

## DRUG PROVOCATION TEST AS A DIAGNOSTIC APPROACH FOR HYPERSENSITIVITY REACTION TO ANTITUBERCULOSIS DRUGS: A REPORT OF TWO CASES

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### ABSTRACT

Pulmonary tuberculosis (PTB) continues to be a public health problem, especially in developing countries. The necessity use of multidrug regimens of antituberculosis drug (ATD) in PTB treatment has been associated with increased risk of drug hypersensitivity reactions (DHRs). DHR is a type of unpredictable reaction, refers to immunologically mediated hypersensitivity reactions. It is observed more frequently in the intensive phase of the PTB treatment with varying degrees of severity. DHR can lead to reduce the patient adherence, thereby leading to stoppage of the drugs by the patient. The definite diagnosis based on drug provocation test (DPT) that should be performed at a hospital. The recommended therapeutic approach is rapid desensitization by reintroducing drugs in safety and optimal under threshold dose until usual daily dose is reached. We present two cases of DHR to ATD, DPT as the diagnosis and rapid desensitization as the therapeutic approach.

**Keywords:** Antituberculosis drug, Drug hypersensitivity reaction, Drug provocation test, Rapid desensitization.

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### INTRODUCTION

Pulmonary tuberculosis (PTB) is a chronic granulomatous infectious disease caused by *Mycobacterium tuberculosis* [1-3]. PTB is a common health problem and is a leading cause of mortality worldwide. There were estimated 10.4 million of incident cases in 2015 and in Indonesia were estimated 1.02 million of incident cases in 2016 [4-6]. PTB also is a challenge for health-care providers worldwide, especially in developing countries. There are some kind regimens antituberculosis drug (ATD) to treat mycobacterial infections. The necessity consuming multidrug regimens has been related with increased risk of drug hypersensitivity reactions (DHRs). DHR is an unpredictable reaction and it refers to an immunologically mediated hypersensitivity reaction. It may be either immunoglobulin E (IgE) mediated or non-IgE mediated, immediate or delayed hypersensitivity reaction [7-9]. DHR may be mild, life threatening, it is a challenge for the physicians. Awareness of the risk groups may reduce the incidence of serious drug-related hypersensitivity reactions [10-12]. We confirmed the component of ATD that induced DHR by performing drug provocation test (DPT). Rapid desensitization is a therapeutic approach, by reintroducing drug in safety and optimal under-threshold dose until the usual daily dose is reached [13-15].

We present two cases of DHR related to ATD, the challenges of diagnostic and treatment.

### CASE REPORT

We present two cases of DHR to ATD collected in the outpatient Department of Internal Medicine, Merpati Clinic, HIV, Allergy and Clinical Immunology Services Unit at Wangaya Hospital in Denpasar, Bali, Indonesia. We collect the data from two patients who visited Wangaya Hospital, in Denpasar, Bali, Indonesia. Written informed consent was obtained from the patients.

#### Case-1

A 27-year-old male patient attended to Wangaya Hospital because he had experienced a generalized urticaria and pruritus, 60 min after taking ATD orally (450 mg rifampicin, 1000 mg pyrazinamide, 750 mg ethambutol, 400 mg isoniazid, and 10 mg pyridoxine) as a single dose for PTB

treatment. The patient presented overall an optimal condition with stable hemodynamic. During the anamnesis, he had a history of drug allergy, but the offending drug was unclear. Based on history taking and clinical manifestation, the diagnosis was a mild DHR related to ATD (Table 1).

The treatment for the patient (Case-1) was by discontinuing the ATD immediately and giving orally 4 mg methylprednisolone twice daily and 10 mg loratadine once daily for 3 days treatment.

The diagnosis of offending drugs based on a clinical history and DPT at hospital. DPT consisted of ingesting or injecting in increasing doses of the offending drug once every 30 min until the usual daily dose was administered or symptoms of DHR occurred. The controlled administration of the drug (each component of ATD, such as isoniazid, ethambutol, pyrazinamide, and rifampicin) to patient with a history suggesting a DHR. This drug was either an alternative, structurally, or pharmacologically related drug or the suspected drug itself [16-18].

Ideally, before DPT, the patient should be clinically stable (no signs and symptoms of DHR). After 5 days clinically stable (wash period), the patient returned to hospital for DPT of ATD. The patient signed an informed consent form and admitted for 1 day care for DPT. There was no DHR related to ethambutol, pyrazinamide, and rifampicin during performed the DPT. There was DHR related to isoniazid (Case 1). DHR occurred at the step 3 of DPT, cumulative time 60 min, drug concentration 3/10, with the dose was 120 mg (threshold dose). DPT result was considered positive because there were some symptoms or signs of an immediate DHR as described previously documented (generalized urticaria and pruritus) at about 60 min after the first dose was administered. DPT determined the offending drug and the safety and optimal under-threshold dose. The safe and optimal under-threshold dose of isoniazid on DPT was one step below the dose on step 3 when DHR occurred. The dose was 80 mg isoniazid (Table 2).

Therefore, rapid desensitization with modified dose or the estimation of safe and optimal under-threshold dose performed by giving 80 mg isoniazid every 30 min until the usual daily dose was reached (400 mg isoniazid) (Table 3).

Table 1: Data of the patient (Case 1)

Case	Sex	Age (years)	ATD regimen	IgE total ( $\mu\text{g/L}$ )	Onset of reaction	Clinical manifestation	Diagnosis
1	Male	27	ATD: 450 mg rifampicin, 1000 mg pyrazinamide, 750 mg ethambutol, 400 mg isoniazid, 10 mg pyridoxine As a single dose	287	60 min	Generalized Urticaria, pruritus  History; Drug allergy (+) The offending drug was unclear	Mild DHR

ATD: Antituberculosis drug, DPT: Drug provocation test, DHR: Drug hypersensitivity reaction

Table 2: Drug provocation test of 400 mg isoniazid

Step	Time (min)	Cumulative time (min)	Drug concentration	Dose (mg)	Cumulative dose (mg)	DHR
1	0	0	1/10	40	40	Mild DHR (+)
2	30	30	2/10	80	120	
3*	30	60	3/10	120	240	
4	30	90	2/10	80	320	
5	30	120 (total 2 h)	2/10	80	400	

\*DHR: Drug hypersensitivity reactions

Table 3: Rapid desensitization by modified dose/the estimation optimal under-threshold dose (80 mg isoniazid) every 30 min until the usual daily dose (400 mg isoniazid) was reached

Step	Time (min)	Cumulative time (min)	Drug concentration	Dose (mg)	Cumulative dose (mg)
1	0	0	2/10	80	80
2	30	30	2/10	80	160
3	30	60	2/10	80	240
4	30	90	2/10	80	320
5	30	120 (total 2 h)	2/10	80	400

Finally, the treatment for Case-1: Isoniazid was 80 mg orally, every 30 min, until the usual daily dose (400 mg isoniazid) was reached (Table 3), simultaneously with other regimen of ATD. The suggestion to the patient was should be carefully and highly awareness to DHR.

#### Case - 2

A 31-year-old female patient came to Wangaya Hospital due to her experienced urticaria, pruritus 60 min after taking ATD (450 mg rifampicin, 1000 mg pyrazinamide, 750 mg ethambutol, 400 mg isoniazid, and 10 mg pyridoxine) as a single dose for PTB treatment. The patient presented overall a good condition with hemodynamic was stable. During the anamnesis, she had a history of drug allergy to penicillin. Based on the clinical manifestation, the patient was diagnosed as a mild hypersensitivity reaction related to ATD (Table 4).

The treatment for the patient was the immediate discontinuing of the ATD and giving orally 4 mg methylprednisolone twice daily and 10 mg loratadine once daily for 3 days treatment.

To confirm the offending drugs of DHR by performing DPT at hospital. DPT for each component of ATD (isoniazid, ethambutol, pyrazinamide and rifampicin) were performed to determine the offending drug and the threshold dose. DPT was performed after clinically stable (no signs and symptoms of DHR). After 5 days clinically stable (wash period), the patient returned to hospital for DPT of ATD. The patient signed an informed consent form and admitted for 1 day care for DPT. There was no DHR related to isoniazid, pyrazinamide, and rifampicin during performing the DPT. There was DHR related to ethambutol (Table 5).

DHR occurred at the step 3 of DPT, cumulative time 60 min, drug concentration 3/10, with the dose 225 mg (threshold dose). DPT result was considered positive because there were some symptoms or signs of an immediate drug reaction as described previously were documented (urticaria and pruritus) at about 30 min after the last dose was administered. The under-threshold dose of ethambutol

based on DPT was one step below the dose on step 3 (225 mg) with drug concentration 3/10. The dose was 150 mg ethambutol. Therefore, rapid desensitization with modified dose or the estimation of safe and optimal under threshold dose performed by giving 150 mg ethambutol each 30 min until the usual daily dose was reached (750 mg ethambutol) (Table 6).

Finally, the recommended therapy for the case-2 was by continuing giving ATD with modified dose of ethambutol (Table 6), simultaneously with other regimens of ATD and some suggestions that the patient should be careful with a highly awareness due to DHR.

#### DISCUSSION AND THE LITERATURE REVIEW

DHR has increased dramatically worldwide. DHR is a subgroup of adverse drug reaction that characterized by reproducible symptoms and/or signs initiated by drug at a dose that is normally tolerated [14,19,20]. Multidrug antituberculosis regimens are associated with various clinical manifestations such as urticaria, generalized pruritus, maculopapular exanthema, lichenoid eruptions, fixed drug eruption, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [21-23].

The offending drug could be clarified by history taking and the definite diagnosis based on DPT result that should be performed at hospital. DPT is a controlled drug administration to patient with a history of DHR. DPT consists of orally or injectly, increasing doses of the suspected offending drug, once every 30 min until the usual daily dose is administered or symptoms of DHR occur. DPT is used as "gold standard" to establish the diagnosis of DHR. It may estimate the safe and optimal threshold dose [15,16].

Rapid desensitization is recommended for the treatment of DHR. It is a strategy of cautiously administering a medication to patients who have a low likelihood of being allergic to it. Rapid desensitization is to

Table 4: Data of the patient (Case 2)

Case	Sex	Age (years)	ATD regimen	IgE total ( $\mu\text{g/L}$ )	Onset of reaction	Clinical manifestation	Diagnosis
2	Female	31	ATD: 450 mg rifampicin, 1000 mg pyrazinamide 750 mg ethambutol, 400 mg isoniazid, 10 mg pyridoxine As a single dose	328	60 min	Urticaria, pruritus History; drug allergy (+) The offending drug was penicillin	Mild DHR

ATD: Antituberculosis drug, DPT: Drug provocation test, DHR: Drug hypersensitivity reactions

Table 5: Drug provocation test of 750 mg ethambutol

Step	Time (min)	Cumulative time (min)	Drug concentration	Dose (mg)	Cumulative dose (mg)	DHR
1	0	0	1/10	75	75	Mild DHR (+)
2	30	30	2/10	150	225	
3*	30	60	3/10	225	450	
4	30	90	2/10	150	600	
5	30	120	2/10	150	750	

\*DHR: Drug hypersensitivity reaction

Table 6: Rapid desensitization by modified dose or the estimation safe and optimal under-threshold dose (150 mg ethambutol) each 30 min, until the usual daily dose (750 mg ethambutol) was reached

Step	Time (min)	Cumulative time (min)	Drug concentration	Dose (mg)	Cumulative dose (mg)
1	0	0	2/10	150	150
2	30	30	2/10	150	300
3	30	60	2/10	150	450
4	30	90	2/10	150	600
5	30	120	2/10	150	750

reintroduce the drugs cautiously, by giving the drug in stepwise fashion and hence not cause a severe DHR. If the DHR occurs, it is hoped that it is minor and easily treated. Most rapid desensitization approach may be carried out in an outpatient setting without intravenous access, but with full preparation to come back to hospital immediately to treat anaphylactic reactions. The initial dose is mostly about 1/100 of the usual dose or as small as possible but reliable (our starting dose is 1/10 of the usual dose). Doses are usually administered at 30 min intervals until the usual daily dose is administered or symptoms of a drug reaction occur. Before each dose, the patient should be questioned and examined for symptoms and signs of DHR [13,16,19,24].

DPT and the first rapid desensitization should be performed at hospital by physicians who are familiar with the standard operational procedure and with the treatment of anaphylaxis. It could be continued as an outpatient with some suggestions [13,15,16,19,24].

In this case report: Case 1; a 27-year-old male patient, experienced urticaria, generalized pruritus 60 min after taking the ATD and the patient with stable hemodynamic, he was also with previous of drug allergy but the offending drug was unclear. The definite diagnostic was confirmed by DPT result. The DPT result was concluded that the patient was hypersensitive to isoniazid with the estimation of safe and optimal under-threshold dose 80 mg.

Case 2; a 31-year-old female patient, experienced urticaria, pruritus 60 min after taking the ATD and the patient with the stable hemodynamic, she was also with previous history of drug allergy to penicillin. The definite diagnostic was confirmed by DPT result and the offending drug (ATD) was ethambutol. Therefore, clinically case-2 was confirmed with DHR related to ethambutol with the estimation of safe and optimal under-threshold dose 150 mg ethambutol.

The recommended therapeutic approach for:

Case 1; rapid desensitization as the therapeutic approach by giving 80 mg isoniazid orally every 30 min, until the usual daily dose (400 mg isoniazid) was reached and simultaneously with 450 mg rifampicin, 1000 mg pyrazinamide, 750 mg ethambutol, and 10 mg pyridoxine as a single dose.

Case 2; rapid desensitization as the therapeutic approach by giving 150 mg ethambutol orally every 30 min, until the usual daily dose (750 mg ethambutol) was reached simultaneously with 450 mg rifampicin, 1000 mg pyrazinamide, 400 mg isoniazid, and 10 mg pyridoxine as a single dose.

The clinicians should be aware of DHR risk during the patient treatment and awareness of the risk groups may reduce the incidence of serious drug-related hypersensitivity reactions. By giving the information to the patient and their family about the DHR risk and coming back to the hospital as soon as possible, when DHR or another adverse effect occurred.

## CONCLUSIONS

The necessity utilization of multidrug regimens has been associated with increased risk of DHR. DHR has various clinical manifestations and it is unpredictable. It should avoid unnecessary drug interruption or suboptimal treatment, in order not to lead a treatment failure or resistance. Diagnosis DHR based on anamnesis (history taking) and to confirm the offending drug, threshold dose by performing DPT. Rapid desensitization is the recommended therapeutic approach.

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#### CONFLICTS OF INTEREST

The author declared that there are no conflicts of interest related to this study.

#### AUTHORS' CONTRIBUTIONS

Ketut Suryana made substantial contributions to conception, acquisition of data, took part in drafting the article or revising it critically for important intellectual content, final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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