



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM

Date: October 11, 2005

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Re: Consult #773 – Received by Clinical Reviewer on October 3, 2005 – A supplemental NDA for modafinil for the indication of ADHD in children and adolescents identified a single case of SJ in a trial of about 600. In addition, there were two other cases of concern (vesiculobullous lesion, and morbilliform rash). Review of AERS has identified 7 unique cases in the post-marketing experience. A regulatory decision is due 10/20. We need someone to evaluate these cases and make a determination. PK studies have identified a sulfone metabolite significantly higher than the parent for young children.

Material Reviewed: Consult request, literature, AERS DataMart Cases.

Review:

The exact relationship of Provigil to the drug rash cases presented is not entirely clear. However, the AERS cases appear to support labeling that would specifically address those concerns and recommend the seeking of medical attention with the acute onset of a rash while on this drug.

Case 1 – A seven year old Asian boy with ADHD who began treatment with modafinil who developed sore throat and fever with a mild rash. According to the report, the timing of the onset of rash vs. dosing with amoxicillin are not clear (day 16 vs. day 17). The rash eventually became extensive and severe. A Rapid Strep Test on day 17 was negative. The patient had extensive skin peeling with mild to moderate skin blistering. No indication of a positive Nikolsky sign was given, nor were biopsy results, if any, described. On study day 23, the rash progressed to mucosal involvement and a diagnosis of erythema multiforme/Stevens-Johnson syndrome was given by a dermatologist.

On review of this case, the case is compatible with a diagnosis of Steven's Johnson syndrome or erythema multiforme major. It is not clear that the condition progressed to a toxic epidermal necrolysis in this patient. Modafinil may have been involved in the patient's drug rash. However, due to the timing, it is not clear whether amoxicillin may have been instead responsible. A viral infection leading to this condition as described is also a possibility. To rule out amoxicillin, a penicillin allergy determination via RAST might be obtained. If negative, that would still leave the possibility that the rash was due either to modafinil or due to a viral infection with an acute hypersensitivity syndrome.

Case 2 – An 11 year old Caucasian girl with ADHD with a maculopapular (morbilliform) rash that developed on day 4. A dermatologist examined the patient and established that the condition was not Stevens-Johnson syndrome, but rather a moderate morbilliform rash. Mucosal blisters or erosions were not present. The patient was treated with an antihistamine and the rash resolved less than a week later.

On review of this case, it is not consistent with a necrotizing dermatitis. A morbilliform drug rash was the likely diagnosis with a Type I hypersensitivity rather than a erythema multiforme type of rash.

Case 3 – An 8 year old white boy with ADHD with a mild fever, rash on the cheeks and severe blisters on the lips 14 days after starting modafinil. The study drug was discontinued and cephalexin and acetaminophen with codeine was given for the fever and pain related to the rash.

This data for this case was too sparse to make a definitive diagnosis. It is not clear whether the rash was attributed to the drug or to a viral infection.

AERS Cases – In addition to the three cases from clinical studies, 5 cases were provided from AERS Datamart that had the terms Stevens-Johnson and erythema multiforme. These cases appear to be consistent with a skin rash that may be attributable to modafinil.

Sulfone metabolite – The presence of a sulfone metabolite suggest the possibility of hypersensitivity in those patients allergic to sulfones. Correlation of sulfone allergy to a rash due to modafinil does not appear to have been documented. Consideration for additional evaluation for such a possibility is recommended.

Recommendations –

- 1) More specific evaluations regarding drug rashes may be requested in future studies with this drug. Drug rashes should be assessed by a qualified dermatologist. Skin biopsy where appropriate should be obtained. Photographs for documentation are encouraged.
- 2) Labeling for modafinil should include an update to the adverse events section and other sections as determined to be appropriate by the medical review team (e.g. WARNINGS and PRECAUTIONS). Parents of pediatric patients and patients should be informed to seek medical attention when a rash is evident after starting therapy with modafinil.
- 3) Follow-up for Case 1 could be conducted with regard to allergy to penicillin vs. modafinil. Follow-up of hypersensitivity reactions for sulfur/sulfone allergy could be conducted. These hypersensitivity reactions might be conducted via evaluation of serum from these subjects for elements associated with allergy, e.g. RAST testing for penicillin and sulfone.

Thank you for giving us the opportunity to assist you. Please do not hesitate to contact the Division of Dermatologic and Dental Drug Products with any additional questions or concerns.

For morbilliform drug rashes and hypersensitivity to penicillin:

(<http://www.clevelandclinicmeded.com/diseasemanagement/allergy/penallergy/penallergy.htm>)

The presence of IgE antibodies to penicillin can be detected through a skin test to penicillin or a radioallergosorbent test (RAST) to penicillin.

The skin test for penicillin demonstrates the presence or absence of specific IgE antibodies to major and minor penicillin determinants. IgE antibodies to major determinants can be detected by using benzylpenicilloyl polylysine (Pre-Pen). Minor determinant reagents are not commercially available, although penicillin G at concentration of 10,000 U/mL has been used as a partial source of minor determinant.⁷ Methods of preparation of the minor determinants have been published elsewhere. Histamine and saline skin tests are used as a positive and negative control, respectively.

Prick testing is done first, and the results are read 15 to 20 minutes later. If the prick test findings are negative, intradermal testing is performed.

The skin test is positive if the major or minor determinant tests have a wheal that is larger than 3 mm that the wheal produced by the negative saline control. Both prick and intradermal tests are done using diluted penicillin G at a concentration of 10,000 u/ml, Pre-pen at full strength and minor determinant mixture if available. If skin test for penicillin using major determinants (benzylpenicilloyl), a mixture of minor determinants and penicillin G is negative, up to 99% of patients will tolerate penicillin. If skin testing using benzylpenicilloyl and penicillin G (as the sole source of minor determinants) is negative, approximately 97% of patients with a negative skin test will tolerate penicillin. However, a few patients who are at risk for anaphylactic reaction will be missed with this testing method because penicillin G does not contain all the minor determinants.

Up to 4% of patients with a negative skin test to both the major and minor determinants will develop non-life-threatening allergic reactions if they receive penicillin again.¹¹ [Anaphylaxis](#) to penicillin in patients with a history of penicillin allergy and a negative penicillin skin test has not been reported.⁴ On the other hand, if a patient has a positive history and a positive skin test to penicillin, there is a 50% or greater chance of an immediate IgE-mediated reaction if penicillin is received again. These patients should receive an equally efficacious alternative antibiotic or be desensitized.

A penicillin skin test predicts only the presence of IgE antibodies for the major or minor penicillin determinants at the time of application and does not predict the future development of IgE-mediated reactions during subsequent courses of penicillin. A penicillin skin test does not predict non-IgE-mediated reactions caused by other immune mechanisms, such as cytotoxic antibody-mediated reactions, antibody-antigen immune complex-mediated reactions, and delayed-type cell-mediated reactions.

The detection of IgE antibodies to penicillin by a skin test is affected by the amount of time between the original allergic drug reaction and the skin test. Many patients with documented IgE antibodies to penicillin by skin test lose the sensitivity with time. It is estimated that up to 80% of patients with a history of immediate reactions to penicillin will have a negative skin test at 10 years.¹² However, these patients may be at increased risk of sensitization to penicillin on subsequent administration compared with the rest of the population.

The RAST and the enzyme-linked immunosorbent assay (ELISA) are also used to detect IgE antibodies, but only to the major penicillin determinant. Therefore, these tests are less sensitive than the skin test. On the other hand, a positive RAST result indicates the presence of IgE antibodies to penicillin, and patients with a positive test should be considered at increased risk for reaction.

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/s/

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