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BRIEF COMMUNICATION

Differential effects of transdermal nicotine on microstructured analyses of tics in Tourette's syndrome: an open study

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ABSTRACT

Background. The treatment of Tourette's syndrome (TS) is often unsatisfactory. However, there is some evidence that transdermal nicotine patch (TNP) application may improve tics of non-smoking TS patients who are refractory to haloperidol treatment.

Methods. In this open study we applied two 10 mg TNP for 2 consecutive days to four TS patients whose symptoms were not controlled by haloperidol and to a never-medicated TS patient, all of whom are non-smokers. The Yale Global Tic Severity Scale (YGTSS) and a quantified video-taped micro-structured analysis of tics (head-shake tics, eye-blinks, vocal tics, facial grimace and other body tics) were both carried out to assess the change after the application of TNP.

Results. TNP application significantly reduced the YGTSS by an average of 50%, with no reported side-effects, for up to 4 weeks but not 16 weeks, as compared with TNP-free period. Consistent with these results, the total counts of tics also showed a significant decrease for up to 4 weeks after the TNP application.

Conclusion. TNP application differentially affected individually quantified tics, which may suggest a differential role of nicotinic receptors in the generation of different tics.

INTRODUCTION

Tourette's syndrome (TS) is a chronic, familial neuropsychiatric disorder of unknown aetiology characterized by persistent motor tics and vocalizations. This life-long condition is the most severe form of the tic disorders, and is rather common. (The population incidence of TS, around 0·5/1000, is likely to be an underestimate (Robertson, 1989).) It is extremely disabling both socially and, in severe cases, functionally (for review see e.g. Robertson, 1989; Handley & Dursun, 1992).

At present, there is no effective treatment although the symptoms can be suppressed temporarily by a variety of psychopharmacological interventions, although with side effects and often a drug-induced deterioration in general functioning. Haloperidol and pimozide are the most widely used agents shown in controlled double-blind trials to reduce tic frequency, but at the doses required they can result in a rejection rate of up to 80% (Robertson, 1989; Handley & Dursun, 1992). Very recently, substantial improvement of tics has been reported after the acute application of the transdermal nicotine patch (TNP) in non-smoking TS patients whose symptoms cannot be controlled with haloperidol (Silver & Sanberg, 1993; Reveley *et al*. 1994; Dursun *et al*. 1994, 1995*a*). In addition to the reported significant improvement of tics as assessed by the Yale Global Tic Severity Scale (YGTSS) (Leckman *et al*. 1989), we also determined and compared the clinical change of individual tics with another method which is based on tic counts on a short,

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but structured, video-taped protocol. We used this additional method because: (i) this method of assessing tics yields highly reliable tic counts and meaningful changes in clinical state during clinical trials and is best suited for psychopharmacological challenge settings (Klein *et al.* 1994); and (ii) individual tics are differentially affected by treatments as they may be modulated by different neurotransmitter systems (Handley & Dursun, 1992).

METHOD

Ethical issues

The project is approved by the Local Ethics Committee and signed informed consent was obtained from each participant.

Application of TNP

TNP (10 mg, Pharmacia) was applied to clean, dry skin on the right or left arm deltoid areas. The first TNP was removed 24 h after application and this was followed by the application of the second TNP. The second TNP was also removed 24 h later.

Inclusion criteria

Patients ($N = 5$) were eligible for the study if: (i) they were neither active nor passive non-smokers; (ii) they were devoid of active or progressive haematological, renal, hepatic, endocrine, cardiac or pulmonary disease; and (iii) they did not have a history of epilepsy, drug addiction or alcoholism.

Diagnostic and clinical assessments

Diagnosis of TS was made according to the DSM-III-R (APA, 1987) criteria. All patients were male, mean age $\pm$ S.D. $= 30{\cdot}6 \pm 16$; one patient was drug-naive (patient A) and the others were on haloperidol medication at different doses i.e. 4 (Patient B), 8 (Patient C), 3·5 (Patient D), 6 (Patient E) mg/day for at least 6 weeks and their medication continued at the same doses during the study. The duration (years) of TS was mean $\pm$ S.D. $= 24{\cdot}2 \pm 15{\cdot}1$ (range: 9–43). Assessments of tic severity were based on the YGTSS (Leckman *et al.* 1989). Five ordinal scales (number, frequency, intensity, complexity and interference) for motor and vocal tics were used (max score is 50). The overall impairment for motor and vocal tics were also rated and noted (Table 1). The YGTSS ratings were carried out blind to patient medication status, from video-taped interviews.

Video-tape recording protocol and the video-taped micro-structural assessments

The video-tape recording system was designed to record tics accurately and minimize volitional suppression of tics when patients are conscious of being scrutinized (Goetz *et al.* 1987). Patients were seated comfortably in a very quiet room (specially designed for recording purposes), facing the camera and feet on floor. The examiner (who was in a separate room) observed and recorded the patients by means of a monitor situated adjacent to, but separate from, the recording room. The quantitative micro-structural assessments of the tics were analysed from video-tapes blind to patient medication status. The patients were all video-taped in the same setting and under the same conditions. All the tics, including excessive eye-blinks, body and head-shake tics, facial grimaces and vocalizations were video-taped and counted for 15 min under three different conditions (each for 5 min): (i) sitting quietly; (ii) reading standard text aloud; and (iii) written calculations (see e.g. Klein *et al.* 1994). The results of the 15 min individual tic total counts are expressed as means $\pm$ standard deviation (S.D.) except for eye-blinks, which are presented as counts per minute (Table 1). In addition, the sum of all the tic counts (except eye-blinks because of the physiological counts) are presented.

Frequency of the video-tape recordings and design of the assessments

The initial pre-TNP YGTSS ratings and the video-tape recordings were carried out 1 week prior to the first TNP application. These assessments were also carried out; (i) 24 h after the first TNP application; (ii) 4 weeks after the first TNP application; and (iii) 16 weeks after the first TNP application. The video-tapes were presented in random order to the assessors. Inter-rater reliability for the behaviours analysed was at least 0·82 (range: 0·82–0·93) (inter-class correlation coefficient), respectively.

Statistical analyses

The non-parametric Wilcoxon Signed Rank test was used to compare the significance of tic change after TNP application.

Table 1. *Long-lasting differential effects of TNP on individually quantified tics and YGTSS in Tourette's syndrome*

	Patient	Head-shake tics	Eye blinks (per min)	Vocalization	Facial grimace	Other body tics	Sum of total tics (except eye blinks)	YGTSS
TNP-free period	A	14	24	3	16	4	37	26 (20)
	B	93	21	40	83	17	233	40 (30)
	C	18	20	2	21	31	72	31 (20)
	D	26	26·6	10	91	28	155	35 (40)
	E	30	22·6	13	66	20	129	33 (30)
	Means ± S.D.	36·2 ± 14·5	22·9 ± 2·6	13·6 ± 6·9	55·4 ± 15·6	20 ± 4·8	125·2 ± 34	33 ± 2·4 (28 ± 8·4)
24 h after TNP	A	0	30	1	25	2	28	
	B	36	16	11	45	5	97	
	C	7	14·3	0	10	14	31	
	D	10	20·6	1	30	6	47	
	E	10	16	1	24	3	38	
	Means ± S.D.	12·6 ± 6·2*	19·4 ± 6·4	2·8 ± 2·1*	26·8 ± 5·6	6·0 ± 2·1*	48·2 ± 12·7*	Not assessed
4 weeks after TNP	A	2	13	0	4	1	7	8 (10)
	B	34	17	8	40	8	90	21 (20)
	C	11	14·7	3	9	18	41	21 (10)
	D	18	20	3	28	10	59	18 (10)
	E	21	17·3	1	23	5	50	16 (10)
	Means ± S.D.	17·2 ± 5·3*	16·4 ± 1·2*	3·0 ± 1·4	20·8 ± 6·5*	8·4 ± 2·9*	49·4 ± 13·5*	16·8 ± 2·4* (12 ± 4·5*)
16 weeks after TNP	A	8	18	3	13	3	27	21 (20)
	B	71	19·4	29	78	19	197	34 (30)
	C	14	17·7	2	15	20	51	27 (20)
	D	30	26	9	88	26	153	34 (20)
	E	28	20·6	12	60	20	120	33 (30)
	Means ± S.D.	30·2 ± 11·0	20·4 ± 1·5*	11·0 ± 4·9	50·8 ± 15·7*	17·6 ± 3·9	109·6 ± 31·6	29·8 ± 2·6 (24 ± 5·5)

*, $P < 0{\cdot}05$ Wilcoxon Signed Rank Test, numbers in parentheses indicate overall impairment for motor and vocal tics.
Medication status: Patient A, drug naive; Patients B–E were all on haloperidol at doses of 4, 8, 3·5 and 6 mg/day respectively.
Data on total number of tics: total number of tics recorded in 15 min during three different tasks (sitting quietly, reading a standard text aloud, written calculations).

RESULTS

The details of results of this study are shown in Table 1. In the text below numbers in brackets indicate percentage reduction of the values as compared with the TNP-free period. The application of TNP resulted in significant reductions in head-shake counts 24 h (65·2%) and 4 weeks (52·5%) but not after 16 weeks (16·6%) of TNP application. There was also a significant reduction in eye-blink counts 4 weeks (28·6%) and 16 weeks (11%) after TNP application, but not after 24 h although there was a trend towards some reduction (15·3%).

Significant reduction in vocalization was present only 24 h (79·4%) after TNP application but not after 4 weeks (78%, two-tailed $P = 0{\cdot}0796$) or 16 weeks (19·1%). Significant reductions in facial grimace were present both 4 weeks (62·4%) and 16 weeks (15·7%) after TNP application but not after 24 h (51·6%). Other body tics were significantly reduced after 24 h (70%) and 4 weeks (58%) but not after 16 weeks (12%). Significant reductions were also present in the total sums of tics (except eye blinks) 24 h (61·5%) and 4 weeks (60·5%) after TNP application but not after 16 weeks (12·4%).

Similarly, significant reductions were seen in the YGTSS assessments 4 weeks (49·1%) but not 16 weeks (9·7%) after TNP application. None of the patients reported any side-effects after TNP application, however visual analogue scales regarding the severity of their tics and their parents/spouses indicated significant improvement after TNP application (data not shown).

It is also important to note that none of the patients had a co-morbid diagnosis of obsessive–compulsive disorder, attention deficit hyperactivity disorder or major depression, which may have influenced the tic severity, rating and overall impairment.

DISCUSSION

In this study the effects of TNP on tic severity and frequency in five TS patients were assessed by the YGTSS and micro-structured video-tape analyses. TNP application significantly reduced the YGTSS by an average of 50% with no reported side-effects for up to 4 weeks but not 16 weeks, as compared with TNP-free period. The total tic counts also showed a significant decrease for up to 4 weeks (but not 16 weeks) after the TNP application; this is in good agreement with the improvement of the YGTSS. This dose regimen appears to be effective in improving the tics of non-smoking TS patients who have not received medication and also whose symptoms cannot be controlled with antipsychotic drugs. The TNP may be effective both as a sole treatment or an addition to haloperidol.

The mechanism of the potentiation of haloperidol effects by nicotine and its long-lasting effects in TS patients is not clear. Since the principal neurochemical systems implicated in the pathogenesis of TS have been the dopaminergic, serotonergic, noradrenergic (Handley & Dursun, 1992), and nicotinic (this study); we suggest the following four possible explanations for the efficacy of TNP in TS.

(*i*) *Hypersensitive nicotinic receptors in TS* Prolonged desensitization of brain nicotinic receptors as a result of administration of nicotine via TNP over 48 h continuously, which may then take over 4 weeks to resensitize. However, to test this hypothesis further, the effects of rapid and bolus administration of nicotine (such as by nasal nicotine spray) on the tics of TS require investigation.

(*ii*) *Hypersensitive postsynaptic dopamine receptors in TS* If this were the case, administration of nicotine via TNP over 48 h would desensitize the hypersensitive dopamine receptors (Prasad *et al*. 1989), possibly as a result of acutely increased dopamine release (Balfour, 1989).

(*iii*) *Hypersensitive 5-HT receptors* (*possibly the 5-HT$_{2A}$ subtype*) An animal model of TS, in which hypersensitive 5-HT$_{2A}$ receptors play a crucial role, has been suggested and furthermore, buspirone, a 5-HT$_{1A}$ receptor partial agonist, has been reported to improve the tics of TS (for review see Handley & Dursun, 1992; Dursun *et al*. 1995*b*). Chronic nicotine intake does not alter the 5-HT$_{2A}$ receptors, but it increases the density of the 5-HT$_{1A}$ receptors (Balfour, 1989). Since there are functional interactions between the 5-HT$_{1A}$ and the 5-HT$_{2A}$ receptors and since 5-HT$_{1A}$ receptor activation inhibits the 5-HT$_{2A}$ receptors (Dursun & Handley, 1993) it is also possible that nicotine blocked the hypersensitive 5-HT$_{2A}$ receptors by increasing the activity of

inhibitory 5-HT_{1A} receptors (Dursun *et al.* 1995*a*).

(*iv*) *Central hypernoradrenergic state* The primary evidence that the noradrenergic system is involved in TS comes from the reported efficacy of clonidine, a selective α_2-adrenoceptor agonist, but the results of the biochemical studies related to noradrenergic systems are controversial (for review see Handley & Dursun, 1992). Indeed, similar to clonidine effects, continuous infusions of nicotine from subcutaneous minipumps significantly decreased noradrenaline in the rat (Balfour, 1989).

The TNP application differentially affected individually quantified tics. This in turn suggests a differential role for the nicotine receptors involved in the generation of the tics of TS. Alternatively, indirect involvement of other neurotransmitter systems in the generation of some tics may be suggested. Indeed, on the basis of some clinical and extensive preclinical data, the possibility that each type of tic in TS is modulated by a different neurotransmitter/receptor system, has been suggested (Handley & Dursun, 1992; Dursun & Handley, 1994). Recently, the 5-HT_{2A} receptor-mediated head-shake tics in mice have been suggested as a possible animal model of TS (Handley & Dursun, 1992). Indeed, morphologically, head-shake tics analysed in this study were very similar to rodent head-shake tics; thus, it may be possible that 5-HT_{2A} receptors modulate human head-shake tics (Handley & Dursun, 1992). There is also evidence that eye-blinking is modulated by both the dopamine-D_2 and 5-HT_{2A} receptors (Karson, 1988; Dursun & Handley, 1991) and, therefore, the mechanism by which the TNP application decreased the increased blink-rate in our patient sample is unclear. The psychopharmacology and receptors involved in the generation of vocalization and facial grimace in TS are unknown so, at present, it is difficult to speculate on precisely how vocalization and facial grimace were improved after TNP application. Nevertheless, it appears that abnormalities of multi-neurotransmitter systems are involved in TS, alternatively, primary dysfunction of the second messengers may explain the reported multi-neurotransmitter abnormalities in this syndrome.

However, this was an open study and therefore confirmatory double-blind, placebo-controlled dose-response studies are required to investigate the effects of TNP on individual tics and to determine and establish the efficacy of TNP in TS.

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