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References

- Opelz G, Terasaki PI. Improvement of kidney-graft survival with increased numbers of blood transfusions. *N Engl J Med* 1978;**299**:799-803.
- Woodruff MFA, van Rood JJ. Possible implications of the effect of blood transfusion on allograft survival. *Lancet* 1983;*i*:1201-2.
- Anonymous. Blood transfusion and allograft survival. *Lancet* 1984;*i*:830-1.
- Burrows L, Tartter P. Effect of blood transfusions on colonic malignancy recurrence rate. *Lancet* 1982;*ii*:662.
- Blumberg N, Agarwal MM, Chuang C. Relation between recurrence of cancer of the colon and blood transfusion. *Br Med J* 1985;**290**:1037-9.
- Foster RS Jr, Costanza MC, Foster JC, Wanner MC, Foster CB. Adverse relationship between blood transfusions and survival after colectomy for colon cancer. *Cancer* 1985;**55**:1195-201.
- Tartter PI, Burrows L, Kirshner P. Perioperative blood transfusion adversely affects prognosis after resection of stage I (subset NO) non-oat cell lung cancer. *J Thorac Cardiovasc Surg* 1984;**88**:659-62.
- Hyman NH, Foster RS Jr, DeMeules JE, Costanza MC. Blood transfusions and survival after lung cancer resection. *Am J Surg* 1985;**149**:502-7.
- Tartter PI, Burrows L, Papatestas AE, Lesnick G, Aufses AH Jr. Perioperative blood transfusion has prognostic significance for breast cancer. *Surgery* 1985;**97**:225-30.
- Blumberg N, Agarwal M, Chuang C. A possible association between survival time and transfusion in patients with cervical cancer [Abstract]. *Blood* 1985;**66**(suppl 1):274.
- Rosenberg SA, Seipp CA, White DE, Wesley R. Perioperative blood transfusions are associated with increased rates of recurrence and decreased survival in patients with high-grade soft-tissue sarcomas of the extremities. *Journal of Clinical Oncology* 1985;**3**:698-709.
- Nathanson SD, Tilley BC, Schultz L, Smith RF. Perioperative allogeneic blood transfusions—survival in patients with resected carcinomas of the colon and rectum. *Arch Surg* 1985;**120**:734-8.

- Ota D, Alvarez L, Lichtiger B, Giacco G, Guinee V. Perioperative blood transfusions in patients with colon carcinoma. *Transfusion* 1985;**25**:392-4.
- Foster RS Jr, Foster JC, Costanza MC. Blood transfusions and survival after surgery for breast cancer. *Arch Surg* 1984;**119**:1138-40.
- Francis D, Judson R. Relation between recurrence of cancer of the colon and blood transfusion. *Br Med J* 1985;**291**:544.
- Frankish PD, McNee RK, Alley PG, Woodfield DG. Relation between cancer of the colon and blood transfusion. *Br Med J* 1985;**290**:1827.
- Weiden PL, Bean MA, Schultz P, Thompson D. Perioperative blood transfusion does not increase risk of colorectal cancer recurrence [Abstract]. *Blood* 1984;**64**(suppl 1):232.
- Blair SD, Janvren SB. Relation between cancer of the colon and blood transfusion. *Br Med J* 1985;**290**:1516-7.
- Johnson J Jr, Carstens R. Ethnic differences in the anatomical distribution of large bowel cancer [Abstract]. *Clinical Res* 1985;**33**:453.
- Snedecor GW, Cochran WG. *Statistical methods*. 7th ed. Iowa, USA: Iowa State University Press, 1980:124-30.
- Anderson S, Auquier A, Hauck WW, Oakes D, Vandaele W, Wiesberg HI. *Statistical methods for comparative studies*. New York: Wiley, 1980:161-77.
- Cox DR. Regression models and life tables. *Journal of the Royal Statistics Society* 1972;**34**:187-220. (Series B.)
- Dixon WJ, Brown MB, Engelman L, et al. *BMDP statistical software*. Los Angeles: University of California Press, 1981.
- Shearer GM, Levy RB. Noninfectious cofactors in susceptibility to AIDS: possible contributions of semen, HLA alloantigens and lack of natural resistance. *Ann NY Acad Sci* 1984;**437**:49-57.
- Hsia S, Shockley RK, Litcher CLK, et al. Unregulated production of virus and/or sperm specific anti-idiotypic antibodies as a cause of AIDS. *Lancet* 1985;*i*:1212-4.
- Shankey TV, Eyster ME. The acquired immune deficiency syndrome in hemophiliacs: a hypothesis. *AIDS Research* 1983;**1**:83-90.
- Ablin RJ. Transglutaminase: a co-factor in aetiology of AIDS? *Lancet* 1985;*i*:813-4.
- Horimi T, Kagawa S, Ninomiya M, et al. Possible induction by blood transfusion of immunological tolerance against growth of transplanted tumors in mice. *Acta Med Okayama* 1983;**37**:259-63.
- Margolese RG, Wainberg MA. Diminished responsiveness of virus co-incubated lymphocytes to T cell growth factor in breast cancer patients. In: Gilmore N, Wainberg MA, eds. *Viral mechanisms of immunosuppression*. New York: A R Liss, 1985:193-203.

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Incidence of rhesus immunisation after genetic amniocentesis

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Abstract

Of 655 Rh negative women without anti-D antibody in their serum at genetic amniocentesis, 361 delivered a Rh positive infant. Prophylactic treatment with anti-D immunoglobulin was not given at amniocentesis. The women were followed prospectively, being given a screening test for antibody after amniocentesis, at delivery, and six months later. Five of these 361 women yielded a positive test result due to anti-D antibody. The immunisation rate after genetic amniocentesis was no higher than the spontaneous immunisation rate during pregnancy. Four women who had two amniocenteses in the same pregnancy and 34 women who had amniocentesis in two consecutive pregnancies with Rh positive fetuses were not immunised. Among six women with anti-D antibody in their serum before amniocentesis the titre of antibody increased in three. Amniocentesis may have worsened the outcome of these pregnancies.

These results suggest that the risk of immunisation in Rh negative women is small.

Introduction

Amniocentesis has been associated with an increased incidence of fetomaternal haemorrhage,^{1,2} and fetal erythrocytes possess immunogenic D antigens at this stage of pregnancy.³ It remains to be shown whether amniocentesis induces anti-D antibodies in unsensitised Rh negative women. To protect the woman against this risk the World Health Organisation has recommended that a small dose of anti-D IgG be given at amniocentesis.⁴ Giving this immunoglobulin, which is capable of passing through the placenta of a pregnant woman, could be associated with fetal morbidity and certainly makes interpretation difficult for the serological laboratory.

We attempted to evaluate whether prophylactic anti-D immunoglobulin at amniocentesis should be introduced in east Denmark, where antenatal prophylaxis is not administered.

Patients and methods

From 1 January 1981 to 31 December 1982, 4127 pregnant women who were planning to give birth in east Denmark had genetic amniocentesis performed at Rigshospitalet in Copenhagen. The study included 692 women who on admission were reported to be Rh negative; their indications for amniocentesis were maternal age (298 women (43%)), participation in a randomised trial of genetic amniocentesis (166 (24%)), Down's syndrome in the family (104 (15%)), and other reasons (124 (18%)). Of these 692 women, 246 delivered a Rh negative child and 85 women were excluded for other reasons (fig 1). We therefore studied 361 women who had a Rh positive child. Table I shows the pertinent clinical data on these women.

All women on whom genetic amniocentesis was performed were followed up with a questionnaire filled in by the hospital where delivery took place. Besides stating complications occurring during pregnancy and delivery and after birth the questionnaire gave the rhesus state of the mother and child and information on whether immunoprophylaxis had been administered to

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Rh-negative women taking part in study.

the mother after delivery. In this way we confirmed that no Rh negative women had been overlooked. The women's serum was examined for rhesus antibodies at amniocentesis, about four weeks later, and at delivery. Women who delivered a live Rh positive baby were sent a letter asking them to have a final blood test taken, either at the hospital or at their general practitioner, a minimum of six months after delivery to ensure that the passively administered immunoglobulin had disappeared from their circulation.⁵

Amniocentesis was performed under real time ultrasound guidance with the full bladder technique, without anaesthesia, and under sterile conditions. Median gestational age (estimated from the biparietal diameter of the fetus) at amniocentesis was 16.5 (range 14-22) weeks. Table I shows the data on amniocentesis.

Serum samples were tested against red cells from several Rh positive donors by saline agglutination at 37°C followed by the indirect antiglobulin test and the two stage papain technique. The specificities of the antibodies in those samples that reacted in the antibody test were identified with appropriate techniques. The concentration of anti-D antibody was recorded as the reciprocal of the highest dilution at which agglutination of cells heterozygous for the rhesus antigen was still macroscopically visible with the saline antiglobulin technique.

Antenatal prophylaxis with anti-D IgG is not administered in Denmark. In a recent Danish study of the causes of rhesus immunisation the prevalence of genetic amniocentesis was no higher in immunised women than in the rest of the pregnant population, indicating that amniocentesis did not appreciably stimulate immunisation.⁶

Results

Five women developed anti-D antibody during or after pregnancy (table I). The incidence of immunisation measured by a screening test for antibody six months after delivery was 0.8% for all Rh negative women (95% confidence limits 0.1 to 1.5). For the 361 Rh negative women at risk—that is, those who delivered a Rh positive infant and were given anti-D IgG on delivery—the incidence was 1.4% (0.2 to 2.6). Five women who had been immunised for the first time were all multiparous (table II): one woman was

TABLE I—Clinical background data and data on amniocentesis (figures are Nos (%) of women unless otherwise stated)

	All Rh negative women (n=655)	Rh negative women who delivered Rh positive children	
		Not immunised (n=356)	Immunised (n=5)
Median age (years) (range)	33 (17-43)	33 (17-41)	36 (23-38)
<i>Parity</i>			
Median No of previous pregnancies	1.8	1.8	1.6
Primigravidas	140 (21)	82 (23)	0
<i>Amniocentesis</i>			
Anterior location of placenta	319 (49)	173 (49)	3 (60)
Perforation of placenta	56 (9)	32 (9)	1 (20)
Repeat amniocentesis	9 (1)	4 (1)	0

immunised during pregnancy and two showed anti-D antibodies on delivery (one of these had had the placenta perforated during amniocentesis). Two more women had anti-D antibody in their serum six months after delivery, though the result of their screening test at delivery was negative: one had had an uncomplicated vaginal delivery, the other a caesarean section. Except for one who required phototherapy for four days (delivered by a woman who was immunised during pregnancy) the infants were unaffected.

Nine women had two amniocenteses in the same pregnancy due to a culture failure of the first sample. None of the four women with Rh positive infants showed anti-D antibody during the observation period. Seventy five women had amniocentesis again in a subsequent pregnancy, and 34 delivered Rh positive infants in both pregnancies; none of these 34 had developed antibodies by their second delivery. Six of the 12 women who had been immunised in a previous pregnancy delivered Rh negative infants. Of the other six, one had a missed abortion in the 19th week, another had a fetal demise in the 29th week, and four delivered live infants. After amniocentesis three of these previously immunised women showed an appreciable increase in titre of anti-D antibody (table III).

Discussion

To our knowledge, ours is the first prospective study of Rh negative women who had amniocentesis without being given anti-D IgG and who were followed up with antibody tests during pregnancy and after delivery. As we did not include control groups we compared our results with the incidence of spontaneous immunisation during pregnancy. The McMaster conference reported an immunisation incidence of 1.1% on the basis of 30 155 first pregnancies checked six months after delivery.⁷ Multigravidas show a higher incidence than primigravidas—2.2% and 1.6% respectively—when screened three days after delivery with a sensitive autoanalyser and the two stage papain technique as in our study.⁸

As 515 (79%) of the women in our study were multigravidas the incidence of spontaneous immunisation during pregnancy might be expected to be higher than 1.1%. The observed incidence of immunisation was 0.8% within three days after delivery and 1.4% (95% confidence limits 0.2% to 2.6%) six months after delivery. Amniocentesis thus did not seem to enhance the risk of rhesus immunisation. The wide confidence interval, however, means that we cannot exclude the possibility that amniocentesis exposes Rh negative women to a slightly higher risk of immunisation. On the other hand, at least three of the five women who developed anti-D antibodies during the study might have been presensitised by events in previous pregnancies (table II), and this may have led us to overestimate the incidence of immunisation in the current pregnancies.

Two retrospective studies on the incidence of rhesus immunisation after amniocentesis without anti-D immunoprophylaxis reported immunisation during pregnancy to be 2.1% among 615 women⁹ and 3.4% among 115 women.¹⁰ In both studies the number of women at risk was estimated, as the rhesus state of the mother and infant was not known in all cases. Among the large, controlled studies of genetic amniocentesis the British study performed by the Medical Research Council was the only one to include an evaluation of the risk of rhesus immunisation in Rh

TABLE II—Results of antibody test and outcome of pregnancy for women immunised during present study (figures in parentheses are titres of anti-D antibody)

Case No	Parity	Anti-D antibody in serum				Neonatal treatment of infant	Possible cause of immunisation
		Before amniocentesis	After amniocentesis	At birth	Six months after delivery		
47	Gravida 5 Para 3	No	No	No	Yes*	None	Amniocentesis; no anti-D IgG given after birth before 1969; or no anti-D IgG given after spontaneous abortion in 1979
306	Gravida 2 Para 2	No	NT Yes† (4)	Yes (32)	NT	Phototherapy	Amniocentesis or no anti-D IgG given after birth before 1969
358	Gravida 2 Para 2	No	No	No	Yes (4)	None	Amniocentesis or caesarean section
363	Gravida 4 Para 3	No	No	Yes (8)	Yes (32)	None	Amniocentesis or no anti-D IgG given after abortion in 1980 (first two children are Rh negative)
397	Gravida 2 Para 2	No	No	Yes (256)	Yes (32)	None	Amniocentesis with perforation of placenta

NT=not tested. *Shown by enzyme technique only. †First antibody test after amniocentesis in the 35th week.

TABLE III—Results of antibody tests and outcome of pregnancy in previously immunised women after genetic amniocentesis during present study

Case No	Parity	No of previous immunised pregnancies	Titre of anti-D antibody before amniocentesis	Maximal anti-D antibody titre after amniocentesis	Gestational week of maximal anti-D titre	Outcome of pregnancy
36	Gravida 2 Para 2	1	2	1000	27	Two intrauterine transfusions. Fetal death 13 weeks after amniocentesis
91	Gravida 3 Para 2	1	<1	8	36	Induction of labour. Phototherapy of the infant
168	Gravida 5 Para 3	3	2048	2048	18	Missed abortion in 22nd week, four weeks after amniocentesis
292	Gravida 2 Para 2	1	<1	<1		Induction of labour
474	Gravida 4 Para 2	1	<1	64	34	Induction of labour. One exchange transfusion and phototherapy of the infant
594	Gravida 7 Para 3	4	2	4	26	Induction of labour. Phototherapy of the infant

negative women who had had amniocentesis: none of 59 women who had been given anti-D IgG were immunised compared with three cases among 58 untreated women.¹¹ These studies, and ours, did not find an increased incidence of immunisation after amniocentesis, suggesting that the risk of rhesus immunisation associated with midtrimester amniocentesis, if any, is quite small. This is supported by the fact that we found no immunisation among the 34 women who had amniocentesis in two consecutive pregnancies with Rh positive fetuses, nor among the four women who had amniocentesis twice in the same pregnancy. Furthermore, immunisation against other blood group antigens, such as Kell, Duffy, or Kidd, was not observed.

Women who had been immunised in an earlier pregnancy, however, might be different. Three of the six women at risk had increased titres of anti-D antibody after amniocentesis. The stimulus provided by amniocentesis may be too small for primary immunisation but could be a potent booster of a secondary immune response. We therefore agree with those investigators who recommend that genetic amniocentesis should be performed only in previously alloimmunised women after careful consideration of the benefits.¹²

Should anti-D IgG be administered at genetic amniocentesis? As fetal red blood cells possess D antigens as strong as those of adult red blood cells³ the potential for alloimmunisation exists with every fetomaternal haemorrhage. Even when amniocentesis is performed after ultrasonic location of the placenta at least 7% to 10% of women undergoing this process have a fetomaternal haemorrhage.¹² As almost half of all pregnant women seem to have a fetomaternal haemorrhage during pregnancy,¹³ it follows that haemorrhage seldom entails immunisation. Nevertheless, the small risk due to fetomaternal haemorrhage seems to be the only advocate for introducing a prophylaxis in connection with amniocentesis.

Prophylaxis is now common practice in several countries, but its effectiveness has not been proved in a controlled study. In a retrospective study of 300 pregnancies in which anti-D IgG was given at amniocentesis one case of immunisation was found.¹⁴ Likewise, the results of the study by the Medical Research Council suggested a protective effect.¹¹ It is therefore possible that anti-D IgG given at amniocentesis may prevent some cases of immunisation.

The primary argument against the administration of anti-D IgG is that it has not been proved that genetic amniocentesis entails a risk of rhesus immunisation. Furthermore, prophylactic administration of anti-D IgG may interfere with suppression of anti-D antibody later: during pregnancy the woman may be regarded as being immunised¹⁵ and thus not given anti-D IgG post partum. Passively administered anti-D IgG may facilitate primary immunisation when the concentration of antigen exceeds that of antibody,¹⁶ thus necessitating one or two further antenatal administrations of anti-D IgG.¹⁷ Some women may also produce anti-immunoglobulin allo-antibodies, thus making later prophylaxis ineffective.¹⁸ Finally, the safety of administering anti-D IgG early in the second trimester has not been definitely assessed. It should also be remembered that anti-D IgG is still a human product, and its production and collection are not completely without hazards.¹⁹

In Denmark, where it has not been considered necessary to administer antenatal immunoprophylaxis to prevent rhesus immunisation during pregnancy, we find it consistent to refrain from administering anti-D IgG at genetic amniocentesis.

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References

- Mennuti MT, Brummond W, Crombleholme WR, Schwarz RH, Arvan DA. Fetal-maternal bleeding associated with genetic amniocentesis. *Obstet Gynecol* 1980;55:48-54.
- Harrison R, Campbell S, Craft I. Risks of fetomaternal hemorrhage resulting from amniocentesis with and without ultrasound placental localization. *Obstet Gynecol* 1975;46:389-91.
- Mackenzie I, Guest CM, Howell PJ. Fetal blood group studies during mid-trimester pregnancy and the management of severe isoimmunization. *Prenat Diagn* 1983;3:41-6.
- World Health Organisation. Prevention of Rh sensitization. *WHO Tech Rep Ser* 1971, No 468.
- Eklund J, Hermann M, Kjelmann H, Pohja P. Turnover rate of anti-D IgG injected during pregnancy. *Br Med J* 1982;284:854-5.
- Tabor A, Bock JE, Jacobsen JC. Rhesus immunization. A review from the east Danish region during the period 1976-1981. *Ugeskr Laeger* 1982;144:3093-5.
- Davey MG, Zipursky A. McMaster conference on prevention of Rh immunization. *Vox Sang* 1979;36:50-64.
- Bowman JM, Chown B, Lewis M, Pollock JM. Rh isoimmunization during pregnancy: antenatal prophylaxis. *Can Med Assoc J* 1978;118:623-7.
- Golbus MS, Stephens JD, Cann HM, Mann J, Hensleigh PA. Rh isoimmunization following genetic amniocentesis. *Prenat Diagn* 1982;2:149-56.
- Murray JC, Karp LE, Williamson RA, Cheng EY, Luthy DA. Rh isoimmunization related to amniocentesis. *Am J Med Genet* 1983;16:527-34.

- 11 Medical Research Council. An assessment of the hazards of amniocentesis. *Br J Obstet Gynaecol* 1978;85(suppl 2):1-42.
- 12 Bowell P, Wainscoat JS, Peto TEA, Gunson HH. Maternal anti-D concentrations and outcome in rhesus haemolytic disease of the newborn. *Br Med J* 1982;285:327-9.
- 13 Clayton EM, Feldhaus WD, Whitacre FE. Fetal erythrocytes in the maternal circulation of pregnant women. *Obstet Gynecol* 1964;23:915-9.
- 14 Tabsh KMA, Lebherz TB, Crandall BF. Risks of prophylactic anti-D immunoglobulin after second-trimester amniocentesis. *Am J Obstet Gynecol* 1984;149:225-6.
- 15 Lim OW, Fleisher II AA, Ziel HK. Reduction of Rh(D) sensitization: a cost-effective analysis. *Obstet Gynecol* 1982;59:477-80.

- 16 Contreras M, Mollison PL. Rh immunization facilitated by passively-administered anti-Rh? *Br J Haematol* 1983;53:153-9.
- 17 Bowman JM. Controversies in Rh prophylaxis. Who needs Rh immune globulin and when should it be given? *Am J Obstet Gynecol* 1985;151:289-94.
- 18 Jerne D. Antibody suppression and antiallotype antibodies. II. Interference of circulatory antiallotype antibodies with prophylactic treatment against Rh sensitization. *Scand J Immunol* 1976;5:1085-9.
- 19 Anonymous. Hazards of apheresis [Editorial]. *Lancet* 1982;ii:1025-6.

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SHORT REPORTS

Skin reactions to terfenadine

Terfenadine is an antihistamine that has been marketed recently. Skin reactions to antihistamines are rare, and the data sheet approved by the Food and Drug Administration states that in clinical trials skin reactions to terfenadine were no more common than those to placebo. We present 108 cases of rash after ingestion of terfenadine.

Cases reports

CASES NOTIFIED TO THE NETHERLANDS CENTRE FOR MONITORING OF ADVERSE REACTIONS TO DRUGS

Most of the 12 patients notified to this centre (table) had taken terfenadine for hay fever or allergic rhinitis. Four, however, had used it for pruritus of unknown cause. The outcome after treatment was stopped was favourable in all patients. Although three patients had also used other drugs, these were continued without adverse effect. In three cases (1, 3, 11) the reaction occurred after use of terfenadine for the first time, but at least two patients (cases 7, 12) had used it before without ill effects.

CASES NOTIFIED TO THE WORLD HEALTH ORGANISATION COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING

In addition to the cases described above, by August 1985 the WHO centre had received 96 reports of skin reactions associated with terfenadine, from the United Kingdom (89 cases), Belgium (four), Canada (two), and the Federal Republic of Germany (one). Sixty seven patients were female (mean age 34 (range 4-80)) and 29 male (mean age 37 (5-77)). Forty three patients developed a rash, described as erythematous in eight cases and maculopapular in 11; 32 patients developed urticaria; and the remaining 21 reports included six cases of angio-oedema, five of photosensitivity reaction, and four of peeling of the skin of the hands or feet, or both. One patient had extensive circinate and confluent erythema that proceeded to desquamation and recurred on rechallenge.

The latent period between first intake of the drug and the onset of the reaction was known in 72 cases and was less than three days in 35 cases and less than a week in 50. The mean latent period of rashes was 8.25 days, of urticaria 14.6 days, and of photosensitivity reactions 39 days. Outcome was favourable in 60 cases and not stated in 23; 13 patients had not yet recovered. Of those patients for whom the indication and dosage were reported, 22 (79%) took terfenadine for hay fever or nasopharyngitis, most taking 120 mg/day by mouth. In 31 reports use of other drugs was mentioned (mainly oral contraceptives), but these either were continued uneventfully or had been used for a long time without problems. Eleven of the 89 patients reported to the Committee on Safety of Medicines

(CSM) (all confirmed by us by reference to the original reports) reacted on challenge. After August 1985, 14 additional cases were reported to the CSM.

Comment

Although a causal relation was not proved in all cases, terfenadine can undoubtedly cause skin reactions, notably urticaria and rashes. There was a clear temporal relation in most cases, and in 14 rechallenge gave an immediate positive result. Although antihistamines, especially derivatives of ethylenediamine and phenothiazine, can readily sensitise the skin after topical administration,¹ skin reactions to orally administered antihistamines are rare.² Terfenadine, however, is not such a derivative and is chemically distinct from most older antihistamines. Antihistamines may cause liberation of histamine,³ and the rapid onset of the reaction after first use in several patients is compatible with such a mechanism. On the other hand, in a third of the reports documented terfenadine was taken for more than a week, suggesting that sensitisation and a subsequent, immunologically mediated reaction may occur. This is supported by the accelerated reaction to rechallenge that occurred in two cases in the Netherlands and the fact that two patients had taken terfenadine previously without adverse effect. Neither the British nor the Dutch formulation contains a colouring agent, and we are not aware of any allergic excipients.

- 1 Nater JP, de Groot AC. *Allergic contact dermatitis from topical drugs. Unwanted effects of cosmetics and drugs used in dermatology*. 2nd ed. Amsterdam: Elsevier, 1985:44.
- 2 Zürcher K, Krebs A. *Cutaneous side effects of systemic drugs*. Basle: Karger, 1980:193.
- 3 Doenicke A. Pseudo-allergic reactions due to histamine release during intravenous anaesthesia. In: Dukor P, Kallós P, Schlumberger HD, West GB, eds. *Pseudo-allergic reactions. Involvement of drugs and chemicals*. Basle: Karger, 1980:224-50.

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Details of 12 cases of skin reactions to terfenadine notified in the Netherlands

Case No	Age (years) and sex	Daily dosage (mg)	Adverse reaction	Time between starting drug and onset of reaction	Rechallenge (time to onset of reaction)
1	11 M	60	Generalised urticaria	Same day	ND
2	28 M	120	Urticaria, nausea	20 days	ND
3	24 F	120	Urticaria	Same day	ND
4	34 F	60	Urticaria on face and arms	1 day	Twice (1 day)
5	18 M	60	Generalised urticaria	Same day	ND
6	22 M	120	Generalised erythematous rash, urticaria	6 days	Once (<1 day)
7	50 M	120	Generalised erythema, facial urticaria	1 day	Once (<1 day)
8	12 M	120	Maculopapular rash, eyelid oedema	11 days	ND
9	30 F	120	Generalised morbilliform rash	14 days	ND
10	57 F	60	Rash	2 days	ND
11	25 F	60	Erythematous rash, bronchospasm	8 days	ND
12	53 F	120	Erythematous rash, drowsiness, vomiting, dyspnoea	Same day	ND

ND=Not done.