Symptoms of Nicotine Toxicity in Subjects Achieving High Cotinine Levels During Nicotine Replacement Therapy

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Received January 20, 2014; accepted April 5, 2014

ABSTRACT

Introduction: Nicotine replacement therapy (NRT) aids smoking reduction and cessation. Although NRT is effective and safe, some smokers may achieve high nicotine levels. The purpose of this study was to determine the incidence and severity of nicotine-related adverse events in subjects with levels of cotinine, a metabolite of nicotine, that increased by >50%, compared with baseline smoking in controlled clinical trials of NRT.

Methods: Data from participants in randomized, double-blind, controlled trials of various formulations of NRT (Nicorette®) including patch, gum, oral inhaler, sublingual tablet, nasal spray, mouth spray, and combinations were extracted from a clinical database. Eligible studies were performed between 1989 and 2010. In addition to baseline, at least one subsequent plasma or salivary cotinine concentration was measured, and adverse events were recorded simultaneously. Of 28 eligible studies, 24 were smoking cessation studies, and 4 were smoking reduction studies.

Results: Cotinine levels that increased by >50% above baseline were recorded during treatment in 746 of 7,120 subjects (10.5%). Nausea was reported in 16 subjects (0.2% of the total, upper 99% confidence limit (CL) 0.4%), vomiting in 2 subjects (0.0%, upper 99% CL 0.1%), palpitations in 5 subjects (0.1%, upper 99% CL 0.2%), dizziness in 11 subjects (0.2%; upper 99% CL 0.3%), and headache in 35 subjects (0.5%, upper 99% CL 0.7%).

Conclusion: Typical symptoms indicating nicotine overdose together with high cotinine levels were rare during treatment with NRT. These findings support the safety of NRT for smoking cessation or reduction.

INTRODUCTION

Nicotine replacement therapy (NRT) was developed to satisfy smokers’ need for nicotine without the harmful effects of cigarettes and as a treatment for nicotine withdrawal symptoms to aid smoking cessation. As conventionally administered during a stop smoking attempt, NRT has demonstrated efficacy and safety (Stead et al., 2012). Although complete cessation is the ultimate goal, use of NRT on top of smoking may reduce the number of cigarettes smoked per day and carbon monoxide levels (Fagerström & Hughes, 2002). Additional studies indicate that precessation treatment with transdermal NRT may offer advantages (Lindson & Aveyard, 2011). Other strategies to optimize the efficacy of NRT include combination of NRT of various routes of administration and fixed high-dose NRT (Carpenter et al., 2013).

Concurrent use of NRT and smoking appears to be quite safe (Fagerström & Hughes, 2002). Most smokers are adept at titrating their nicotine intake and maintain their plasma nicotine levels within a narrow range. Titration seems more precise during treatment with flexible formulations of NRTs such as gum compared with nicotine patches (Fagerström & Hughes, 2002). However, even high patch doses do not seem to result in substantial physiological or subjective effects (Fredrickson et al., 1995). NRT increases sympathetic drive, but tolerance develops, and NRT appears to be safe in patients with acute coronary syndromes (Woolf et al., 2012). Systematically collected data on the subjective effects of high nicotine levels due to NRT or simultaneous NRT and smoking are lacking.

Nicotine has a half-life of 1–2 h, whereas cotinine, the primary metabolite of nicotine, has a half-life of around 20 h (Benowitz, Hukkanen, & Jacob, 2009). In clinical trials of NRT, salivary or plasma cotinine levels better reflect steady-state exposure to nicotine than do nicotine levels (Benowitz, Hukkanen, & Jacob, 2009). Clinical trials show substantial decreases in cotinine levels in people who stop smoking using NRT (Benowitz, Hukkanen, & Jacob, 2009; Haustein, Krause, Haustein, Rasmussen, & Cort, 2003). On the other hand, in some who continue smoking...
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while using NRT nicotine concentrations may double or treble (Fagerström & Hughes, 2002). Likewise, combination or high-dose NRT may result in higher nicotine levels than with conventional NRT or even with cigarette smoking (Fredrickson et al., 1995; Honisz et al., 1997). To assess the safety of high cotinine levels, we conducted a retrospective pooled analysis of randomized, double-blinded controlled studies in smokers trying to quit or reduce with NRT. We determined the incidence of symptoms known to be related to nicotine overdose including nausea, vomiting, palpitation, dizziness, and headache (Benowitz, 1988) together with cotinine levels above an arbitrarily chosen cutoff of >50% above baseline in these trials.

METHODS

The McNeil clinical database of all randomized, double-blind, controlled studies of smoking cessation or reduction with NRT (solely Nicorette®, manufactured by McNeil AB, Sweden) performed between 1989 and 2010 was searched. Formulations of NRT included nicotine 15mg/16hr transdermal patch, nicotine 25mg/16hr transdermal patch, nicotine 2 or 4 mg chewing gum, nicotine inhaler 10mg, nicotine 2mg sublingual tablet, nicotine nasal spray 0.5mg/spray, nicotine mouth spray 1mg/spray, and various combinations of NRT formulations (e.g., patch plus gum, patch plus inhaler). Inclusion criteria were active treatment with an NRT product currently approved for the treatment of tobacco dependence or a combination of two of these products; the treatment was being used for any currently approved indication for the treatment of tobacco dependence (i.e., smoking cessation, smoking reduction, reduction to quit, or temporary abstinence from smoking); the instructions for use and dosage recommendation were generally in line with approved recommendations; data were available on plasma or saliva cotinine value at baseline (during normal smoking) and at least one cotinine level during treatment with NRT; and adverse events were reported and recorded at the same timepoints as plasma or salivary sampling for cotinine analysis. None of the studies enrolled subjects with severe or symptomatic cardiovascular disease, females who were pregnant or breast feeding, or individuals with current alcohol or other substance abuse.

Clinical trials of prototype formats of NRT were not included, and trials in which the use or dosage of NRT differed substantially from usual recommendations were also excluded. Trials of NRT for conditions other than tobacco dependence were excluded. Studies performed in the late 1970s and early 1980s with data archived on paper only were not accessible in the electronic database.

The search identified a total of 28 eligible prospective, controlled trials of NRT (Supplementary Tables 1a–c). In 19 of the 28 studies, the primary study objective was to investigate the efficacy of NRT for smoking cessation (Bohadana, Nilsson, Rasmussen, & Martinet, 2000; Glover et al., 2002; Hjalmarson, Franzon, Westin, & Wiklund, 1994; Hjalmarson, Nilsson, Sjostrom, & Wiklund, 1997; Kornitzer, Boutsen, Damaix, Thijs, & Gustavsson, 1995; Leischow et al., 1996; Paolelli et al., 1996; Puska et al., 1995; Sachs, Sawe, & Leischow, 1993; Schneider et al., 1995, 1996; Stapleton & Sutherland, 2011; Stapleton et al., 1995; Sutherland et al., 1992; Tönnesen, Norrøgaard, Simonsen, & Säve, 1991; Tönnesen et al., 1999; Tönnesen, Lauri, Perfekt, Mann, & Batra, 2012; Tönnesen, Norrøgaard, Mikkelsen, Jörgensen, & Nilsson, 1993; Wallström, Nilsson, & Hirsch, 2000). Four studies investigated the efficacy of NRT for smoking reduction (i.e., cutting down smoking before making a quit attempt) (Batra et al., 2005; Bolliger et al., 2000; Renard et al., 2006; Wennike, Danielsson, Landfeldt, Westin, & Tönnesen, 2003). The remaining studies investigated the effect of stopping or reducing smoking with NRT on respiratory symptoms (Bohadana, Nilsson, Westin, Martinet, & Martinet, 2006), postcessation weight gain (Danielsson, Rössner, & Westin, 1999), hematomalological parameters (Haustein, Krause, Haustein, Rasmussen, & Cort, 2004), or had a combination of endpoints (Kralikova, Kozak, Rasmussen, Gustavsson, & Le Houezec, 2009; Tönnesen et al., 2005).

In each study, the cotinine level at baseline represented the subjects' nicotine intake during smoking only (i.e., before NRT administration). For all evaluable subjects, cotinine levels that increased by >50% from the baseline value were listed, and all clinic visits were checked for reports of any adverse events that were considered to be indicators of possible nicotine overdose including nausea, vomiting, palpitation, dizziness, and headache, typical symptoms of overdose (Benowitz, 1988). Other symptoms such as excess sweating (0 cases) and abdominal pain (3 cases) were too rare for analysis. Adverse events were queried since the last visit (and including the current visit day) and collected from an open-ended question on the case report form. They were coded according to the WHO coding (majority of studies) or in a few studies, Medical Dictionary for Regulatory Activities (MedDRA) code list. The label (preferred term) from the coding was used for the tabulations.

Statistical methods

This was a pooled analysis of 28 studies. The rate of nicotine-related adverse events was collected and tabulated. For subjects with a cotinine value that increased by >50% from baseline on more than one occasion, all these visits were included, but each adverse event counted once per subject. Upper 99% confidence limits for the frequencies were calculated using SAS 9.2 (PROC FREQ and option “exact”).

RESULTS

The 28 studies included a total of 12,758 evaluable subjects, of whom 7,120 received NRT and had two cotinine levels measured. In the majority of studies, subjects smoked at least 10–15 cigarettes per day at baseline and had smoked for at least 3 years. The median increase in cotinine levels among those included in these analyses was >50%–60% (representing levels induced by NRT and any concurrent smoking). A cotinine value that increased by >50% from baseline was recorded at least one visit during treatment in 746/7,120 subjects (10.5%); of this group, 69/746 (9.2%) had symptoms. Among the total subjects, the incidence of adverse events and high cotinine levels was 69/7,120 (0.97%), and they were mostly categorized as mild or moderate. Adverse events summarized per product are shown in Table 1.

DISCUSSION

The findings support the safety of NRT in subjects trying to stop or reduce smoking. Symptoms consistent with nicotine overdose were only very rarely noted, and most were mild or
<table>
<thead>
<tr>
<th>Treatment and proportion with high cotinine levels, ( n/N ) (%)</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Palpitation</th>
<th>Dizziness</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>( % )</td>
<td>99% UCL</td>
<td>( n )</td>
<td>( % )</td>
</tr>
<tr>
<td>Combination 65/816 (8.0)</td>
<td>0</td>
<td>0.0</td>
<td>0.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Gum SR 29/255 (11.4)</td>
<td>0</td>
<td>0.0</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Inhaler 45/392 (11.5)</td>
<td>5</td>
<td>1.3</td>
<td>3.3</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Inhaler SR 90/334 (26.9)</td>
<td>0</td>
<td>0.0</td>
<td>1.4</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Microtab 40/187 (21.4)</td>
<td>5</td>
<td>2.7</td>
<td>6.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>NNS 17/670 (2.5)</td>
<td>1</td>
<td>0.1</td>
<td>1.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>ONS 32/252 (12.7)</td>
<td>1</td>
<td>0.4</td>
<td>2.6</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Patch 298/3,314 (9.0)</td>
<td>4</td>
<td>0.1</td>
<td>0.3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Miscellaneous trials</td>
<td>0</td>
<td>0.0</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Supplementary Table 1c) 130/900 (14.4)</td>
<td>16</td>
<td>0.2</td>
<td>0.4</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>Total 746/7,120 (10.5)</td>
<td>16</td>
<td>0.2</td>
<td>0.4</td>
<td>2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Note. Percentages and upper 99% confidence limits (UCLs) are shown according to treatment formulation. SR = smoking reduction; NNS = nicotine nasal spray; ONS = oromucosal nicotine spray.
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moderate. Strengths of this analysis include the large number of studies and systematic recording of adverse events.

The current pooled analysis updates previous studies that investigated the relationship between elevated nicotine levels and adverse events. A review of studies performed between 1976 and 2000 found that concurrent use of cigarettes and NRT was associated with few adverse events, even when nicotine concentrations were double or treble baseline values, and the adverse events were mainly mild (Fagerström & Hughes, 2002). Only 2 of the 28 studies in the present analysis (Bolliger et al., 2000, Kralikova et al., 2009) were included in the previous review (Fagerström & Hughes, 2002). The present data were all from a single manufacturer of NRT; however, they comprised about one third of studies in a recent meta-analysis (Stead et al., 2012).

We found relatively higher proportions of high cotinine levels in users of the inhaler for smoking reduction and users of microtabs compared to other formulations. Incidence of nicotine overdose symptoms was too rare to be compared statistically across treatment formulations or to compare high cotinine days versus lower cotinine days. This is not surprising given that smokers have large tolerances to nicotine already. Most regular smokers are adept at self-titrating their nicotine intake, maintaining their plasma nicotine levels within a narrow range (Russell, 1988). For example, the Lung Health Study found that cotinine levels were similar in ex-smokers using nicotine gum, smokers who concomitantly used nicotine gum and smoked, and smokers who only smoked over the course of 5 years (Murray, Nides, Istvan, & Daniels, 1998). Treatment with high patch doses may lead to quite high mean cotinine levels. In a study of a 44-mg transdermal patch percent, nicotine replacement in quitters averaged 158% and cotinine replacement was 112% on average (Fredrickson et al., 1995). In another study, mean replacement was consistently >100% in subjects receiving 44-mg patches (Dale et al., 1995). These doses were not used in studies in the current analyses. Two studies used 25-mg patches (Paoletti et al., 1996; Tönnesen et al., 1999). Furthermore, two of the reduction studies used 4-mg gum during concomitant smoking (Batra et al., 2005; Wennike et al., 2003). Studies of NRT lozenges were not available as approval for the lozenges was based on bioequivalance with other NRT products.

Identifying factors associated with high cotinine levels was beyond the scope of the current analysis. Interindividual variability in concentrations of cotinine is considerable, even among smokers treated with the same dose and formulation of NRT (Gourlay, Benowitz, Forbes, & McNeil, 1997). Clinical factors and baseline levels seem to account for only a small proportion of the variability (Gourlay et al., 1997). Although age and sex are major determinants of nicotine metabolism, important factors include cytochrome P450 genotypes and other genetic factors (Johnstone et al., 2006), not measured in these studies.

CONCLUSION

Elevated cotinine levels associated with symptoms of nicotine overdose are rare during NRT treatment.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1a–c can be found online at http://www.ntr.oxfordjournals.org.

FUNDING

None declared.

DECLARATION OF INTERESTS

GG, EK, JMW, and ÅW are employees of McNeil AB, a company developing and manufacturing smoking cessation medication.

ACKNOWLEDGMENTS

Full access to the clinical database was provided by McNeil AB, the owner of the data analyzed in this study.

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