Topical Minoxidil for Extended Areate Alopecia

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A double-blind cross over study on the effect of 3 months' treatment with 1% topical minoxidil on 23 individuals with alopecia areata was performed. Thirteen of the patients showed some increase in terminal hair growth, the difference between the number of responders to placebo and minoxidil lotion being significant (p<0.005). However, in one case only, the result was cosmetically satisfying. In two male patients the blood pressure increased coinciding with the withdrawal of the minoxidil lotion. Key words: Alopecia totalis; Alopecia universalis; Topical treatment; Withdrawal hypertension. (Received May 29, 1984.)

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Minoxidil (2,4-diamino-6 piperidinopyrimidine-3 oxide) is a potent antihypertensive drug. It is a peripheral vasodilator, especially enhancing the cutaneous blood flow. It does not reduce the blood pressure of normotensive individuals (1). Side effects of systemic minoxidil are hypertrichosis, fluid retention, reflex cardiac stimulation, ECG-changes, angina pectoris, tachycardia, nausea, fatigue, dyspnoea and gynecomastia (2, 3). The hypertrichosis which occurs over the forehead, periorbital area, ears, face, extremities and lower back in at least 80% of the patients slowly diminishes after discontinuation of the drug (4). The cutaneous side effects are generalized papular eruption (2), pigmentation changes (3), coarsening of the skin, flushing, prickling of the skin, bullous eruptions and pseudoporphyria. Besides hypertrichosis colour changes of the hair and alopecia have been reported associated with minoxidil treatment (5). Stimulated by case reports on regrowth of hair in baldness during systemic minoxidil treatment (6, 7), topical application of minoxidil has been introduced for treatment of alopecia (1, 8).

The present report concerns a double-blind cross over study on the effect of 1% minoxidil lotion in extended alopecia of areate type in 23 patients.

MATERIAL AND METHODS

23 out-patients—10 women and 13 men, aged 12-57 years, median 29—with extended alopecia of areate type (areata 4, subbotalis 5, totalis 2, subuniversalis 5, universalis 7) with hair disease duration from ½-23 years, median 4.5 years, were studied. Each patient was provided with either 1% minoxidil lotion (ground minoxidil tablet 1%, propylene glycol 10%, aqua purificata 20%, spiritus fortis onto 100%) or placebo lotion (microsized cellulose 11.7%, maize starch 5%, propylene glycol 10%, aqua purificata 20%, spiritus fortis onto 100%). The patients were instructed, on having shaken the minoxidil lotion to apply 0.5 ml (corresponding 5 mg ground minoxidil) to the scalp in a thin layer every morning and evening for three months. After the night application a thin layer of petrolatum was applied for occlusive purposes according to Weiss et al. (1). Subsequent to 1-month wash-out period the alternative test/placebo lotion was used for the next three months. After a final 1-month wash-out period the trial was finished (Fig. 1).

The patient was seen with 1 month's intervals. At the start of the trial, by the end of month 3, 4, 7, and 8 increase in general hair growth was evaluated by clinical estimation combined with photographic registration. On these occasions also blood sedimentation rate, Hb, leucocytes, differential count, aspartate-aminotransferases, alkaline phosphatases, blood potassium and sodium and creatinine and urinalysis as well as ECG were checked. At every visit the blood pressure was measured three times with no less than 1 min interval after resting in horizontal position for at least 15 min. Changes in the
The experimental design for the randomized double blind cross over study.

Fig. 1. The experimental design: (+) placebo or minoxidil lotion. Blood pressure control and clinical follow-up once monthly. (I) Blood pressure control, clinical follow-up, laboratory screening, ECG, evaluation of changes in terminal hair growth on the scalp.

parameters were recorded as significant when exceeding the limits for normal values. All subjective complaints were noted.

For each patient personal atopy, organ specific autoimmune features and thyroid diseases as well as the modality of previous therapeutical approaches were recorded.

The final statistical evaluation of the therapeutical effect on hair growth was performed by the $X^2$ test with Yates' correction (MacNemar's test).

RESULTS

By the parameter increase in terminal hair growth on the scalp by clinical evaluation combined with photographic registration 13-7 women and 6 men out of the 23 patients—responded positively to the minoxidil lotion. In one patient regrowth occurred in the placebo period as well as in the minoxidil period. None responded to the placebo lotion exclusively. Ten patients showed increase in terminal hair growth only during the minoxidil period. The positive response to the minoxidil lotion versus placebo was highly significant ($p<0.005$).

However, clinically the quality and amount of the regrowing hair was not very impressive and one patient only—with areate affection—achieved cosmetically acceptable regrowth.

As a rule the limited regrowth occurred after 1 to 2 months' treatment. After withdrawal of the active lotion hair loss was seen in 4/13, complete stop of progression in hair growth in 5/13, and reduced progression in hair growth in 4/13, all after 1–2 months. A tendency towards better response in the less extended cases was noted (Fig. 2). The responders were of the same age as the non-responders (median ages 29 versus 27½ years), but the responders had a longer disease duration than the non-responders (median durations 6½ versus 3 1/3 years).

Blood pressure. One female and one male had from the start labile blood pressure at the upper limit of the normal value (170 systolic, 115 diastolic, and 150 systolic, 100 diastolic). In the female—an atopic, aged 36—the blood pressure normalized gradually over some months apparently independent of the phase of the trial. In the male, aged 45, the blood
pressure further increased (systolic 160–180, diastolic 105–115) after the minoxidil lotion was discontinued.

At the start of the trial one male, aged 43, who had had a heart attack 3 years before, showed a slightly elevated aspartate aminotransferase value (47 units/litre: normal values 10–40). One month after the minoxidil phase his blood pressure had increased from the previous normal value (140/90) to 180/120, and his aspartate aminotransferase level showed temporarily a further increase (asparate aminotransferase 91 U/l). Five months after the withdrawal of the minoxidil his blood pressure remained increased. 

Laboratory screening. No significant changes in the values were seen in any patient except those mentioned above.

ECG. From the start the ECG of all the patients was normal and no significant changes were observed.

Topical side effects. Four patients experienced temporarily scaling and slight itching with or without occurrence of acuminate papules or follicles, but in one patient only this occurred in the minoxidil period.

CONCLUSION AND DISCUSSION

The present study confirms that topical minoxidil as a 1% lotion is capable of producing some terminal hair regrowth in the areate type of alopecia even in long-standing and extended cases. However, within the observation period cosmetically acceptable hair growth was an exceptional event among these severely affected individuals. In 1981 Weiss et al. (1) experienced positive response to topical minoxidil on hair growth in alopecia areata and recently Fenton & Wilkinson (9) in a modified double-blind cross over study reported response to topical minoxidil in about 80% of their patients who were less severely affected than those here studied. Cosmetically acceptable regrowth was seen in 16 of 30 patients in their study.

Hitherto no serious side effects of topical minoxidil have been reported. Blood pressure elevation has been reported to occur as a rebound phenomenon following withdrawal of systemic minoxidil treatment (10). The amount of minoxidil topically applied in the present study and in the study of Fenton & Wilkinson (9) approximates 5 mg twice a day. However, it cannot be excluded that small amounts of minoxidil can be measured in the blood second to such topical application (8).

The development of the increase in the blood pressure in two males in the present study after the withdrawal of topical minoxidil might very well be coincidental. Concerning the patient with a marginally increased aspartate aminotransferase perhaps indicating decreased ability in the liver to metabolize minoxidil, it cannot be completely disregarded that the withdrawal of topical minoxidil might have played a causative role.

REFERENCES
Familial Alopecia areata—Genetic Susceptibility or Coincidence?

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Three generations of a non-consanguineous Italian family and 40 subjects suffering from alopecia areata (AA) and residing in Northern Italy were studied. There were 321 healthy control subjects of both sexes. Six family members from three generations were affected with alopecia universalis. The subjects were HLA-phenotyped using different HLA-A, B and C antigen specificities. No significant association was found between HLA-A, B and C antigens and AA patients at the population level. Segregation analysis showed that affected members shared a common haplotype, HLA-Aw32, B18,-.

Key words: Familial alopecia areata; HLA-phenotyping; Common haplotype. (Received September 19, 1984.)

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Alopecia areata (AA) is a common hair disease whose etiopathogenesis still remains to be elucidated. In the past few years some reports suggested the possibility that immunologic and genetic factors may play an important role in this disease (1-5). The familial incidence of AA is between 10% to 20% (6). To investigate further the importance of the genetic factors in the AA patients, we have studied 40 subjects with AA and particularly three generations of a non-consanguineous Italian family in which six members had alopecia universalis (AU). The HLA-Aw32, B18,- haplotype was noted in all affected members of three generations.

MATERIAL AND METHODS

Three generations of a non-consanguineous Italian family and other 40 AA patients residing in Northern Italy were studied. Of the six affected family members, five were men. All six affected members showed a similar clinical pattern of AA (alopecia universalis) (disease expressiveness) with early outcome in age, similar in all members (disease penetrance). Patients II-1 and II-2, on several occasions, had experienced the spontaneous regrowth and subsequent loss of their hair. All six patients showed nail pitting, a common occurring phenomenon in patients with AA. In our family there was no history of thyroid disease, vitiligo, rheumatoid arthritis, pernicious anemia, Addison's disease, diabetes mellitus connective tissue disorders or atopy. In AA patients HLA typing was performed by the microlymphocytotoxicity standard test for the following specificities: A1, A2, A28, A3, A9, A10, A11, A29, Aw30, Aw31, Aw32, Aw33, B5, B7, B8, B35, B12, B13, B40, B47, B41, B14, B18, B15, B16, B17, B21, B22, B27, Cw1, Cw2, Cw3, Cw4, Cw5, Cw6.

There were 321 healthy control subjects of both sexes. None had a history of AA. All subjects lived in the same geographical area as the patients and were typed at the same time as the patients. The significance of possible deviations between the frequencies observed in the patients and in the control subjects has been evaluated by means of $\chi^2$ analysis ($2\times2$ contingency tables) with the correction of