THE MANAGEMENT OF HYPERSENSITIVITY REACTIONS TO THE PRIMARY ANTI-TUBERCULOUS DRUGS

By K. C. Ng, N. K. Virabhak and S. C. Poh

SYNOPSIS

The proper management of hypersensitivity reactions to the primary anti-tuberculous drugs is still not quite clear in the minds of some and this has resulted in the failure of treatment and the development of drug resistant organisms in some cases. This paper presents our methods of management and the experience with 62 such cases.

All patients suspected to have drug allergy were admitted and the offending drug or drugs were determined. The patients were then desensitized to the offending drug or drugs under cover of promethazine or steroids or both. Desensitisation was successful in 87% of the cases attempted. The success rate for single drug allergy was 99%, 71% for dual drug allergy and 50% for triple drug hypersensitivity. The average duration taken for desensitisation was 17 days, 31 days and 45 days respectively.

With care, patience and manipulation of the drugs, almost all cases can be successfully desensitised.

INTRODUCTION

One of the important causes of failure of treatment in tuberculosis is hypersensitivity reactions to the three primary drugs, that is, Streptomycin (SM), Para-aminosalicylate (PAS), and Isoniazid (INH). In a recent study in Singapore, we reported an overall incidence of hypersensitivity reactions of 9·4% in 660 new cases[3]. This agrees with findings reported by Smith and Zirk[4] and Kalinowski *et al*[2].

The management of these reactions is important as development of drug resistant organisms and even death are known to occur through mismanagement.

This paper reports our experience of 62 cases previously reported[3] and the management of such cases in general.

METHOD

All patients suspected of having allergic drug reactions e.g. fever, chills or rigors, rash, suffused eyes and tearing, joint pains, lymphadenopathy, myalgia and hepatomegaly with or without jaundice were admitted for observation.

All the anti-tuberculous drugs were stopped. A total white cell count, differential count, eosinophil count and serum glutamo-pyruvic transaminase were done. To hasten the amelioration of the symptoms, either an antihistamine, usually chlorpheniramine maleate or promethazine, a steriod, usually prednisolone, or both were exhibited depending on the severity of the reaction and the response. Prednisolone was always given if there was jaundice. When all the reactions had subsided for 3 days, challenge doses of the three drugs were given as follows:—

Drug	1st Dose	2nd Dose	3rd Dose
INH	50 mg.	100 mg.	300 mg.
SM	250 mg.	500 mg.	1 Gm.
PAS	2·5 Gm.	5·0 Gm.	10 Gm.

In cases with severe reactions, the challenge doses were reduced, particularly in cases developing jaundice or exfoliative dermatitis.

INH was the drug used first for challenging as it was the least likely to give reactions. The next drug used was SM as it caused less reactions than PAS and also because if it did not give a reaction then the combination of SM/INH could be restarted. Lastly the patient was challenged to PAS. In this way the offending drug or drugs could be determined. Should hypersensitivity reactions occur with one drug, these were allowed to completely subside before the next drug was challenged.

Chest & Medical Unit III, Tan Tock Seng Hospital, Singapore.

K. C. NG, M.B., M.R.C.P.E., D.T.C.D.(Wales), Senior Registrar.

N. K. VIRABHAK, M.Med.(S'pore), Senior Registrar.

S. C. POH, A.M.(S'pore), M.B., M.R.C.P.E. D.T.C.D.(Wales), Consultant Chest Physician.

DESENSITISATION PROCEDURE

If the patient was hypersensitive to only one drug, then the other two drugs were continued while desensitisation to the third drug was started after covering the patient for two days with promethazine or prednisolone or both. Generally, for mild reactions, promethazine 25 mg. t.d.s. alone was used and if this was inadequate, then prednisolone 10 mg. t.d.s. was added. In very severe cases, both drugs were used. The drug schedule for desensitisation was as follows for the average case:—

	INH (mg.)	SM (Gm.)	PAS (Gm.)
1st day	10	0·05	0·5
2nd ,,	20	0·1	1·0
3rd ,,	30	0·2	2·0
4th ,,	40	0·3	3·0
5th ,,	50	0·4	4·0
6th ,	75	0·5	5·0
7th ,,	100	0·6	6·0
8th ,,	150	0·7	7·0
9th ,,	200	0·8	8·0
10th ,,	250	0·9	9·0
11th ,,	300	1·0	10·0

In severe cases, the initial few doses were reduced and the increment in dosage delayed for 2 to 3 days.

Should reaction occur, then the dose was reverted to the previous dose and continued at this dosage for a few days before increasing again. Alternatively, the same dose was continued for a few days but the promethazine and prednisolone were increased. Generally, desensitisation for each drug should be completed in two to three weeks depending on the severity of reaction, or at the most four weeks, to prevent emergence of drug resistant organisms.

If the patient was found to be allergic to two of the three drugs and the disease was minimal and the patient was generally well, then all drugs were stopped and desensitisation to one drug started. When this was completed, then the patient was put back on two drugs, while desensitisation to the third drug was then started. On the other hand, if the disease was severe and the anti-tuberculous treatment had to be continued, then the patient was put on two of the second line drugs, usually pyrazinamide (PZ) and ethionamide (ETH) or ethambutol (EMB) while desensitisation was instituted in the usual way. The third drug to which the patient was not allergic to was continued with the two second line drugs. When the patient was desensitised to the offending drugs, the second line drugs were discontinued.

If the patient was hypersensitive to all three primary drugs, then the patient was covered with three second line drugs, that is, PZ, ETH or EMB and injection Kanamycin during the period desensitisation was in progress.

RESULTS

Of the 660 cases studied, 62 patients had reactions, 32 were male and 30 were female (Table I).

TABLE I

INCIDENCE OF HYPERSENSITIVITY REACTIONS

	Total	Male	Female
No. on treatment	660	468	192
No. with reaction	62	32	30
% with reaction	9·4	6·8	15·6

There were 6 cases hypersensitive to INH, 30 to SM and 45 to PAS. The incidence to individual drugs is given in Table II.

TABLE II

INCIDENCE TO INDIVIDUAL DRUGS

	INH	SM	PAS
No. with reaction	6	30	45
No. at risk	660	627	652
% with reaction	0·9	4·8	6·9

Thirty-nine patients had reaction to only one drug, 18 to two drugs and only 3 to all three drugs. Two cases were not challenged. One had severe exfoliative dermatitis and jaundice and died twenty-seven days later. The other died before any challenge dose could be given. Both showed extensive liver necrosis at necropsy. The relative percentages are given in Table III. Those with double drug reaction were mostly due to SM and PAS.

TABLE III

INCIDENCE OF REACTION TO ONE OR MORE DRUGS

	No.	% of Total Patients
Reaction to one drug	39	5·9
Reaction to two drugs	18	2·8
Reaction to three drugs	3	0·4
Not challenged (died)	2	0·3
TOTAL	62	9·4

Of the 62 cases, desensitisation was attempted in 53 patients and was successful in 46 cases and failed in 7 cases (Table IV). Of the seven failures, three were to SM and three to PAS with one failure to both SM and PAS.

TABLE IV
RESULTS OF DESENSITISATION

Desensitisation	No.	%
Not attempted	9	—
Successful	46	87
Failed	7	13

Of those 46 successful cases, 33 were due to one drug, 12 to 2 drugs and 1 to 3 drugs. The success rates for the three groups were thus 99%, 71% and 50% respectively (Table V).

TABLE V
SUCCESS RATES OF DESENSITISATION

	No.	Desensitisation Done	No. Successful	% Successful	No. of Days Taken (Ave.)
Reaction to 1 drug	39	34	33	99	17
Reaction to 2 drugs	18	17	12	71	31
Reaction to 3 drugs	3	2	1	50	45
Not challenged	2	—	—	—	—
TOTAL	62	53	46	87	—

Table VI shows the 7 cases of desensitisation failures. Of the 4 cases unsuccessfully desensitised to SM, one was also allergic to INH and PAS but was successfully desensitised to the two latter drugs. Two were also allergic to PAS but were successfully desensitised to it. The last case was also allergic to PAS and was unsuccessful to desensitisation. One of these patients who failed to be desensitised to SM had peptic ulcer and steroids could not be exhibited.

TABLE VI
DESENSITISATION FAILURES

No.	INH	SM	PAS
1	S	F	S
1	—	F	S
1	—	F	S
1	—	F	F
1	—	S	F
1	S	—	F
1	—	—	F
7	0	4	4

F = Failure S = Successful

Of the 4 PAS failures, one patient was also hypersensitive to INH and one to SM but both were successfully desensitised to the latter two drugs. One, already mentioned above was also allergic to SM and failed to be desensitised to it.

Of the 9 cases where desensitisation was not done, 2 died, 2 had had more than 60 grams of SM and SM was therefore discontinued, 2 had severe reaction to PAS, 1 patient had severe reaction to both SM and PAS and 2 were not keen to have desensitisation done.

In the desensitisation procedure, promethazine alone was given in 22 patients, prednisolone alone in 6 cases and 25 cases required both (Table VII).

TABLE VII
DESENSITISATION AGENTS REQUIRED

	Promethazine	Prednisolone	Both	Total
No.	22	6	25	53
Not attempted	—	—	—	9
TOTAL	—	—	—	62

The average number of days taken for desensitisation to one, two and three drugs was 17, 31 and 45 respectively (Table V).

COMMENTS

Desensitisation to the primary anti-tuberculous drugs is usually a tedious procedure and needs patience and skill on the part of the doctor and co-operation from the patient. It is usually easier to desensitise to one drug than to multiple drugs. Our success rate to one drug was 33 out of 34 cases or 99%. Smith and Zirk[4] were successful with SM in 31 out of 34 cases and with PAS in 50 out of 51 cases. Kalinowski *et al*[2] had 265 successes out of 271 attempts or 97%. However, these authors did not say how many of these successful cases were due to double drug allergy. Our success rate for double drug allergy was 71%, failure to desensitise to one drug being regarded as a case of failure. There were only 3 cases with triple drug allergy. One was not desensitised because of severe reactions to PAS and SM, one was successful and the other failed to be desensitised to SM.

We used either promethazine or prednisolone or both while desensitising the patient. Crofton and Douglas[1] found that desensitisation under cover of corticosteroids unsatisfactory because of "rebound" phenomena. Smith and Zirk[4] used steroids only in about half their cases and Kalinowski *et al*[2] made a limited use of prednisolone and corticotrophin. We usually start with promethazine but if this does not give adequate coverage, then

prednisolone is added. The advantage of prednisolone is that it shortens the length of desensitisation and gives a sense of general well being to the patient during this trying period. The patient must be under adequate cover of anti-tuberculous drugs, either primary or second line drugs when prednisolone is given, particularly in the far advanced cases.

As expected, it was quicker to desensitise to one drug allergy (17 days) than to double drug allergy (31 days). These would seem to be reasonable to prevent emergence of drug resistant organisms, one of the noted complications of hypersensitivity reactions.

Two patients with jaundice died before a challenge dose was attempted. Severe jaundice in the presence of drug allergy would appear to be an ominous sign. In retrospect such cases should not be challenged, particularly to PAS, and should be started on steroids immediately. A change of drug regime may be necessary.

It is concluded that it should not be too difficult to desensitise a patient with hypersensitivity reaction to the anti-tuberculous drugs. With care, patience and manipulation of the drugs almost all cases can be desensitised. Our success rate for double drug allergy could have been higher but for reliance on the second line drugs for a change of regime in some cases.

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