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Case Report

Commersial Drug Patch Test for Identifying Etiologic Drug of Adverse Cutaneous Drug Reaction

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ABSTRACT

Adverse cutaneous drug reaction (ACDR) is a challenging condition for clinician, especially in determining the etiologic drug. Identification of etiologic drug become more difficult when the patient consume multiple drugs at once. Cellular immunity response is the main mechanism underlying exanthematous eruption, the most common type of ACDR. Patch test rise as the reliable diagnostic modality to find the etiologic drug as this test represent the same mechanism as ACDR. In this paper, we reported commercial drug patch test application testing Griseofulvin, Amoxicillin, Ibuprofen, Aspirin and Clindamycin in 37 years old woman with history of drug induced-exfoliative dermatitis six months ago. Patch test technique involves patient preparations, test drug formulation, test drug patching and evaluation on day 2, 4 and 7. The suspected drug consist of Griseofulvin, Ibuprofen and Clindamycin. Amoxicillin was chosen as the cross reacted drug for Griseofulvin while Aspirin was chosen as the cross reacted drug of Ibuprofen. All tested drugs were formulated as homogenous powder with 10% concentration and mixed with white paraffin. The evaluation result showed positive reaction towards Griseofulvin and weak positive reaction towards Amoxicillin.

Keywords : commercial drug patch test, adverse cutaneous drug reaction, exfoliative dermatitis.

INTRODUCTION

Adverse cutaneous drug reaction (ACDR) is any undesirable effect involving the structure and function of the skin, appendages and mucous membrane. The forms of ACDR vary from mild skin eruption to life-threatening conditions. (Shear NH., Knowles SR, 2008, Nayak, S. & Acharjya B. 2008) The occurrence of drug induced cutaneous eruptions is quite frequent, with a prevalence of 2-3% of all total inpatients and 2% of all events are severe and can be fatal. The United States recorded more than 100,000 deaths occur each year due to drug induced cutaneous reactions. (Nayak, S. & Acharjya, B. 2008)

The diagnosis of ACDR can be made simply based on history taking and physical examination. However, deliberating the causative drug is always a challenging matters for

physicians. This condition will be more difficult in circumstances where patients take several types of drug at the same time. Previous clinical and laboratory studies have indicated that pathogenic mechanism of cellular immune response is the main pathomechanism of the development of drug reaction, either the maculopapular or the bullous exanthematous type. Based on these knowledges, patch test, altogether with other modality such as delayed-reading intradermal test, lymphocyte transformation test and drug challenges, is a potential diagnostic modality for detecting the causative drug. (Romano A. et. al, 2008, Lachapelle JM. 2009)

The use of patch tests to determine the suspected substances in ACDR has been published since the late 1980s and its benefits have been recognized to date, in the era of the 2000s. The advantage of doing a drug patch test is that this technique can be applied to various forms of commercial drugs, unlike intradermal drugs which require that the form of the drug be tested in the form of injection. In addition, patch tests can also be done outside the hospital environment because this technique very rarely causes side reactions. (Barbaud A., 2005)

Reported in this paper, a 37-year-old woman who underwent a commercial drug patch test to determine which triggers were suspected of causing exfoliative dermatitis conditions experienced in the previous six months.

CASE REPORT

A 37-year-old female patient came to dermatology and venereology clinic of the Regional General Hospital Dr. Saiful Anwar (RSSA) Malang for allergy test. About six months earlier, the patient had a reddish and scaly rashes all over her body with a suspected causative drug of Griseovulfin and Ibuprofen. Six months before, patient showed flu-like symptoms which were then treated with Ibuprofen that was bought out of the counter. One week after, patient started to acknowledge the appearance of red rash on her body. The rashes first appear on the abdomen that caused patient to seek for treatment and was given Griseofulvin by local physician. One day after taking Griseofulvin, the rashes spread faster to the whole trunk, and arms. Within one week, the rashes spread to all over the body. The patient was brought to hospital due to this condition and was suggested to be admitted but the patient refused. Patient received oral medication methylprednisolone, some unknown ointments and moisturizers and got better after one month treatment.

About four weeks ago the patient experienced pain and swelling on her right palms. The patient then went to the RSSA dermatology and venereology clinic and was diagnosed with cellulitis. The patient was then treated with saline compress and oral clindamycin 3x300 mg. Within three days after, the patient complained that his right palm was started to looked redder and scaly. Patients consulted to dermatologist and was suggested to stop taking clindamycin due to suspicion

of allergy and replaced with cefadroxil antibiotics for five days. Complaints of swelling, redness and scales on the palms healed in one week.

Before undergo a commercial drug patch test, patient was prohibited to take antihistamine and immunosuppressant drugs within one week before the test, not consume corticosteroids within two weeks before and had to inform any changes that occur in the skin of the back area where patch test will be done. In this patient, six types of drugs will be tested, namely Griseovulfin, Amoxicillin, Ibuprofen, Aspirin, and Clindamycin. In addition to the drugs to be tested, the materials and equipment needed for the drug patch test consist of a 7 mm or 11 mm Chamber, a marker marker (Gentian Violet), Magnifying lamp, hypoallergenic plaster, tweezers / stick, 70% alcohol cotton and cotton , gloves / handschoon, ruler and scissors, stationery, microgram scales, and pestle and mortar.

The formulation of tested drugs was made by crushing the tablets into smooth homogenous powder using pestle and mortar. The powder was then weighed and 30% of the total weight was taken and then mixed with white paraffin. The order of drug formulations is shown in Figures 2.

Figure 2. The tested drug formulation. The medicine to be tested is first mashed into homogeneous powder using a pestle and mortar (B) then all the medicinal powder preparations are weighed on a microgram (B) scale. About 30% of the powder was then taken and mixed with white paraffin using a toothpick (C and D).

Before testing the drug, the patient first signed an informed consent. The patient was positioned in an upright sitting position with both arms crossed holding the right and left shoulders. The area to be affixed was the interscapula sinistra and the test area was then cleaned using an alcohol swab and allowed to dry.The drug powder which has been mixed with white paraffin was then placed in a 7 mm Finn Chamber and placed on the skin in the region of the interscapula sinistra using non-alergenic plaster. The patient was told to avoid activities that cause

excessive sweating, bathing and other activities that may dispatch the chambers. The sequence of the drug patch test procedure is shown in Figure 3.

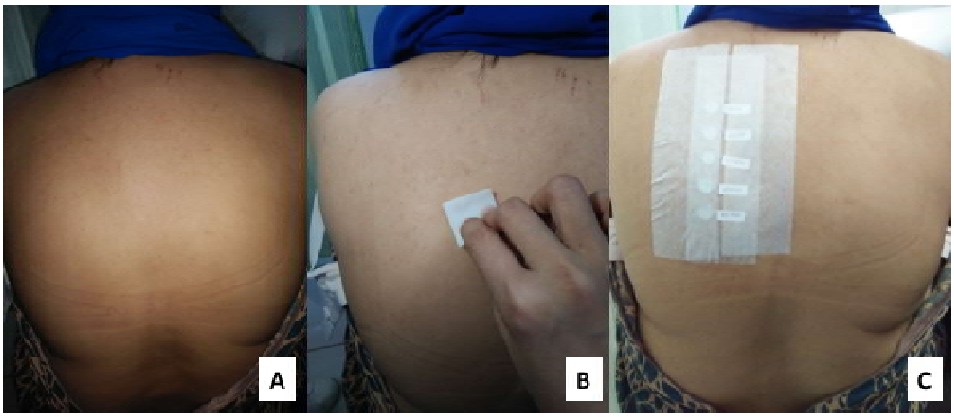

Figure 3. The process of attaching finn chambers containing a mixture of drugs to be tested. The patient's back was inspected to ensure there is no lesion that can affect the patch test process (A). Next, the area to be tested was cleaned using an alcohol swab and allowed to dry (B). The finn chamber-tape containing the drug to be tested was placed in the interscapula area of the sinistra parallel to the vertebra (C).

The results were read out on the 2nd, 4th and 7th day after the chamber installation. On day 2, the reading was done 1 hour after the chamber is removed. Finn chamber removal was carried out slowly using tweezers to pull the ends of the plaster so as not to add extra pressure or friction to the test area. Evaluation of the skin condition of the test region on day 2, 4 and 7 can be seen in Figures 4, 5, 6, respectively. The results of readings on day 2, 4, and 7 are summarized in table 1.

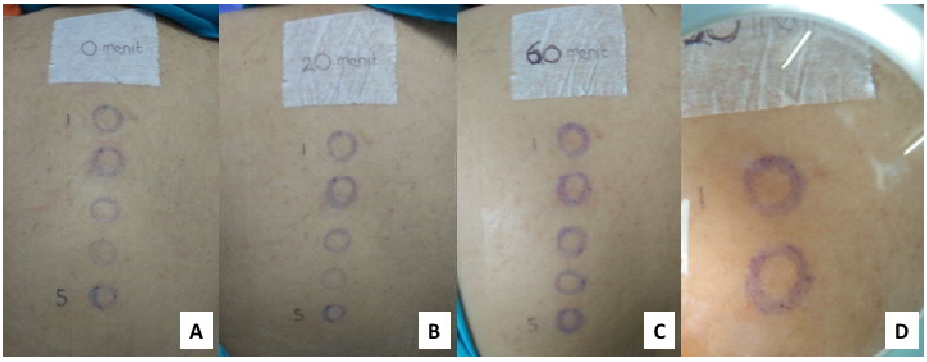

Figure 4. Results of the patch drug commercial test reading on day 2 (48 hours). Results were evaluated at least 20 minutes and 60 minutes after removing the plaster to ensure there was no remaining pressure effect. During the evaluation shortly after the plaster was removed, minimal erythema papules and macules appeared at the location of chamber no.2 (A). At a reading of 20

minutes later there was no change (B). At a reading of 60 minutes later the erythema macules were seen in the chamber area no. 1 and the erythema papules and macules in the chamber area no. 2 (D).

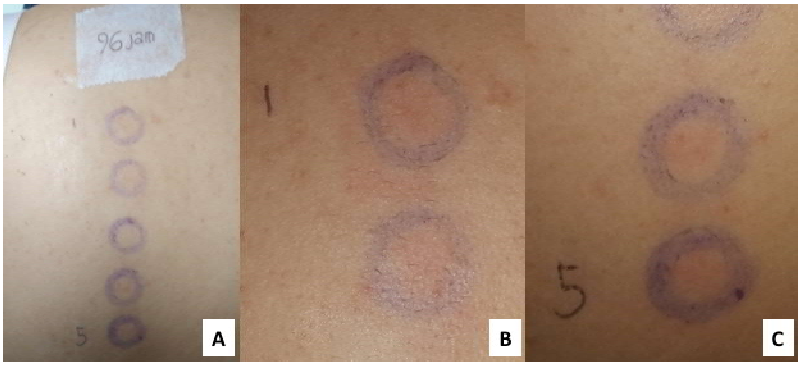

Figure 5. The results of the patch drug commercial test readings on day 4 (96 hours) (A). At the evaluation, there was an erythema macula at the location of chamber no. 1 and papules and erythema macules at the location of chamber no. 2 (B). In addition, macula erythema was also obtained at the location of chamber no. 4 (C).

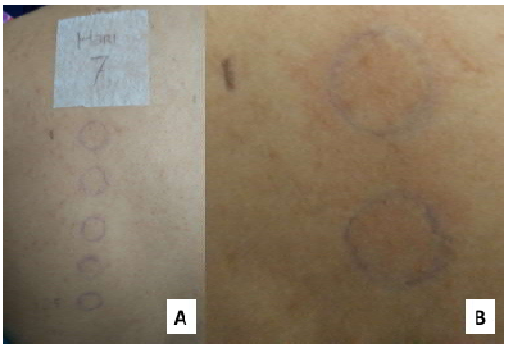

Figure 6. Results of the reading of the patch test for commercial drugs on day 7 (168 hours) (A). At the evaluation, there was a mild erythema macule at the chamber no.1 and 2 (B) locations. Erythema is no longer found in other chamber locations.

Table 1. Results of the drug patch test

No	Tested Drugs	D-2	D-4	D-7	Description
1	Amoxicillin	?+	?+	?+	Doubtful
2	Griseofulvin	+	+	?+	Mild Reaction
3	Clindamycin	-	-	-	Negative
4	Aspirin	-	?+	-	Doubtful
5	Ibuprofen	-	?+	-	Doubtful

The results of the patch test readings of commercial drugs on day 2 was positive on Griseofulvin and doubtful on Amoxicillin. On the 4th day it was found positive on Griseovulfin and doubted on Amoxicillin, Aspirin and Ibuprofen. On the 7th day it was found to be doubtful on Griseofulvin while other drugs were found to be negative. Based on the overall reading, it was concluded that the patient was allergic to Griseofulvin and has predisposition to be allergic with Penicillin class of drug. Allergy to Aspirin is still in doubt.

DISCUSSION

Finding the relationship between the emergence of ACDR and one or more suspected drugs is a difficult task for clinicians. The initial stage in identifying the causative drug is to evaluate the medication list that is owned by the patient, including medicines purchased without a prescription. The first data that needs to be obtained includes the name of the drugs consumed in the last month, the date of consumption and the dosage. The second is to explore the history of skin reactions to drugs or food. It is also necessary to think about other causes such as viral and bacterial infections that can cause exanthems. (Nayak, S. & Acharjya B. 2008)

In this case, patient was diagnosed with exfoliative dermatitis six months before coming to the RSSA clinic with a suspicion of causative drugs of Ibuprofen and Griseofulvin. Griseofulvin was consumed 4 days before onset and Ibuprofen about 1 week before onset. The patient had never taken both types of drugs and no other drugs were taken for a duration of 3 months before the onset. The patient was also suspected of having clindamycin allergy due to complaints of scaly erythematous patches on her arms and palms 3 days after oral clindamycin consumption one month ago.

It was previously known that the patch test was able to produce the same mechanism as the ACDR mechanism, which was proven by research conducted by Barbaud et al in 2002. In that study it was found that biopsy results from maculopapular rash of patients with ACDR and biopsy obtained from the positive patch tests location similarly express the ICAM-1 (CD54) adhesion molecule on keratinocytes or ELAM-1 (CD62E) on endothelial cells. (Barbaud A. 2009) Previous findings by Britschgi in 2001 also concluded that the immunophenotyping results from patch test rash and acute skin lesions both express CD4 and IL-8. (Britschgi, M., et. al., 2001)

Based on the clinical evidence, patch test is included in category B which means that this test has moderate evidence of strength. (Barbaud A. 2009) Previous research found that drug patch test can provide 87% positive results in cases of eruption caused by cellular immune response. (Alanko K. 1994) However, the predictive value for a patch test for a drug cannot be determined.

In addition to the suspected drug, it is also necessary to test drug that can cross-react with the suspected drug. In our case, the patient was tested for Ibuprofen, Aspirin, Griseofulvin,

Amoxicillin, and Clindamycin drugs. The types of drugs and their cross reactions are shown in Figure 3.1.

Regarding ACDR variations, not all types of ACDR can be tested with patch test. The types of ACDR that are recommended for patch testing are acute generalized exanthematic pustulosis (AGEP), eczematous eruptions (with no history of previous contact with allergens), exanthematous maculopapular eruptions, exfoliative dermatitis, fixed drug eruptions (bullosa and non-bullosa), drug eruptions. granulomatous type, hypersensitivity syndrome (DRESS), lichenoid drug eruptions, photosensitivity (photoallergic drug eruption; in this case photo patch testing is needed), pityriasis rosea-like eruptions, pseudolymphomatous drug eruptions, psoriasiform drug eruptions and systemic reactions of allergic contact dermatitis. On the other hand, the types of ACDR that are still controversial for patch testing include erythema multiforme, purpura, Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and vasculitis. (Lachapelle JM., 2009)

Patch tests are carried out using commercial drugs and if possible pure active ingredients and vehicles. Patch tests should be carried out on drugs that have structural similarities to each other or are in the same pharmacological family to detect cross-reactions. Immediate readings (within a period of time 20 minutes) is needed to check for an urticaria reaction. Readings are then carried out on day 2, 4, and 7, and in cases of fixed drug eruption, patch tests need to be done on normal skin and pigmented residual skin from the location of FDE lesions. (Lachapelle JM., 2009)

Patch tests should only be done within a period of 6 weeks to 6 months after complete recovery from the previous ACDR due to concerns that patch test treatment before 6 weeks will give false positive results whereas after 6 months will give false negative results. A minimum of 6 weeks' time is needed to avoid the possibility of remaining drug suspects in the body that have not fully experienced clearance. Meanwhile, due to the lack of knowledge related to whether a positive reaction can persist or only last for a moment, it is recommended that the maximum time to do a drug patch test is within 6 months after complete recovery from ACDR. (Johansen J. D., 2015) In our case, we did a patch test 5 months after the patient was declared complete recovery from ACDR.

The determination of the tested drug concentration is still controversial as the sensitivity limits of various pure drug substances have not yet been determined. For practical approaches, generally 10% drug concentration is used. When using the commercial form, in the form of mashed tablets, 30% is the highest concentration which is still possible to obtain a homogeneous dilution of the drug in petrolatum, water or alcohol. However, if the weight of the active ingredient and vehicle are known beforehand, then a final concentration of 10% can be chosen. (Friedmann P. S., & Ardern-Jones M., 2010)

Regarding the chosen vehiculum, a number of literature states that drugs can be mixed in petroleum, distilled water or alcohol, in accordance to the type of drug to be tested. (Romano et. al.,

2008, Friedmann P. S. & Ardern-Jones M. 2010, Schnuch, et. al., 2008) Acetylsalicylic acid, beta lactam and amoxicillin, and ibuprofen are all formulated with a concentration of 10% and dissolved in petroleum. There is still no literature explaining the precise concentration and vehiculum for clindamycin. (Friedmann P. S. & Ardern-Jones M., 2010) In our case we applied 10% of the total weight of each homogeneous powder of aspirin, amoxicillin, griseofulvin, ibuprofen and clindamycin.

The reading of the results is carried out on days 2, 4 and 7 to estimate the possibility of an initial reaction (eg a reaction due to abacavir occurring after 24 hours) or a reaction that appears slow (eg 6-7 days as shown) can occur in glucocorticoid drugs and beta lactam antibiotics). (Johansen J. D., et. al., 2015)

The interpretation of drug patch test results is based on the results of inspection and palpation on the morphology of skin rashes (erythema, infiltrate, papules and vesicles). The globally adopted criteria is the ICDRG criteria. Based on the ICDRG criteria, if no skin reaction is obtained then it is given a negative sign (-) which means a negative reaction. If there is a faint erythema color change, a question mark followed by a positive sign (? +) can be given, which is interpreted as a doubtful reaction. For erythema in addition to infiltration with / without papules can be given a one positive sign (+) which is interpreted as a weak positive reaction. If erythema, infiltration, papules and vesicles are obtained, two positive (+) signs can be given to be interpreted as a strong positive reaction. When clear erythema is accompanied by infiltrate and overlapping vesicles, it can be given three positive signs (+++) and interpreted as an extreme positive reaction. Finally, if a varied morphology is found in the form of bullas and necrosis, it can be marked (IR), which is interpreted as an irritant reaction. The results of "+", "++", "+++" on the 72nd hour reading are interpreted as allergic. If a crescendo or plateau reaction pattern is obtained, it is suspected to be allergic, whereas if a decrescendo pattern is obtained, it is suspected in the direction of irritants. (Lazzarini R., Duarte I. & Ferreira A. L., 2013).

In patients, the results of the reading of the patch test commercial drug for Griseofulvin positive one (+) on the reading day 2 and 4 and a question positive sign (? +) on the reading day 7. The patient was interpreted as having a mild allergy to Griseofulvin. In addition, the results of question positive marks (? +) on Amoxicillin were obtained on the readings day 2, 4, and 7 so that they were interpreted as doubtful. For aspirin and ibuprofen, question and positive marks (?+) were obtained only on day 4 readings, while those on day 2 and day 7 were negative (-). The patient was interpreted not to be allergic to Aspirin and Ibuprofen. Finally, negative results were obtained on the reading days 2, 4, 7 for Clindamycin so that patients were interpreted not to be allergic to Clindamycin.

False positives can be caused by impurity of the test material, irritation due to the vehicle, lack of antigen dilution in the vehicle, reactions arising from the adhesive, local pressure effects

produced by solid material outside the material (e.g tight clothing) and finally the excited skin syndrome (angry back). The causes of false negative are lack of antigen penetration, false timing for reading, previous treatment with corticosteroids or UV radiation on the test location, systemic therapy with corticosteroids and / or immunosuppressant drugs, degradation of allergen, separate testing of each component (in this case, new substances cause allergic reactions only when the components are mixed), the test material is wet or lost, the substance being tested is photosensitizing and photopatch testing is not carried out, and the inability to reproduce conditions as same as the location of dermatitis (e.g different condition of skin moisture in the area that has contact dermatitis and the area undergoing the test). (Barbaud A., 2009)

In our patient, efforts are made to prevent false positive results by using generic commercial preparations with a single active ingredient, removing the drug shell and grinding the caplet before smoothing the ingredients, applying a 10% concentration as recommended, using non-allergenic adhesive, giving 15-20 minutes time before reading after removal of the finn chamber to avoid the effects of pressure and advise patients not to wear tight underwear during attachment.

To avoid false negative we conducted reading time of day 2,4,7 according to recommendations, forbade patient to use topical corticosteroids in the tested area, prohibited the use of corticosteroid drugs and systemic immunosuppressants, suggested patient to avoid activities that cause profuse sweating and protect the back area from water during daily bath.

In terms of safety, drug patch tests can re-induce ACDR as reported using acyclovir, amoxicillin, beta lactam antibiotics, carbamazepine, clobazepam, and several other drugs. (Barbaud A., 2005) However, these patients did not get ACDR relapses even up to one month after the test .

CONCLUSION

One diagnostic modality that can be used to overcome the clinician's problem in determining the drug that causes ACDR cases, patch tests, is a procedure that requires proper preparation and execution techniques. Involves not only clinicians but also the patient. Some things to consider in patient preparation are forbidding patients to use topical corticosteroids in the area to be tested or taking corticosteroid drugs and systemic immunosuppressants for a certain period of time, advising patients not to wear tight underwear during attachment, and asking patients to avoid activity which causes sweating and wet the back area. In the case of preparation of test drugs, care should be taken to use the purest drug preparations, the application of appropriate drug concentrations and vehicle types, and the use of non-allergenic adhesive. Although the patch test falls under category B which means that this test has moderate evidence of strength, the practice and experience of the clinician conducting the patch test greatly influences the results and this methodology can be an excellent tool for determining the diagnosis and etiology of ACDR.

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