Drug Patch Test as a Diagnostic Test to Determine the Culprit Drug of Cutaneous Adverse Drug Reaction (CADR)

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Abstract

Background: Cutaneous Adverse Drug Reaction (CADR) is a frequent problem in clinical practice since there were new drugs or drug misuse, which leads to high morbidity and mortality rate. It is often difficult to determine the offending drug only from the history. Provocation test, intradermal test or skin prick test are of significant value, but having higher risk to re-precipitate life-threatening reaction. Drug patch test (DPT) is a test, which is performed to CADR patient to determine the culprit drug. The main advantages of DPT are, it gives rarely adverse reaction and any commercialized form of drugs can be used.

Methods: This is a retrospective study, aimed to analize the clinical relevance between anamnesis and DPT result in patient with history of CADR. All patient, who were performed with DPT in one year period in Dr. Soetomo General Academic Hospital Surabaya Indonesia, were evaluated in this study.

Results: There were 14 patients with history of CADR, who performed DPT; consist of 7 maculopapular eruption cases, 4 Stevens-Johnson Syndrome (SJS) cases, 1 Fixed Drug Eruption (FDE) case, 1 Acute Generalized Exanthematous Pustulosis (AGEP) case and 1 Drug Reaction with Eosinophilia and Systemic Reaction (DRESS) case. There were 9 patients (64.3 %), who got positive result of DPT. The relevance between anamnesis and positive result of DPT were shown in 8 patient (88.9%) of 9 patient with positive DPT result.

Conclusion: DPT has important role in identifying the culprit drug in CADR, especially when multiple drugs are involved.

Keywords: *CADR, drug patch test, clinical relevance*

Introduction

Definition of adverse drug reaction (ADR) from World Health Organisation (WHO) is an unexpected response to drug, that occured in human normal dose. The incidence of ADR in the hospital was 6.5%, and the mortality rate was 2%. The most common ADR is cutaneous adverse drug reaction (CADR) (30-45%), which 2-7% of them was severe reaction (severe CADR). Study in Dermatology and Venereology Ward Dr. Soetomo Hospital showed that the highest frequent offending drug groups was antibiotic. Severe CADR gave high morbidity, in United States of America it became one of the most common causes of death.[1–3]

A study in Singapore showed that ADR in ward occured in 202 from 90.910 patient in 2002, the most common from was CADR (95.7%). Other study in China showed the risk of severe CADR was 0.03/1.000 patients (0.02/1.000 patients in SJS, and 0.01/1.000 in erythroderma and DRESS).[4,5]

CADR is a frequent problem in clinical practice since there were new drugs or drug misuse, which leads to high morbidity and mortality rate. It is often difficult to determine the offending drug only from the history. Provocation test, intradermal test or skin prick test are of significant value, but they are having higher risk to re-precipitate life-threatening reaction. Drug patch test

(DPT) is a test, which is performed to CADR patient, using suspected drug materials to determine the culprit drug.[6,7]

A study by Damayanti et al showed the incidence of severe CADR (SCADR) at dr. Soetomo Hospital ward was 14 patient in 2015; consist of 10 SJS cases, 2 TEN cases and 2 AGEP cases. Other study by Anggraeni et al showed the incidence of CADR at Dermatology and Venereology Outpatient Clinic Dr. Soetomo Hospital Surabaya in 2015 was 87 from 17.871 patient (0.48%); consist of maculopapular eruption (56.32%), SJS/TEN (17.24%) and FDE (17.24%).[8,9]

After DPT procedure, relevance analysis between anamnesis and DPT result should be done to make the conclusion and the next management of CADR. There are still a few literature discussing the clinical relevance in DPT.[6,7] This study evaluates the clinical relevance between anamnesis and DPT result in patient with history of CADR. This study was a retrospective-descriptive study, collecting secondary data from medical record of DPT procedure in CADR patient in one year in Dermatology and Venereology Outpatient Clinic Dr. Soetomo General Academic Hospital.

Methods

This study was a retrospective study, that evaluated the positive relevance of DPT result in patients with history of CADR. The data was taken from the medical record of CADR patients, who were performed with DPT. All patient, who were performed with DPT in one year period in Dr. Soetomo General Academic Hospital Surabaya Indonesia, were evaluated in this study. This research has been approved by Ethical Committee of Dr. Soetomo General Academic Hospital Surabaya Indonesia (623/Panke.KKE/X/2017).

Results

The distribution of CADR cases in one year period showed, that CADR cases in Dermatology and Venereology Ward was 27 from 68 patients (39.7%), and CADR cases in Dermatology and Venereology Outpatient Clinic was 87 from 17.871 patients (0.48%). In this study, there were 14 patients with history of CADR, who performed DPT in one year period. The type of CADR consist of maculopapular reaction (7 patient), SJS (4 patients), FDE (1 patient), AGEP (1 patient) and DRESS (1 patient). From 14 patients, the most common age was in the range of 15-22 years old. (Table 1) (Table 2)

From 14 patients, the suspected drugs of CADR may consist of more than 1 drugs. The most common suspected drug were antibiotic (22 cases), such as ofloxacin, ethambuthol, dapsone, rifampicin, cefadroxil, ciprofloxacin, levofloxacin, cefixim, amoxicillin, erythromycin, ceftriaxone, cotrimoxazole, gentamycin, isoniazide, prazinamide; and NSAID (non steroid antiinflamation drugs) (19 incidences), such as mefenamic acid, natrium diclofenac, ketoprofen, paracetamol, piroxicam, acetaminophen, ibuprofen, antrain. The other suspected drug were anticonvulsan (5 cases; consist of carbamazepine, clobazam, phenitoin), antihypertension (1 case; propanolol), and proton pump inhibitor (1 patient; omeprazol).

From anamnesis, the most common underlying disease that made the patient consumed the suspected drugs were tuberculosis (4 patients), and common cold (3 patients). The other underlying diseases were pain, stomachache, hemifacial spasm, seizure, hyperthyroid, meningo-encephalitis and other infection condition. (Table 3) (Table 4)

There were 9 patients (64.3 %), who got positive result of DPT. The relevance between anamnesis and positive result of DPT were shown in 8 patient (88.9%) of 9 patient with positive DPT result. The most frequent type of CADR in this study was maculopapular eruption (50%), which had positive DPT relevance for ethambuthol, mefenamic acid, cefadroxil, paracetamol. SJS occured in 4 patients, which had positive DPT relevance for ciprofloxacin and carbamazepine. Other positive DPT relevance occured in FDE (1 patient, for mefenamic acid), AGEP (1 patient, for paracetamol), and DRESS (1 patient, for cefadroxil and propylthiouracil). From 8 patients who had positive DPT relevance, antibiotic and NSAID was the most frequent culprit drug that had positive DPT relevance (50%).

Table 1: Distribution of CADR cases

	Cases	Number of patients
Ward	CADR	27 (39.7%)
	Patients total number	68
Outpatient clinic	CADR	87 (0.48%)
	Patients total number	17.871

Table 2: Distribution of patients' age

Age	Number of patients (n=14)
<14 years old	3 (21.4%)
15-44 years old	7 (50%)
45-60 years old	3 (21.4%)
>60 years old	1 (0.07%)

Table 3: Distribution of CADR type

Type of CADR	Number of patients (n=14)
Maculopapular eruption	7 (50%)
SJS	4 (28.6%)
FDE	1 (7.1%)
AGEP	1 (7.1%)
DRESS	1 (7.1%)

Table 4: Distribution of DPT result, and the relevance of DPT result

DPT result (n=14)	**Positive result**	**9 (64.3%)**
	Negative result	**5 (35.7%)**
Relevance of DPT result (n=9)	Positive relevance	8 (88.9%)
	No relevance	1 (11.1%)

Discussion

CADR is a frequent problem in clinical practice, which leads to high morbidity and mortality rate. It is often difficult to determine the offending drug only from the history. Provocation test, intradermal test or skin prick test are of significant value, but they are having higher risk to re-precipitate life-threatening reaction.[6,7]

In this study, the most common underlying diseases in this study was tuberculosis (4/14 patients), that gave maculopapular eruption. All of them received

antituberculosis drugs, that may consist of ofloxacin, ethambutol, dapsone, rifampicin, ofloxacin, isoniazid or pirazinamide. An epidemiologic study in England, showed the incidence of CADR caused by antituberculosis drugs was 5.1% (occured in 67 from 1.371 patients, who received antituberculosis drugs). The frequency of CADR increased from 2.3% at the age 0-19 to 4.6% at the age 20-39, 7.1% for age 40-59 and tp 8.4% for those age 60 and over. Multidrug antituberculosis regimen is associated with many clinical patterns of CADR, ranging from mild and moderate, such as maculopapular exanthematous eruption, lechenoid eruption, FDE and urticaria, to severe form, such as AGEP, SJS/TEN. This is an importance warning for country who has higher occurance rate of tuberculosis infection.[10,11]

Some literatures showed, that anticonvulsan, antibiotic and NSAID were the most common etiologic drug in drug eruption. A study in China showed antibiotic, anticonvulsan and China traditional medicine were the most common etiologic drug.[3,4]

From 8 patients in this study, who had positive DPT relevance, antibiotic and NSAID was the most frequent culprit drug that had positive DPT relevance (50%). A study in dr. Soetomo Hospital ward in 2015, the most common suspected drug in SCADR was antibiotic and anticonvulsant (64.3% each). The suspected antibiotic in this study were cefadroxil (2 cases), ethambuthol (1 case), and ethambutol (1 case). Cefadroxil is one of cephalosporins drug group. Cephalosporins are among the most commonly-used antibiotics in the routine infections. It can cause a range of hypersensitivity reactions, from mild, delayed-onset CADR to life-threatening anaphylaxis in patients with immunoglobulin E (Ig E)-mediated allergy.[9,12]

There were 9 from 14 patient (64.3%) that were performed for DPT, received NSAID after suffering from the underlying diseases (such as common cold, in order to relief the pain, and as antipiretic drugs). NSAID were mefenemic acid, natrium diclofenac, ketoprofen, ibuprofen, paracetamol, piroxicam, acetaminophen, and antrain. At Dr. Soetomo General Academic Hospital Surabaya, the incidence of CADR in 2015 caused by paracetamol and mefenamic acid as one of NSAID group were the highest rate after amoxycillin (18.39% for paracetamol and 14.94% for mefenamic acid). A study by Damayanti et al, at Dr. Soetomo General Academic Hospital Surabaya in 2015 showed, that paracetamol was the most common etiologic drug (50%).[8,9]

Borges et al in 2010 showed that prevalence of drug eruption caused by NSAID was 21-25% from all ADR cases. NSAID were consumed as therapy of pain, fever or inflamation. Many people consumed NSAID, so that NSAID is one of the most common etiologic drug in CADR. NSAID can caused acute reaction (such as urticaria or angioedema) or delayed reaction. Delayed reaction occured more than 24 hours after NSAID exposure (as monotherapy or NSAID multiple cross reaction), such as maculopapular eruption, FDE, SJS, TEN, or AGEP.[13–16]

Important management of CADR after the emergency and the eruption was managed, is performing procedure to determine the etiologic drug of the reaction. Drug Patch Test (DPT) is patch test performing in CADR patients, by applying the Finn chamber in the skin, and evaluating the localized reaction in the skin. The drug or agent can be made from solution, powder or from the active form of drug, which was powdered. The agent should be applied in the skin (usually at the upper back area). The media of the agent was petrolatum, water or alkohol. The result of DPT was evaluated on the 48 hours, 72 hours, and if the result was still negative, it can be evaluated on th 7th day.[6,17]

DPT was indicated for type IV hypersensitivity (delayed type hypersensitivity) CADR. The morfology was exanthematous, blistering or pustular eruption. DPT was recommended especially in AGEP, maculopapular exanthematous reaction, DRESS, lichenoid drug eruptions, photosensitivity, erythroderma, and FDE.[17]

In this study, the positive result of DPT was 9 from 14 patients (64.3%). The relevance between anamnesis and positive result of DPT were shown in 8 patient (88.9%) of 9 patient with positive DPT result. The most frequent type of CADR in this study was maculopapular eruption (50%), which had positive DPT relevance for ethambuthol, mefenamic acid, cefadroxil, paracetamol. From 8 patients who had positive DPT relevance, antibiotic and NSAID was the most frequent culprit drug that had positive DPT relevance (50%). Positivity of DPT result in CADR is 7.5-54%, depends on patients selection, type of CADR, and suspected drugs. Patients

selection consists of age, genetic, history of allergy, or immunological status. The celullar immunity response in HIV patient with low CD4 level decreased, and gave false-negative DPT result. Sensitivity of DPT is high for maculopapular eruption, and AGEP, but it is low for urticaria, SJS, TEN, or vasculitis). Sensitivity of DPT is high for CADR caused by diltiazem, abacavir, betalactam antibiotics, anticonvulsan, tetrazeam, and pseudoephedrine. The sensitivity of DPT also depends on the rute of administration, duration, dose, macromolecules size and hapten of the drugs.[6,7]

Negative result of DPT in CADR occured in 30-50%. Negative result of CADR may be caused by drug metabolite which did not appear after procedure (drug metabolite appeared after the drug was metabolized in the liver), no immunological involvement, low drug bioavaibility or low drug penetration in DPT. Besides, the body's response to drug administration is also influenced by age, hepatic function, kidney function, pregnancy, presence of viral infections, drug/food interactions, immunosuppression, comorbid factors, and lifestyle, which can change over time in an individual. Genetic polymorphisms may play a role in the function or gene expression in pharmacokinetics and pharmacodynamics. Genetic polymorphisms can determine changes in gene expression or gene function that affect the immune response, such as the Human Leukocyte Antigen (HLA) gene, which forms a specific type of immunological system-mediated drug eruption.[7,17,18]

The negative result of DPT did not exclude the possibility of hypersensitivity reaction in CADR. If the DPT result was negative, other examination such as drug provocation test should be considered.

Conclusion

DPT has important role in identifying the culprit drug in CADR, especially when multiple drugs are involved. The main advantages of DPT are that it can be done without hospital surveillance because it gives rarely adverse reaction and any commercialized form of drugs can be used. Relevance analysis between DPT and anamnesis should be done to make the conclusion and the next management of CADR.

Ethical Clearance: Taken from Ethical Committee of Dr. Soetomo General Academic Hospital Surabaya Indonesia (623/Panke.KKE/X/2017).

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