

## PAPERS AND SHORT REPORTS

## Topical minoxidil in the treatment of alopecia areata

DAVID A FENTON, JOHN D WILKINSON

## Abstract

A modified double blind crossover study was performed to assess the effect of 1% topical minoxidil as compared with placebo in 30 patients with alopecia areata and alopecia totalis. The active preparation produced a highly significant incidence of hair regrowth. A cosmetically acceptable response was noted in 16 patients. No side effects were seen.

The study confirmed that topical minoxidil will induce new hair growth in alopecia areata but that it is less likely to do so in more severe and extensive disease. Furthermore, patients with alopecia universalis and totalis may not respond at all. Nevertheless, as compared with other drugs minoxidil applied topically is relatively non-toxic, is easy to use, and has no systemic or local side effects.

## Introduction

Many drugs may cause hypertrichosis<sup>1</sup>; in some, such as the psoralens and benoxaprofen, the mechanism is probably phototoxic, whereas in others it may be due to hormonal modulation or vasodilatation. In most cases, however, the mechanism is unknown.

Minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) is a potent oral vasodilator which acts directly on vascular smooth muscle and is usually reserved for resistant hypertension. Given systemically it appears to be one of the few drugs capable of converting vellus to terminal hair.<sup>2</sup> Hypertrichosis occurs in practically all patients treated with minoxidil<sup>3</sup>; the increased hair growth usually affects the forehead, temples, eyebrows, forearms, and even the nose.<sup>4</sup> In 1980 Zappacosta reported reversal of male pattern alopecia in a patient receiving oral

minoxidil for hypertension.<sup>5</sup> Isolated case reports subsequently suggested that minoxidil applied as a topical agent might be efficacious in alopecia areata.<sup>1,6</sup>

In view of the unpredictable course of alopecia areata and its tendency for natural resolution we carried out a modified double blind crossover trial to assess the effects of topical minoxidil and placebo in patients suffering from alopecia areata and alopecia totalis.

## Patients and methods

Thirty patients with alopecia areata were studied. They consisted of patients already being seen as outpatients and an uninterrupted sequence of patients attending the outpatient department. Ages ranged from 6 to 85 years (median 43.4 years); 13 were female and 17 male. The age at onset of alopecia ranged from 2 to 85 years (median 30.2 years), and the total duration of disease before entry to the trial ranged from three months to 42 years (median 5 years). Most of the patients had extensive patchy alopecia areata, three had ophiasis pattern, and nine had alopecia totalis or universalis.

Patients were allocated to one of four treatment groups: (1) active ointment, (2) placebo ointment, (3) active lotion, (4) placebo lotion. All four preparations were made on a one off dispensing basis to the following formulas<sup>7</sup>: (1) 1% minoxidil ointment—ground minoxidil tablets 10 mg × 20, Unguentum Merck to 20 g; (2) placebo ointment—lactose 2.5 g, Unguentum Merck to 20 g; (3) 1% minoxidil lotion—ground minoxidil tablets 10 mg × 20, propylene glycol 2 ml, distilled water 4 ml, industrial spirit 95% to 20 ml; (4) placebo lotion—lactose 2.5 g, propylene glycol 2 ml, distilled water 4 ml, industrial spirit 95% to 20 ml.

The 1% minoxidil lotion was prepared to match that used by Weiss *et al.*<sup>6</sup> Both active preparations were the same as those used by Fenton and Wilkinson.<sup>1</sup> The patients applied the allocated preparation to the affected areas (thinly and evenly) twice daily. The maximum daily amount applied was based on the minimum oral dose of 5 mg twice daily, and patients used a maximum measured dose of 0.5 ml of the lotion and 0.5 g of the ointment twice daily. Patients were allocated to active or placebo, lotion or ointment according to a random code. After 12 weeks of treatment non-responders were crossed over to the other preparation in the same base. Patients who had apparently responded to the first preparation continued with that treatment.

All patients were seen before treatment and at monthly intervals. The following variables were recorded: pulse and blood pressure; activity or inactivity of the disease; presence of hair regrowth, and whether this was vellus or terminal and patchy or complete; any side effects; serial photography; presence or absence of a personal or

Department of Dermatology, Wycombe General Hospital, High Wycombe, Bucks

DAVID A FENTON, MB, MRCP, registrar in dermatology  
JOHN D WILKINSON, MB, MRCP, consultant dermatologist

Correspondence to: Dr David A Fenton, Department of Dermatology, St Thomas's Hospital, London SE1.

family history of alopecia areata or vitiligo or any other organ specific autoimmune disease; presence of a family history of asthma, eczema, or hay fever; serum antibodies for antinuclear factor, and smooth muscle, mitochondrial, gastric parietal cell, reticulin, and thyroid antibodies; presence or absence of nail dystrophy.

## Results

At three months there was a significant difference in response between the active and placebo treatment groups (table I) ( $p < 0.01$ ; Fisher's exact test for two tailed hypothesis). After three months the non-responders were crossed over. From the placebo ointment group four out of five non-responders subsequently responded to the active formulation after crossover and one withdrew; in the placebo lotion group six out of six non-responders subsequently responded to the active lotion and two withdrew. The non-responders from the active lotion and ointment groups remained non-responders after crossover.

After the second three months of the trial there was again a significant difference in effect between the active and placebo treatments ( $p < 0.01$ ; Fisher's exact test for two tailed hypothesis). Overall there was a statistically significant difference in response between patients treated with the active and placebo preparations (table I) ( $p < 0.001$ ;  $\chi^2$  test with continuity correction)—that is, 21 out of 26 patients receiving the active preparations responded (81%) as opposed to one out of 19 receiving placebo (5%).

Although the response appeared to be marginally quicker and better in those using the ointment, there was no statistically significant difference between lotion and ointment. In most patients hair regrowth was seen within six weeks of starting the active formulation.

There appeared to be an appreciable difference in response between patients with patchy alopecia areata and those with alopecia totalis and universalis (table II). The more extensive the disease the worse the prognosis, but patients with ophiasis pattern of hair loss responded better than expected. Neither a personal or family history of atopy nor a family history of alopecia areata appeared adversely to affect the response or prognosis but the presence of nail dystrophy did seem to. Neither total duration of disease nor duration of current episode of disease appeared adversely to affect the response.

At the end of six months 22 patients had regrown some hair: three had only vellus hair, three had hair which was longer than vellus but not quite normal terminal hair ("intermediate" hair), and 16 had cosmetically acceptable terminal hair (table III; figure). Three patients withdrew after three months; all had been allocated placebo, and none had regrowth of hair. One patient had complete spontaneous hair regrowth while receiving placebo.

In the active ointment group the two non-responders were both atopics with alopecia universalis. Of the non-responders in the active lotion group, one had alopecia universalis and one alopecia totalis.

Regrowth of eyelashes and eyebrows occurred in three patients

TABLE I—Numbers of patients responding at three and six months

	No of patients showing some response at three months	Overall response rate in 27 patients at six months*
Placebo ointment	0/6	6.7%
Placebo lotion	1/9	
Active ointment	8/9	73.3%
Active lotion	3/6	
Total No of responders	12	22

\*Three other patients withdrew at end of first three months, two with patchy alopecia areata and one with alopecia universalis; all had been receiving placebo.

TABLE II—Analysis of patients entering trial (responders and non-responders)

	On entry	Responders	Non-responders
Total No	30		
Atopic	12	7	5
Alopecia areata	21	18	1
Alopecia totalis	5	2	3
Alopecia universalis	4	3	3
Family history of alopecia areata	4	2	2
Hypertension		2	
Nail dystrophy	8	2	6
Ophiasis pattern (out of 21)	3	3	
Serum autoantibodies	5	3	2

TABLE III—Patterns of hair regrowth

Terminal hair	.. ..	16	Complete regrowth	.. ..	21
Vellus hair alone	.. ..	3	Patchy regrowth	.. ..	2
Intermediate hair	.. ..	3	Regrowth at sites distant to treatment	.. ..	3



Typical appearances of alopecia areata before and after minoxidil.

who treated only the scalp with the active formulation. Of those who regrew vellus hair alone, two had used active lotion and one active ointment; all three were atopic, and one had ophiasis pattern of hair loss.

## Discussion

There have been many treatments suggested for alopecia areata. Most are unsatisfactory either because of side effects or because the hair regrowth is vellus only and therefore cosmetically unacceptable. Often the alopecia returns once the treatment is discontinued.

Our initial results show that topical minoxidil can induce regrowth of hair in a substantial proportion of patients suffering from alopecia areata. Out of 26 patients, 21 showed some response, though in only 16 was this cosmetically acceptable. Nevertheless, as compared with most other treatments topical minoxidil appears to be relatively non-toxic, is easy to use, and is free from any local or systemic side effects. In none of the patients treated was there any change in pulse rate or blood pressure or any cutaneous side effect.

In the study of Weiss *et al* local hair regrowth occurred in two out of three patients within four to six weeks of treatment.<sup>6</sup> A similar proportion responded in our study.

Hypertrichosis induced by minoxidil bears close resemblance to that seen with diazoxide.<sup>8</sup> Although these agents are not related chemically, both block calcium uptake via the cell membrane within the vascular smooth muscle cells<sup>9</sup> and both are potent vasodilators, acting primarily on systemic arterioles and having little effect on veins. This produces a decreased arteriolar resistance<sup>10</sup> and reduced cardiac afterload, thus causing an increase in blood flow. Burton *et al*<sup>8</sup> suggested that an increase in cutaneous perfusion may be responsible for the hypertrichosis, and indeed there is a noticeable increase in cutaneous blood flow with minoxidil.<sup>11</sup>

Although it would be easy to accept that the mechanism of action of hair regrowth seen with topical minoxidil might be due to vasodilatation, control studies using topical glyceryl trinitrate have failed to produce hair regrowth, suggesting that arteriolar rather than venular dilatation is required. Hair regrowth at sites distant to those treated (eyebrows and eyelashes in three patients) might also be due to a systemic effect of absorbed minoxidil,<sup>1</sup> but similar observations have been made in patients with alopecia areata treated with local 2,4-dinitrochlorobenzene and primula sensitisation. The hypertrichosis does not appear to be hormonal in origin since plasma

testosterone and urinary hydroxysteroid and ketosteroid concentrations are normal during minoxidil treatment, thereby excluding androgenic stimulation.<sup>12 13</sup>

Microscopical examination of hair grown during systemic treatment with minoxidil shows an intermediate type of hair with pigmentation and intermittent medullation and a normal shaft.<sup>4</sup> Some of the hairs grown during treatment with topical minoxidil were classified as intermediate in type, being longer than vellus hair but too fine and thin to be terminal hair (table III). Some patients' regrowth never progressed beyond this intermediate phase and was not cosmetically acceptable, while others went on to develop terminal hair.

Although we have little doubt that topical minoxidil can induce new hair growth in patients suffering from alopecia areata, those with more severe and extensive disease have a worse response and those with alopecia universalis and alopecia totalis are less likely to respond. It is not possible at this stage to say whether treatment with minoxidil will affect eventual prognosis. The few post-treatment biopsies that we have performed suggest that the disease is still active despite regrowth of hair. Only time will tell whether this treatment will find an established place in the management of patients with alopecia areata or whether hair that has regrown will be retained when treatment is discontinued. Topical minoxidil, however, appears to have at least two virtues: firstly, it now appears clear that it can induce some hair regrowth and may be a useful stopgap measure in patients suffering from alopecia areata, to see them through until spontaneous resolution occurs; and, secondly, it appears to be relatively safe, with no topical or systemic side effects having been encountered during this study.

We are grateful to Mr J R Ennis, of the Oxford Regional Health Authority, for valuable help with the statistical analysis of this paper.

## References

- Fenton DA, Wilkinson JD. Alopecia areata treated with topical minoxidil. *J R Soc Med* 1982;**75**:963-5.
- Rook A, Dawber R. *Diseases of the hair and scalp*. Oxford: Blackwell Scientific, 1982:362.
- Dargie JH, Dollery CT, Daniel J. Minoxidil in resistant hypertension. *Lancet* 1977;ii:515-8.
- Burton JL, Marshall A. Hypertrichosis due to minoxidil. *Br J Dermatol* 1979;**101**:593-5.
- Zappacosta AR. Reversal of baldness in patient receiving minoxidil for hypertension. *N Engl J Med* 1980;**303**:1480-1.
- Weiss VC, West DP, Mueller CE. Topical minoxidil in alopecia areata. *J Am Acad Dermatol* 1981;**5**:224-6.
- Lomas SM. Minoxidil ointment and liquid. *Pharmaceutical Journal* 1982;**229**:6190:193.
- Burton JL, Schutt WH, Caldwell IW. Hypertrichosis due to diazoxide. *Br J Dermatol* 1975;**93**:707-11.
- Chidley CA, Gottlieb TB. The pharmacologic basis of antihypertensive therapy: the role of vasodilator drugs. *Prog Cardiovasc Dis* 1974;**27**:99-113.
- Lowenthal DT, Afrime MB. Pharmacology and pharmacokinetics of minoxidil. *J Cardiovasc Pharmacol* 1980;**2**:suppl 2:93-106.
- Humphrey SJ, Wilson E, Zins GR. Whole body tissue blood flow in conscious dogs treated with minoxidil. [Abstract.] *Fed Proc* 1974;**33**:583.
- Earhart RN, Ball J, Nuss DD, et al. Minoxidil induced hypertrichosis: treatment with calcium thioglycolate depilatory. *South Med J* 1977;**70**:442-5.
- Ryan JR, Jain AK, McMahon FG. Minoxidil treatment of severe hypertension. *Current Therapeutic Research* 1975;**17**:55-6.

(Accepted 12 July 1983)

# Mortality among British veterinary surgeons

L J KINLEN

## Abstract

**A total of 3440 veterinary surgeons resident in Britain were followed up from 1949-53 until 1975. A roughly twofold increase in mortality from suicide was observed and also a decreased mortality from respiratory diseases. There was no excess of deaths from leukaemia or other cancers as recently reported from the United States and as implied by the hypothesis that veterinary surgeons are unusually exposed to oncogenic viruses.**

## Introduction

Veterinary surgeons are likely to be more than usually exposed to the viruses that cause Marek's disease, feline lymphomas, bovine lymphosarcoma, and other animal tumours. If any such animal viruses caused cancer in man an increased mortality from cancer might occur among veterinary surgeons. I therefore carried out a prospective study of mortality among British veterinary surgeons.

## Methods

With the cooperation of the Royal College of Veterinary Surgeons information was abstracted from its records for 1949 and 1950 of all registered veterinary surgeons resident in Britain. Because of the possibility that young veterinary surgeons might be at increased risk of leukaemia the study group was extended to include recently qualified graduates who registered in the years 1951-3. The details abstracted included name, date of birth (when available), university of graduation, and date of registration. Date of birth was available for only a small proportion of individuals and had usually to be sought from the relevant university.

Details of deaths that had occurred among the study population before the end of 1975 were obtained from the obituary lists of the Royal College of Veterinary Surgeons, which are published regularly, and copies of the death certificates were obtained. In the case of veterinary surgeons who were no longer registered but who had not been notified to the Royal College of Veterinary Surgeons as having died, their status up to the end of 1975 was determined with the help of local colleagues and also the Office of Population Censuses and Surveys through the National Health Service Register. Again, any relevant death certificates were traced. Details of emigration among the study group were noted as indicated in the records of the Royal College of Veterinary Surgeons, which show the current address of all registered members. In addition, the National Health Service Register was able to give the date of emigration of certain former members of the college.

The number of person years at risk was calculated for each sex by five year age group and calendar year up to the end of 1975, periods spent abroad being excluded. Expected numbers of deaths from different causes were calculated by multiplying the person years in each category of sex, age, and calendar period by the corresponding

Cancer Research Campaign Cancer Epidemiology Research Group,  
University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE

L J KINLEN, FRCP, director of group and Gibb fellow