau & Pomerleau 1990), or as a result of cortisol's role in the reinforcement of smoking (Reuter & Hennig 2003).

It is hypothesized that interventions which counteract sub-normal levels of cortisol during the first days of smoking abstinence may reduce cigarette cravings and withdrawal and, ultimately, increase abstinence rates. Anecdotal reports suggest that glucocorticoids may be beneficial for reducing cigarette withdrawal (Bourne 1985), but previous controlled studies exploring this issue could not be indentified. A study was conducted to examine whether giving oral hydrocortisone (HC, synthetic cortisol), on the first day of smoking abstinence, significantly reduces tobacco withdrawal symptoms and the desire to smoke among temporarily abstinent smokers, relative to a placebo. In addition, the effects of HC on reports of withdrawal symptoms and desire to smoke following exposure to smoking cues was tested. The

most effective pharmaceutical aids to smoking cessation have all been shown to work through reducing withdrawal symptoms and desire to smoke. Therefore, prior to considering conducting larger trials with smoking cessation as an outcome, this trial sought evidence that supplementation with corticosteroids is effective for reducing tobacco withdrawal symptoms and desire to smoke.

Methods and Materials

Study Participants

The study recruited male and female smokers aged 18 to 65 years, smoking ≥10 cigarettes a day for at least three years, who smoke their first cigarette within 30 minutes of waking, have an expired carbon monoxide (CO) reading ≥10ppm, are not planning to quit smoking during the next month, are not receiving psychiatric treatment, do not have a history of severe depression, are not receiving oestrogen therapy and are not night shift workers. Those currently taking corticosteroids and those with cautions for using oral corticosteroids (British National Formulary 2009) were also excluded. Participants were recruited using posters and advertisements in local newspapers. Those completing the study were paid £100 for their time and travel.

Design and Procedures

A nurse screened all volunteers via the telephone. Cautions for using corticosteroids were further checked with each volunteer's physician. Participants attended the laboratory in the late afternoon for baseline assessments. Smoking status was confirmed with an expired carbon monoxide (CO) level (Smokerlyzer, Bedfont Scientific Ltd, UK) of ≥10ppm. A baseline (i.e. pre-smoking abstinence) saliva sample was provided for cortisol. Cortisol levels in a spot sample taken in the late afternoon correlate strongly with a more complete estimate of diurnal cortisol activity (Edwards et al 2001). Participants provided written informed consent and the local ethics committee gave its approval. A flow diagram is presented in Figure 1.

All participants then underwent a low dose dexamethasone suppression test (Pruessner et al 1999) to check for normal functioning of cortisol regulation, as a potential confounder of the effect of hydrocortisone on tobacco withdrawal. It is normal to have suppression of cortisol on the day following ingestion of the corticosteroid dexamethasone. To establish pre-dexamethasone morning cortisol

levels, the morning following baseline assessments participants were instructed to take saliva samples on waking and 30 minutes later. Previous studies have used these two times for this purpose (Kunz-Ebrecht et al 2004, Steptoe et al 2004). Participants were instructed to then take a tablet of 1mg dexamethasone (Organon Laboratories Ltd, UK) at between 22:00 and 23:00 hours. To determine post-dexamethasone morning cortisol levels, the following morning participants sampled their saliva on waking and 30 minutes later.

In this placebo controlled double-blind cross-over study, participants completed three medication periods (40 mg HC, 20mg HC and placebo in counterbalanced order) and two washout periods of three to five days. The placebo was a lactose capsule identical to the capsules containing the active medication. Drug packaging and randomization was completed by Nova Laboratories Ltd, UK. Hydrocortisone (Merck Sharp & Dohme Ltd UK) was administered in doses consistent with standard treatment guidelines for cortisol deficiency (British National Formulary 2009). Single doses of hydrocortisone have no documented adverse side-effects.

After a dexamethasone washout period of 12 to 15 days, participants were instructed not to smoke, or use nicotine products, from 11pm until after attending an assessment the following afternoon. Previous studies show that, among relatively heavy smokers, 12 to 15 hours of temporary smoking abstinence is sufficient to induce severe cravings and withdrawal (e.g. Ussher et al 2001, Ussher et al 2006b, West et al 2006). They received a telephone reminder to abstain. Following overnight abstinence, participants were instructed to take the medication on waking, so as to mimic the normal morning rise in cortisol (Pruessner 1999). Following a washout period, during which participants smoked as usual, the above procedure (i.e. overnight smoking abstinence and medication taken on waking) was repeated for the remaining two medications. Across the morning of taking each medication subjective ratings of tobacco withdrawal symptoms and desire to smoke ratings were made on waking and 2hrs, 4hrs and 6hrs after waking. Participants were asked to make the waking rating (baseline/pre-medication) immediately before taking the medication.

In addition, on the day of taking each medication participants returned to the laboratory in the afternoon for a further assessment. The effect of the medications on tobacco withdrawal and desire to smoke was assessed when participants were exposed to cigarette cues. The cue- exposure procedure followed an established protocol (LaRowe et al 2007, Waters et al 2004). On arriving at the laboratory the procedure

was explained to participants and they placed their cigarettes and lighter in a covered box. Instructions for the cue-exposure were delivered via an audio recording. Prior to exposure, participants rated their desire to smoke and withdrawal symptoms. The box lid was removed and participants were instructed: (i) "Please look at the cigarettes and lighter" (15 s); (ii) "Now, please take out a cigarette and handle it as you would before you light up." (15 s); (iii) "Also, please smell the cigarette." (10 s), and (iv) "Next, please pick up the lighter and strike it once, as if you were going to light the cigarette (but do not actually light it). Continue handling the cigarette as you would between puffs." (50 s). After 90 s, of exposure they were instructed "While still holding the cigarette in your smoking hand, please complete the ratings." After rating desire to smoke and withdrawal symptoms they were asked to return the cigarette to the packet.

Measures

Demographic and smoking characteristics, including nicotine dependence (Heatherton et al 1991) and expired CO were measured at the baseline assessment. Overnight smoking abstinence was confirmed with an expired CO reading of <8ppm. To determine salivary cortisol participants inserted a cotton roll in their mouth for a timed period of 2 minutes and returned the roll to a salivette (Sarstedt, Germany).

For the pre-smoking abstinence measure of salivary cortisol, to minimize any acute effects of smoking on cortisol, participants were required to abstain from smoking for at least 30 minutes before the samples (Reuter et al 2002). Participants provided the morning saliva samples at home and they were asked not to eat, drink (other than water) or take exercise until they had provided the saliva. They were instructed to store the salivettes in a freezer until their next laboratory visit. For the afternoon saliva samples participants were instructed not to drink alcohol or take vigorous exercise on the day until after the samples, or to eat or drink (except water) within 30 minutes of the visit. Before assay, all the saliva samples were stored at 20°C. Samples were thawed and then spun at 3500 rpm for 10 minutes to recover the saliva. Cortisol concentration was determined by an enzyme linked immunoassay developed specifically for the determination of cortisol in saliva (Salimetrics LLC). Assay reliability met the manufacturer's specifications.

Subjective withdrawal symptoms and desire to smoke were assessed using the Mood and Physical Symptoms Scale (MPSS, West & Russell 1985), which has good psychometric properties (West & Hajek 2004; West et al 2006; West & Ussher in

press). The withdrawal symptoms assessed were irritability, depression, hunger, anxiety, restlessness, poor concentration and stress. For example, 'How irritable do you feel right now?' or 'How strong is your desire to smoke right now?' (1=not at all, 4=somewhat, 7=extremely). Participants were given a palm-top computer (Palm, Tungsten E2) to record their ratings and to receive prompts of when to make ratings. Compliance with electronic assessment tends to be higher than for paper-based assessment (Stine et al 2003).

Results

A flowchart is presented in figure 1. The demographics of the sample are presented in table 1. Compared with national data for England, the participants tended to smoke slightly more cigarettes per day and to have slightly higher tobacco dependence scores. No participants reported adverse events. Of the 44 individuals providing valid cortisol samples for the dexamethasone suppression test, 40 showed cortisol suppression of at least 25%, one showed suppression of only 9%, for one person cortisol increased by 8%, and for two cortisol levels more than doubled.

The analysis was conducted for those completing all three treatments. Desire to smoke and the eight withdrawal symptoms were compared between the three treatments (Table 2). There was a significant 'period effect' (i.e. results differed according to whether the treatment was the first, second or third received), and therefore all analyses are adjusted for period, but the period/treatment interaction was not statistically significant. There was a statistically significant trend for lower levels of depression and anxiety with higher levels of hydrocortisone. For three withdrawal symptoms (irritability, concentration and stress), significantly lower levels were observed when taking 20mg HC compared with placebo, but there was no further decrease with 40mg HC, and hence no significant dose response effect. There was little apparent effect of treatment on desire to smoke.

The afternoon cortisol measurements made at the pre-smoking abstinence baseline assessment and after each of the three treatments were compared using Friedman's test ($p<0.001$; $n=42$). Post-hoc Wilcoxon tests revealed no significant difference between cortisol levels measured at the pre-abstinence baseline and those measured post-abstinence on the placebo treatment (Table 3); for 22 subjects cortisol levels decreased, while for 24 they increased. There was a statistically significant increase in cortisol levels after the 40mg HC treatment compared with baseline (adjusted

p=0.012), but the increase over baseline was not significant for the 20mg HC treatment.

The effect of treatment on withdrawal symptoms and desire to smoke did not differ significantly between those participants who showed a reduction in cortisol during abstinence whilst on the placebo treatment compared with their baseline assessment, and those whose cortisol levels increased.

Withdrawal symptoms were also measured immediately before and after handling a cigarette whilst still abstinent, during the afternoon visit for each treatment. There were no statistically significant changes in any of the withdrawal symptoms, or in desire to smoke, as a result of cigarette handling.

Conclusion

The findings suggest that taking a single dose of oral hydrocortisone on the first day of smoking abstinence may reduce some withdrawal symptoms, namely, depression, anxiety, irritability and stress. There was no evidence to suggest that HC might reduce the desire to smoke. The findings for depression are of particular importance as there was a dose-response effect on depression and depression is associated with relapse to smoking. The observed benefits of HC were not more pronounced among those experiencing a greater decline in cortisol on abstaining from smoking, therefore it is unlikely that these benefits are due to HC compensating for a marked drop in cortisol following smoking cessation. The participants were only temporarily abstinent from smoking and further studies are needed to confirm these findings in those attempting to quit and to examine the effects of HC on quit rates.

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Table 1. Baseline characteristics (N=48)

Characteristic	**Mean (SD)**
Age (years) (range=18-60)	38.4 (11.5)
Full-time education (years)	13.4 (3.3)
FTND score (range 2-9)	5.6 (1.7)
Smoking rate, cigarettes a day (range=10-40)	19.3 (6.3)
Carbon monoxide level (ppm) pre-smoking abstinence (range10-28)	15.3 (4.4)
Pre-dexamethasone cortisol (nm/l) (range 3.2 to 24.4)	13.1 (4.8)
Post-dexamethasone cortisol (nm/l) (range 0.4 to 36.3)	3.8 (6.9)
	Number (%)
Female	33 (69)
Caucasian	36 (84)
Managerial/professional occupation	16 (33)
Married/living with partner	12 (25)

ppm=parts per million

FTND=Fagerström Test for Nicotine Dependence

Table 2: Desire to smoke and withdrawal symptoms following abstinence, compared between treatment groups, adjusted for period

	20 mg vs placebo		**40 mg vs placebo**		**40 mg vs 20 mg**		
	*B**	*p*	*B**	*p*	*B**	*p*	*p for trend*
Desire to smoke	-0.21	0.32	-0.02	0.91	0.18	0.30	0.91
Irritability	**-0.35**	**0.049**	-0.20	0.34	0.14	0.34	0.34
Depression	-0.08	0.52	**-0.48**	**0.001**	**-0.39**	**0.008**	**0.001**
Tension	-0.24	0.10	-0.23	0.24	0.01	0.96	0.23
Hunger	-0.14	0.25	-0.21	0.22	-0.07	0.64	0.22
Anxiety	**-0.40**	**0.016**	**-0.50**	**0.007**	-0.10	0.50	**0.006**
Restlessness	-0.14	0.38	-0.15	0.44	-0.01	0.96	0.44
Concentration	**-0.28**	**0.048**	-0.27	0.19	0.02	0.90	0.19
Stress	**-0.34**	**0.036**	-0.22	0.23	0.12	0.48	0.23

* B represents the average increase or decrease in withdrawal score for the given treatment versus its comparator

Table 3: Change in afternoon cortisol levels (nmol/l) between the baseline assessment visit and following each treatment (n=42)

Treatment	*Change compared with baseline (nmol/l):*			
	Mean	*(SD)*	*Range*	*p*
Placebo	0.3	(11.0)	-36.0 to 39.0	0.85
20mg HC	2.6	(19.0)	-26.8 to 78.4	0.68
40mg HC	9.3	(19.1)	-28.9 to 87.4	0.002

Figure 1 Summary of procedure

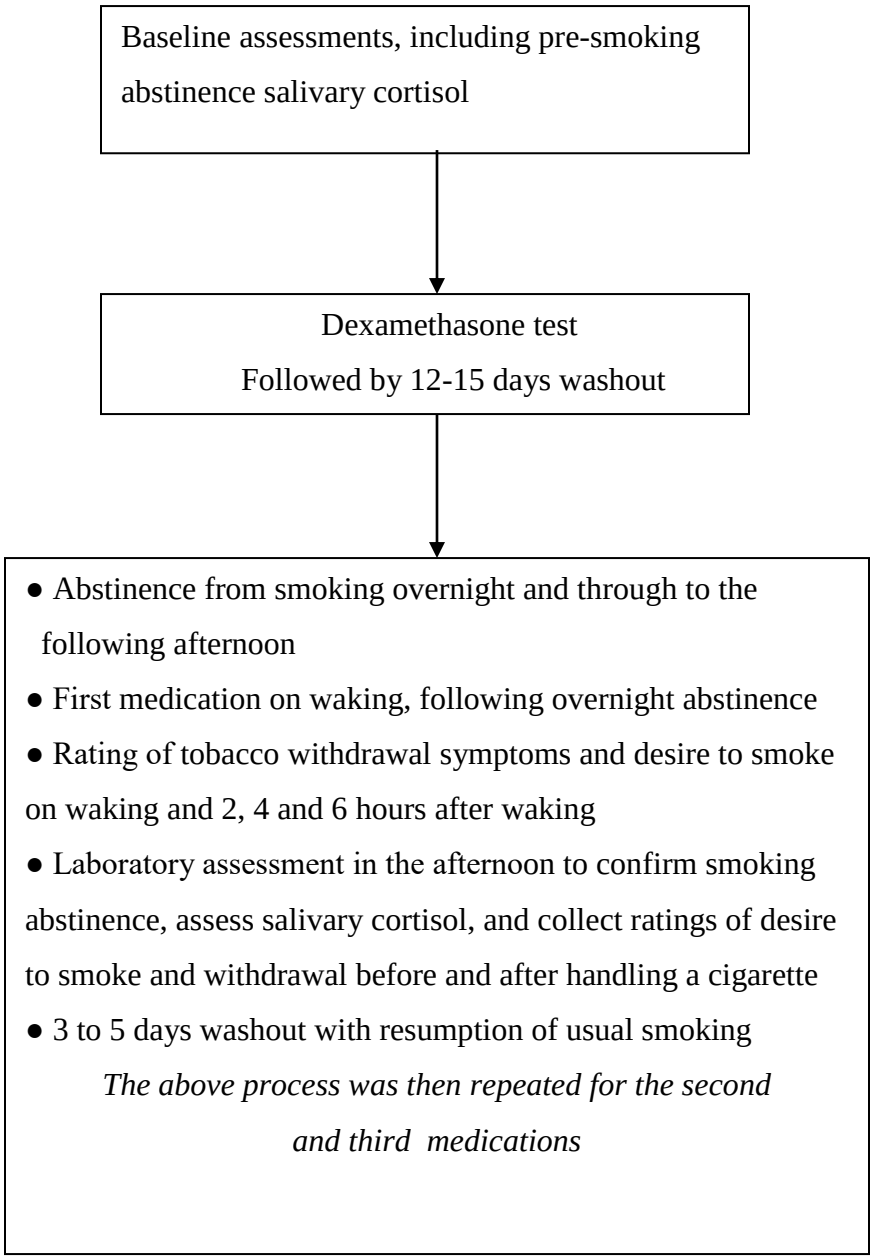

Figure 2: Participant flowchart