

Treatment of pulmonary aspergillosis with di-iodohydroxyquinoline

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Horsfield, K., Nicholls, A., Cumming, G., Hume, M., and Prowse, K. (1977). Thorax, 32, 250-253. Treatment of pulmonary aspergillosis with di-iodohydroxyquinoline. Thirteen patients with a clinical diagnosis of pulmonary aspergillosis were treated with the anti-amoebic drug di-iodohydroxyquinoline, 1500-1800 mg/day orally, for 20 days. All were precipitin positive before treatment and all but one became negative after treatment. Sputum became negative in all of the 10 patients in whom it had been positive before treatment. Clinical improvement was marked in four patients, moderate in three, and slight in three, no change occurring in the remaining three. These results suggest that di-iodohydroxyquinoline may be of value in the treatment of pulmonary aspergillosis.

The treatment of fungal infections of the lungs is in many cases unsatisfactory; the report by Jesiotr (1973) of the use of emetine hydrochloride in pulmonary aspergillosis was therefore of considerable interest. Emetine has to be given by injection and is potentially toxic, and this prompted us to investigate the use of another anti-amoebic agent, di-iodohydroxyquinoline. In this paper we report 13 cases of pulmonary aspergillosis treated with this drug. No attempt was made to carry out a controlled trial; this was a preliminary investigation to see whether the drug might be of any therapeutic value.

Methods

The activity of di-iodohydroxyquinoline (DIHQ) against aspergillus was first tested *in vitro*. Agar plates were poured using 10 ml aliquots of Sabouraud's dextrose agar (Oxoid). Wells measuring 50×5 mm were cut in the agar and filled with various concentrations of DIHQ. The plates were then lawn inoculated with a spore suspension and incubated for four days at 28°C and 37°C. Inhibition to a radius of 10 mm was seen at a concentration of 50 µg/ml. No success was obtained using impregnated discs. Sputa were reported positive for *Aspergillus fumigatus* if hyphae were seen in the sputum and cultures grew the organism.

Thirteen consecutive patients with a clinical diagnosis of pulmonary aspergillosis were treated with DIHQ, 1500 to 1800 mg/day, for 20 days. All had a history of asthma and were precipitin positive. Ten had positive aspergillus skin tests and 10 had positive sputum, two of which had been positive 6-12 months previously but negative immediately before treatment began. Skin tests were performed using Bencard solutions and serum precipitin tests by the method of Longbottom and Pepys (1964), using both untreated serum and serum concentrated to one-fifth volume.

Case histories

CASE 1 R.J., aged 39, male. Life-long asthmatic, almost continuous for last 10 years. Sputum had grown aspergillus every time for four years. Blood eosinophilia of $2.4 \times 10^9/l$. Shadows on chest radiograph. Required 15 mg prednisolone daily. He was given two 20-day courses of DIHQ, after which the radiograph cleared and the sputum became negative for the first time. Prednisolone dosage reduced to 5 mg/day. Better for one year after treatment than for many years previously.

CASE 2 S.P., aged 32, female. Recurrent asthma since childhood. Recent recurrent attacks with changing shadows on radiograph. Aspergillus in

sputum. Treated with 20-day course of DIHQ plus ACTH for three months. Shadows on radiograph cleared, sputum nil, and now symptom-free for six months.

CASE 3 C.G., aged 52, male. Bronchiectasis and three previous attacks of pneumonia. Two further relapses of pulmonary infection in 1974 and 1975, when aspergillus was grown from sputum, and blood eosinophilia present. Following DIHQ sputum became negative.

CASE 4 R.A., aged 64, female. Cough, wheeze, and dyspnoea for one year along with clinical features of thyrotoxicosis. Aspergillus grown in sputum. Thyroid tests equivocal. Treated with DIHQ and prednisolone, 5 mg daily. Cough and dyspnoea cleared and sputum cultures negative. Prednisolone stopped. Thyrotoxicosis confirmed.

CASE 5 H.B., aged 55, female. Asthma and cough for 10 years with attacks, especially in April and September. Aspergillus in sputum and around windows at home. After DIHQ sputum became negative but later recurred. No change in clinical course.

CASE 6 G.B., aged 39, male. Asthma started as a child. Troublesome for four years, attacks controlled by steroids. Skin test and precipitins positive for aspergillus. After treatment subjectively improved and had only one attack in six months.

CASE 7 M.B., aged 29, male. Asthma started as a child. Four years' ACTH from age 16, three courses of steroids since. On sodium cromoglycate and salbutamol. Treatment with DIHQ produced dramatic improvement. Free of asthma for one year, precipitins and skin test became negative.

CASE 8 I.F., aged 51, female. Asthma for 20 years with bronchiectasis. Exacerbations required steroid therapy. After DIHQ asthma much better controlled, with a reduction in need for salbutamol inhaler. One acute exacerbation since, controlled for the first time without steroids.

CASE 9 V.H., aged 56, male. Asthma for 16 years, especially when winter feeding on a farm. Required steroids for attacks, then continuously for four years from 1971, but then changed to beclomethasone. Before DIHQ he had had two to five severe attacks a year for 14 years. After treatment he had been free of exacerbation for nine months.

CASE 10 J.M., aged 48, male. Left lower lobectomy for congenital cystic disease 1950. In 1972 started with bronchitis, haemoptysis, and wheezing. Also suffered from depression. Skin test negative for the aspergillus group, but ++ for *A. fumigatus*. After treatment with DIHQ he reported subjective improvement only.

CASE 11 W.P., aged 66, female. Asthma for 30 years. Wheezy almost continuously. Strongly positive precipitins and violent skin reaction to aspergillus. Much troubled with coughing up bronchial casts. After DIHQ background disability less and fewer acute attacks. Bronchial casts have disappeared.

CASE 12 L.R., aged 38, female. Asthma since childhood. Bronchiectasis. Asthma worsened in 1971 and has required salbutamol and short courses of oral steroids for five years. After DIHQ asthma more easily controlled and has required no more steroids.

CASE 13 J.W., aged 46, male. Asthma since childhood. Exposure to asbestos at work. Does not respond well to usual treatment with antibiotics and steroids. Aspergillus persistently present in sputum. Radiograph shows persistent small left basal effusion. No improvement in clinical course after DIHQ.

Results

Table 1 shows a summary of the results of treatment with respect to skin tests, pulmonary function tests, and degree of clinical improvement. Four patients were markedly improved, three moderately, three slightly, and three not at all. Table 2 shows the results of examination of the sputum for *A. fumigatus* and Table 3 the results of the precipitin tests.

Discussion

In pulmonary aspergillosis the clinical features, radiographic appearances, skin test, precipitins, and sputum culture are not consistently related to each other and may vary independently and apparently spontaneously. Assessment of the response to therapy is therefore very difficult, but the fact that 12 out of 13 patients became precipitin negative, and that all of the 10 patients with positive sputum became culture negative suggests that the treatment did in fact have some effect. A very gratifying degree of improvement

Table 1 Results of skin tests, FEV₁/FVC, and degree of clinical improvement in 13 patients with pulmonary aspergillosis treated with di-iodohydroxyquinoline (the skin test was for the aspergillus group)

Case	Skin tests		FEV ₁ /FVC		Clinical improvement
	Before	After	Before	After	
1	+	—	0.65/2.21	1.70/3.87	Marked
2	++	+	1.78/2.67	2.79/3.25	Marked
3	+	—	ND	ND	Slight
4	—	ND	0.67/1.00	1.66/2.20	Slight
5	++++	++	0.66/1.39	1.33/1.87	None
6	+++	++	1.54/2.41	1.21/2.20	Slight
7	++++	—	3.30/4.85	3.30/4.71	Marked
8	++++	++++	1.43/2.20	1.21/1.98	Moderate
9	—	—	2.81/3.75	2.09/3.87	Marked
10	—	—	1.43/2.86	1.60/2.58	None
11	++++	+++	0.99/1.98	1.10/1.86	Moderate
12	+	—	1.05/2.50	0.72/1.44	Moderate
13	+++	+++	2.20/3.73	1.27/2.19	None

ND = not done.

Skin test results:

—	Erythema	Weal
+	< 1 mm	
++	≤ 3 mm	
+++	≤ 5 mm or	≤ 3 mm
++++	any	and 3 to 5 mm
++++	any	stronger reaction

Table 2 Results of examination of sputum for *Aspergillus fumigatus* before and after treatment with di-iodohydroxyquinoline. Examinations after treatment were made at intervals of one or two weeks

Case	Before treatment		Period positive	Last positive before treatment ended	After treatment	
	+ve	-ve			+ve	-ve
1	22	2	4 yr	During course	0	2
2	4	0	1 yr	During course	No sputum	
3	13	4	4 yr	1 w	1	2
4	1	0	—	3 w	0	3
5	11	3	1 yr	1 w	0	3
6	0	3	NSP	—	0	4
7	1	3	—	10 m	0	4
8	0	6	NSP	—	0	3
9	0	4	NSP	—	0	3
10	2	5	1 yr ¹	2 w	0	3
11	5	0	6 m ¹	3 w	0	2
12	0	3	NSP	—	0	2
13	4	2	3 yr	2 m	0	3

NSP = never sputum positive.

Table 3 Results of precipitin tests, expressed as number of lines of precipitation, in 13 patients with pulmonary aspergillosis before and after treatment with di-iodohydroxyquinoline

Case	Before treatment	After treatment		
		1 month	5 months	12 months
1	3	0	0	0
2	2	0	0	0
3	2	0	0	0
4	1	0	0	0
5	2	0	0	0
6	1	0	0	0
7	2	0	0	0
8	1	0	0	0
9	2	0	0	0
10	4	0	0	0
11	5	0	0	0
12	1	0	0	0
13	7	2	0	0

occurred in patients 1, 2, 7, and 8, in three of them after years of disability, and it seems unlikely that this would have occurred by chance. In another six patients slight to moderate improvement was noted, part of which may have been due to concomitant steroid therapy, and part of which was subjective. Nevertheless some real benefit was obtained in these patients. Patients 1 and 4 were on prednisolone, and patient 2 on ACTH while taking DIHQ, but since these patients remained precipitin negative after cessation of steroid therapy and since their loss of reactivity was absolute, it was not felt that the negative tests were a consequence of steroid modification of their response.

DIHQ is easily taken by mouth and has few toxic effects; only one easily controlled skin rash

occurred during treatment (patient 1). One difficulty is that the drug is irregularly absorbed, and as no attempt was made to monitor blood levels we do not know whether therapeutic levels were achieved or not.

The results of this study suggest that di-iodohydroxyquinoline may be of value in the treatment of pulmonary aspergillosis, and possibly of other fungal infections as well. It would be of great help if a reliably absorbed preparation could be developed.

References

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emetine hydrochloride. *Scandinavian Journal of Respiratory Diseases*, **54**, 326–332.

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