Smoking treatment guided by genetic markers.

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Abstract

Introduction: Among drug addictions, smoking ranks first as a cause of morbidity and mortality and is a risk factor for six of the eight leading causes of death in the world. Nicotine is the main addictive component of tobacco. In nicotine replacement therapy (NRT), varenicline and bupropion are the approved medications for smoking cessation, but results from smoking cessation clinics suggest that many variables influencing treatment response remain unknow.

Objective: To determine the adherence, tolerability and effectiveness of a smoking cessation program based on nicotine or bupropion, in patients with tobacco dependence, selected according to the genotypes of the enzymes that metabolize the two drugs.

Clinical findings: Twenty-one smokers, 67% men, with mean age of 46.2±11.7 years, were included in this series. Their smoking began at 17.8±6 years and they had been smoking for 28±13 years.

At baseline, they smoked 17±12 cigarettes per day (CPD), had made 3.7±2 quit attempts, the NDSS (Nicotine Dependence Short Scale Screening Scale) score was 22±5 (cut-off point for nicotine dependence: 11 or more points).

Treatment: Patients had free telephone access to the treating physician and, every week, a consultation consisting of counseling and monitoring of the prescribed pharmacological treatment according to CYP2A6 (encoding the enzyme that metabolizes nicotine) and CYP2B6 (encoding the enzyme that metabolizes bupropion) genotypes. Nicotine was used in 14 mg transdermal patches for the first month and then 7 mg for the second month, supplemented with chewing gum for withdrawal management and bupropion in a 300 mg controlled-release form, 1-2 times a day.

Results: After 8 weeks of treatment and 4 weeks of observation, 15 subjects (71.4%) responded partially/totally. CPD consumption dropped from 17±12 at the beginning of the study to 2.2±3.5 at the end of the study, which corresponds to a reduction of 195 cigarettes/day. Seven of eight patients treated with bupropion (87.5%) and seven of thirteen treated with nicotine (54%) had a partial/total response. Only one patient receiving nicotine discontinued the medication due to gastrointestinal intolerance (nausea and vomiting). The relapse rate, assessed one month after drug treatment, was zero. Good genotype-phenotype correlation was found in individuals treated with bupropion, but not in those treated with nicotine.

Clinical relevance: The inclusion of pharmacogenetic markers for the choice of nicotine or bupropion in a smoking cessation program may improve adherence, drug tolerability, and treatment effectiveness.

Keywords: Bupropion, CYP2A6, CYP2B6, nicotine, case report, smoking.

Resumen

Introducción: Entre las adicciones por drogas, el tabaquismo ocupa el primer lugar como causa de morbimortalidad y es factor de riesgo para seis de las ocho principales causas de muerte en el mundo. La nicotina es el principal componente adictivo del tabaco. En la terapia de reemplazo con nicotina (TRN), la vareniclina y el bupropion son los medicamentos aprobados para tratamiento del tabaquismo, pero los resultados de las clínicas de dejación del tabaquismo sugieren que aún se desconoce muchas variables influyentes en la respuesta al tratamiento.

Objetivo: Determinar la adherencia, la tolerabilidad y la efectividad de un programa de dejación de tabaquismo basado en nicotina o bupropion, en pacientes con dependencia al tabaco, seleccionados según los genotipos de las enzimas que metabolizan los dos fármacos.

Hallazgos clínicos: Se incluyeron en esta serie 21 fumadores, 67% hombres, con edad promedio de 46,2±11,7 años. Su tabaquismo comenzó a los 17,8±6 años y llevaban fumando 28±13 años. Al inicio del estudio fumaban 17±12 cigarrillos por día (CPD), habían hecho 3,7±2 intentos de dejar de fumar y el puntaje NDSS (escala breve de evaluación de dependencia de la nicotina, por sus siglas en inglés) fue de 22±5 (punto de corte para dependencia a nicotina: 11 o más puntos).

Tratamiento: Los pacientes tenían libre acceso telefónico al médico tratante y, cada semana, una consulta consistente en consejería y control del tratamiento farmacológico prescrito según los genotipos CYP2A6 (que codifica la enzima que metaboliza la nicotina) y CYP2B6 (que codifica la enzima que metaboliza el bupropion). Se empleó nicotina en parches transdérmicos de 14 mg el primer mes y luego de 7 mg el segundo mes, complementados con chicles para manejo del síndrome de abstinencia y bupropion en forma de liberación regulada por 300 mg, 1-2 veces al día.

Resultados: Después de 8 semanas de tratamiento y 4 de observación, 15 sujetos (71,4%) respondieron en forma parcial/total. El consumo de CPD bajó de 17±12 al inicio del estudio, a 2,2±3,5 al final del estudio, que corresponde a una reducción de 195 cigarrillos/día. Siete de ocho pacientes tratados con bupropion (87,5%) y siete de trece tratados con nicotina (54%) tuvieron respuesta parcial/total. Solo un paciente formulado con nicotina suspendió el medicamento por intolerancia gastrointestinal (náusea y vómito). La tasa de recaídas, evaluada un mes después del tratamiento farmacológico, fue de cero. Se encontró buena correlación genotipo-fenotipo en los individuos tratados con bupropion, pero no en los tratados con nicotina.

Relevancia clínica: La inclusión de marcadores farmacogenéticos para la elección de nicotina o bupropion en un programa de dejación de tabaquismo puede mejorar la adherencia, la tolerabilidad al fármaco y la efectividad del tratamiento.

Palabras clave: Bupropion, CYP2A6, CYP2B6, nicotina, reporte de casos, tabaquismo.

Introduction

According to the World Health Organization, smoking tops the list of substances of abuse that cause the most drug-related illnesses and deaths in the world (1). Deaths attributed to smoking are mainly related to cancer, respiratory diseases, cardiovascular diseases, impaired mental health, and increased use of other drugs (2,3).

Nicotine is the main addictive component of tobacco, acting through nicotinic receptors expressed in brain regions involved in the reward, emotion, learning and memory systems of the prefrontal cortex and limbic system, areas involved in addictive behavior (4).

Psychotherapeutic, environmental, and pharmacological interventions are useful in supporting people who wish to quit smoking, with the combination of counseling and pharmacotherapy being the most effective option (2). Although abstinence rates with pharmacological treatment far exceed those obtained with placebo, up to 50% of patients have relapsed after 90 days of follow-up and no more than 42% and 19% of those who quit smoking remain abstinent six and twelve months later, respectively (5). This shows the need to discover more effective treatments, which requires a better understanding of the factors contributing to nicotine addiction and response to medications.

There are three internationally approved drugs for the treatment of smoking: nicotine, varenicline and bupropion, which constitute a small number of therapeutic options; cytisine has shown benefits, but its role in treatment protocols is not yet defined (6).

Heritability (the fraction of risk attributable to genetic factors) in addiction severity is accepted to be 40% to 70% (7). Numerous genes appear as candidates for influencing nicotine addiction and response to smoking treatment, but most attention has been focused on the genes coding for the main enzymes responsible for nicotine (CYP2A6) and bupropion (CYP2B6) metabolism, as well as on the genes coding for nicotinic receptors (CYP2A6) and bupropion (CYP2B6) (8).

The CYP2B6*4 variant (rs2279343, c785 A>G) leads to higher expression of the enzyme, so that individuals with the mutated AG and GG genotypes have accelerated metabolism of bupropion compared with carriers of the native AA genotype. Consequently, at similar doses of bupropion, native homozygotes would have higher and more persistent serum concentrations of the drug, compared with faster metabolizers who have the G allele; this would explain the greater success in smoking cessation in patients carrying the native AA genotype who are treated with bupropion (9). The CYP2A6 gene is also polymorphic and, compared to the native genotype, some alleles are associated with lower response to nicotine, particularly those that translate into a “poor metabolizer” phenotype, including those carrying the SNP rs56113850 and those sharing the rs1137115 (51G>A) polymorphism (10).

The growing problem of tobacco abuse and the limited effectiveness of current treatment protocols justify the search for new therapeutic alternatives that improve adherence rates and minimize relapses and morbidity and mortality associated with this addiction. The identification of genetic markers that influence the response to different pharmacological options represents a promising strategy to achieve more effective precision medicine. In this series of patients treated with a pharmacogenetic approach, we found improved retention, abstinence, relapse, and tolerability rates, compared to the results reported in conventional treatments.

Description of the cases

Twenty-one patients were included, 67% of whom were male (14/21), aged between 27 and 64 years (46.2±11.7 years) and with a body mass index of 24±3. Only 6 people had no other cardiovascular risk factors and 15 were not taking any medication.

The age of onset of regular cigarette smoking was 17.8±6.4 years, the duration of smoking was 28±13.4 years and patients consumed an average of 17±12 CPD, had made 3.7±2 previous quit attempts and the NDSS score was 22.4±4.8. Sixty-two percent of the individuals (13/21) had a family or work environment prone to smoking. Table 1 shows these same variables discriminated by gender, where there were no significant differences between men and women with respect to the smoking phenotype.

Table 1. Smoking phenotypes, discriminated by gender.

Phenotype	Men (n=14)	Women (n=7)	P
Age (years, mean±SD)	46,5±13	45,7±9,5	0,9
BMI (kg/m2)	24±4	24±2	1,0
Risk factors (yes/no)	10/14	5/7	0,8
Drug use (% users)	29	29	1,0
Smoking onset age (years, mean±SD)	16,5±6	20,3±7,5	0,4
Smoking duration (years, mean±SD)	30±14	25,5±14	0,5
CPD (mean±SD)	20±13	12±6	0,2
Previous attempts (mean±SD)	3,6±2,6	4±1	0,4
Pro-smoking environment (% positive)	64	57	0,2
NDSS (mean±SD)	22±5	23±5	0,9

«Heritability (the fraction of risk attributable to genetic factors) in addiction severity is accepted to be 40% to 70%.»

BMI: body mass index; CPD: cigarettes per day; NDSS: brief nicotine dependence screening scale.

P: Chi-square or Mann-Whitney, depending on the type of variable.

Patients were prescribed nicotine or bupropion according to CYP2A6 (encoding the enzyme that metabolizes nicotine) and CYP2B6 (encoding the enzyme that metabolizes bupropion) genotypes. Nicotine treatment was performed with 14 mg transdermal patches in the first month and then 7 mg in the second month, supplemented with chewing gum for withdrawal management, while patients treated with bupropion were prescribed controlled-release forms of 300 mg, 1-2 times a day. All patients received counseling once a week and had telephone access to the treating physician. After 8 weeks of treatment and 4 weeks of observation, 15 subjects (71.4%) were partial/full responders. CPD consumption dropped from 17±12 at baseline to 2.2±3.5 at the end of the study, corresponding to a reduction of 195 cigarettes/day. Seven of eight patients treated with bupropion (87.5%) and seven of thirteen treated with nicotine (54%) had partial/total response. The relapse rate, assessed one month after pharmacological treatment, was zero. A good genotype-phenotype correlation was found in individuals treated with bupropion, but not in those treated with nicotine.

The patients reported satisfaction with the treatment; only one patient formulated with nicotine discontinued the drug due to gastrointestinal intolerance (nausea and vomiting).

Discussion

The phenotype of the smokers in the study, corresponding to middle-aged individuals, with male predominance, relatively high prevalence of cardiovascular risk factors (71%) and smoking initiation at 17 years of age, coincides with the reports of numerous studies.

The averages of years of cigarette smoking (~28 years), number of cigarettes consumed per day (~17), failed quit attempts (~4), and NDSS scores (~22) show a group of people with severe smoking characteristics, but motivated to quit smoking.

The retention rate achieved in this case series (71.4%) is similar or higher than that reported in other studies and corresponds to the 15 individuals who at the end of the eighth week of treatment had completely stopped smoking (7/15), or had only reduced cigarette consumption (8/15), which is also described, since 100% abstinence is almost never achieved (11). In any case, a reduction in cigarette consumption of 195 cigarettes/day in our case

series is clinically important and is in line with the harm reduction strategy for psychoactive drug use.

The fact that only one patient had to discontinue treatment due to nicotine intolerance, that there were no severe adverse reactions, and that four weeks after completion of medication no study participant relapsed, reflects the good safety margins of the two drugs used and reinforces the view that smoking cessation programs are relatively simple to implement, do not require resources or highly skilled personnel, and are cost-effective, although it is clear that relapse rates in smoking are high and increase over time (5).

The better therapeutic response to bupropion (7 of 8 patients) than to nicotine (7 of 13 patients) has been documented in some studies (12), although in others they find that nicotine and bupropion are equi-effective (6,13).

When including the genetic variable in the analysis of the results, we found that neither of the two CYP2A6 gene polymorphisms was associated with any of the phenotypic characteristics of the smokers, nor with the response to nicotine, since 50% of the patients with the native genotype (6/12) did not respond to the drug, which is a response rate similar to that reported in nicotine treatments that do not take genotype into account. Regarding this lack of phenotype-genotype correlation, there is no consensus since some studies find correlation and others do not (14-16).

On the contrary, in the case of bupropion, 7 of the 8 patients treated according to genotype (homozygotes or native heterozygotes for the CYP2B6 gene) successfully completed treatment, which is consistent with other reports (12,17) and supports the proposal that CYP2B6 genotype is a good predictor of response to this drug.

It is hoped that the results presented will generate interest for the formulation of more powerful research exploring the role of pharmacogenetics in the response to medications used in smoking cessation programs.

Conclusion

The inclusion of pharmacogenetic markers for the choice of nicotine or bupropion in a smoking cessation program can improve program adherence and drug tolerability and, in the case of bupropion, treatment effectiveness.

Legal Aspects

The study was approved by the Ethics Committee of the Universidad Tecnológica de Pereira. Written consent was obtained for genotyping, treatment, and publication of the results, preserving the confidentiality of

patient data. Copies of the signed consents are available for review by the Editor-in-Chief of this journal.

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Conflict of Interest

The authors declare that they have no conflicts of interest in relation to this study.

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