Nicotine replacement therapy and ischaemic stroke

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INTRODUCTION

Smoking is a known risk factor for stroke. Nicotine replacement therapy (NRT) is advocated as a means of aiding smoking cessation. The use of NRT has been shown by Silagy et al (2004) to be efficacious. Studies by Benowitz and Gourlay (1997) into the safety of NRT have concluded it to be safe in patients with known cardiovascular conditions, although its role in cerebrovascular disease has not been extensively studied.

This report will illustrate the case of a patient who developed an ischaemic stroke shortly after starting NRT in patch form, but who also continued to smoke.

The authors will also present a further 14 cases (12 previously unpublished) of cerebrovascular disease shortly following (mean 40 days) use of NRT, as reported to the Medicines and Healthcare products Regulatory Agency (MHRA) (formerly Medicines Control Agency), and two cases reported by Jackson (1993) and Pierce (1994). The possible role of NRT in causing stroke in association with smoking will also be discussed.

DISCUSSION

The role of nicotine in ischaemic stroke is controversial. Most studies on the safety of nicotine centres on its potential cardiovascular toxicity. As discussed by Benowitz and Gourlay (1997), nicotine, whether inhaled or absorbed transdermally, has a number of adverse effects on the vascular system. Nicotine increases myocardial oxygen demand through its adrenergic haemodynamic effects, may cause platelet activation and may cause vasoconstriction through its possible role in the inhibition of prostacyclin production.

In 2002, a review outlined the possible role of nicotine in ischaemic stroke and various novel mechanisms, in which nicotine may act on the cerebrovascular architecture (Hawkins et al, 2002). Nicotine is known to exert complex effects on cerebrovascular blood flow and the integrity of the blood brain barrier, causing alteration of brain signalling pathways and cerebral endothelial function. Some of these factors may have shared pathophysiology with nicotine's known cardiovascular effect, but others are certainly novel and exclusive to the cerebrovascular system.

The question raised was whether the observed data presented of ischaemic stroke in association with NRT in the presence or independently of smoking could be the result of coincidence in a high-risk population.

The safety of NRT investigated in a recent meta-analysis by Greenland et al (1998) concluded that there were no excess adverse events (myocardial infarction, tachycardia, arrhythmia, angina or stroke) in patients using transdermal nicotine patches. However, these investigators cautioned that their meta-analysis lacked the necessary power to exclude such risks with statistical significance because of the exclusion criteria of most studies.

The Lung Health Study (Murray et al, 1996) demonstrated that there was no excess overall cardiovascular risk in concomitant smokers on NRT, but this study included only a small number of patients with stroke. Biologically, modest increases in plasma nicotine concentrations are known to occur when transdermal nicotine is combined with smoking, as shown by Foulds et al (1992).

It is evident that causality cannot be inferred from anecdotal case reports and adverse incidents reported to MHRA. However, the fact that ischaemic events occurred in 14 patients shortly following NRT (mean 40 days treatment) suggests this may not be coincidental.

CASE REPORT

A 52-year-old right-handed businessman developed sudden onset of non-fluent dysphasia, weakness and sensory disturbance on the right side of his body 3 weeks after starting Nicorette patches (21 mg). He continued to smoke 3–5 cigars a day while on these patches. The patient had a history of depression and excessive alcohol intake.

Examination confirmed an expressive dysphasia with verbal fluency limited to five words beginning with 'C' or 'S' but with no problems in comprehension, naming or praxis. Rapid alternating movements were impaired on the right and reflexes were brisker on the right side, although both planters were flexor. Cardiovascular and general examination was unremarkable.

Magnetic resonance imaging (MRI) brain scan confirmed a left anterior cerebral artery territory infarct. The following blood tests were normal or unhelpful: erythrocyte sedimentation rate (ESR), C-reactive protein, protein culture and sensitivity, antithrombin, antiphospholipid coagulant, treponemal serology, thyroid screen and autoantibody screen. The patient was found to have mildly raised triglyceride (2.42 mmol/l) and low density lipoprotein (LDL) cholesterol (4.61 mmo/l). Electrocardiogram (ECG), echocardiography and carotid Dopplers were all normal.

Two previous cases of stroke following nicotine patches have been reported by Jackson (1993) and Pierce (1994). In addition, the Medicines and Healthcare products Regulatory Agency (MHRA) have received 12 further cases of cerebrovascular disorders following nicotine replacement (*Table 1*).

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TABLE 1.
Summary of cases of cerebrovascular disease following use of nicotine replacement therapy (NRT).

Patient	Sex	Age (years)	Mode of NRT	Dose/day	Duration of NRT to event	Description of event
1	M	59	Chewing gum	2–4 mg	7 months	Transient ischaemic attack when NRT dose doubled
2	F	60	Transdermal Patch	17.5–35 mg	3 months	Subarachnoid haemorrhage 1 month after stopping NRT
3	M	45	Patch	-	1 month	Ischaemic stroke
4	F	63	Patch	-	11 days	Ischaemic stroke
5	F	53	Patch	-	—	Ischaemic stroke
6	F	29	Patch	-	3 days	Cerebral haemorrhage; angiogram showed no underlying causes
7	F	40	Patch	-	1 week	Cerebellar infarction
8	F	28	Patch	-	—	Ischaemic stroke
9	F	54	Patch	30 mg	40 days	Ischaemic stroke
10	F	60	Patch	21 mg	17 days	Ischaemic stroke
11	F	-	Patch	21 mg	6 days	Ischaemic stroke
12	M	69	Patch	21 mg	2 months	Ischaemic stroke (+concurrent smoker)
13	F	62	Patch	30 mg	22 days	Transient cerebral artery spasm
14	M	40	Patch	10 mg	4 hours	Subarachnoid haemorrhage and 17 days later middle cerebral artery spasm 4 hours after transdermal patch

Patients 1–12 were cases reported to the Medicines and Healthcare products Regulatory Agency (MHRA). Cases 13 and 14 were case reports found on literature (Jackson, 1993 and Pierce, 1994 respectively)

CONCLUSIONS

NRT may be associated with ischaemic stroke and cerebro-vasospasm, although the risk of stroke is probably higher in those who continue to smoke on NRT.

Notwithstanding this observation, the benefits of smoking cessation using NRT outweigh all such risks. However, patients and their physicians need to be better informed about the use of NRT. HM

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