Original Article

Basophil Activation Test in Immediate-Type Hypersensitivity Reactions to Betalactams Using CD63 and CCR3 in Thailand

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Objective: To determine usefulness of basophil activation test [BAT] in diagnosis of immediate betalactam [BL] allergy, and compare the role of diagnosis BAT with standard testing, skin test [ST], and drug provocation test [DPT] in patients with history suspected of drug allergy in Thailand.

Materials and Methods: Cross-sectional study of fifteen patients with an history of immediate hypersensitivity reactions to common BL drug group, at Ramathibodi Hospital between 2010 and 2012. All subjects underwent ST, and DPT if ST was negative. BAT was done in all patients.

Results: Fifteen patients (10 children and 5 adult), including seven male and eight female cases with history of highly indicated immediate type allergic reactions to beta lactam were examined. Five presented with anaphylaxis and 10 with urticarial rash/angioedema. From fifteen patients, eight patients were confirmed allergic to BL, where four had ST positivity, and four had positive DPT. The present study found one patient with severe anaphylaxis that had negative ST, but could not undergo DPT due to underlying diseases. The alternative test BAT yielded positive result. Four of the eight patients were confirmed as BL allergic patients with positive BAT (50%). None of the patients with negative drug testing had positive BAT. Estimated sensitivity of ST was similar to BAT at 50%, while specificity of BAT in the present study was 100%. The result yielded higher sensitivity, such as 62%, when we combined both tests together (ST and BAT). The authors observed BAT positive results in 75% of patients with positive ST, and 25% of patients positive DPT.

Conclusion: BAT has an advantage in patients contraindicated to perform DPT. Moreover, BAT can avoid the risk of reproducible reactions from in vivo testing, especially in high-risk patients allergic to BL. BAT is a promising alternate investigation tool ensuring patients' safety.

Keywords: BL hypersensitivity, Drug allergy, Drug hypersensitivity, Immediate type hypersensitivity, Drug allergy testing

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Betalactams [BL] and derivatives are a class of broad spectrum antibiotics. They contain a BL ring in their molecular structures. This consists of penicillin deivatives (penams), cephalosporin (cephems), monobactams, and carbapenems. Most of BL antibiotics work by inhibiting cell wall biosynthesis of pathologic micro-organism. Today, they are widely used agents and are some of the most commonly prescribed antibiotics in clinical practices. Recently, the incidence report of adverse drug reactions [ADR] from penicillin in children was 14.9% of all reported events in 2007[(1)].

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Another prospective drug hypersensitivity reaction [HSR] surveillance cohort in adult patients at Ramathibodi Hospital between 2008 and 2009 reported that BL accounted for 33% of all agents suspected to cause HSR. However, the incidence of definite true drug allergy in the group reporting unexpected reaction was approximately 10%, while 90% of patients were not truly allergic[(2)]. Patients with a history of suspected drug allergy should be investigated to confirm diagnosis. Otherwise, unnecessary avoidance and excessive exposure to alternative drugs to prevent risk of allergy may lead to increased medical costs and increases the risk of drug-resistant organisms. Moreover, patients who were under-diagnosed for severe drug allergy still having chances to have serious reactions if they are re-exposed to the cross-reactive substances.

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Standard drug testing for immediate HSR consists of in vivo tests, starting from primary skin tests [ST], including skin prick test [SPT] and intradermal test [IDT]. If this primary test was negative, then a drug provocation test [DPT] and others in vitro testing, consisting of specific Immunoglobulin E [IgE] and basophil activation test [BAT] need to be done[3]. However, ST has several limitations, such as poor sensitivity, which was reported from 55% to 70% of true positive rate[4], lack of standard allergens for drug without intravenous preparation problem, denial to cooperate due to the painful procedure of IDT, particularly in young children, and risk of serious systemic reaction. Co Minh HB and working group had reported systemic reactions after BL ST in 1.3% of 998 patients or in 8.8% of patients with positive results[5]. However, a large US data had revealed lower incidence of systemic reaction of 0.12% from 1,710 patients, or 2.3% of patients with positive results[6].

Patients with negative ST could undergo DPT, which could produce allergic symptoms. Even though, the reactions are usually less severe and controllable with medication, the physician who performs drug testing should be aware of rapidly occurring anaphylaxis or serious reactions, which may cause death. DPT is contraindicated in patients with severe medical illness conditions, such as cardiovascular disease, chronic respiratory disease and infection, and pregnancy because of the risk of severe reactions and difficulty in controlling symptoms[7].

The European Network for Drug Allergy [ENDA] has devised a short diagnostic algorithm for immediate allergic reactions to BL[8,9]. Patients with negative ST should be evaluated by in vitro testing to increase the work-up sensitivity and screen patients before undergoing DPT. In vitro testing is safe and would be appropriate for children as it requires a single blood sample.

Commercially available in vitro test using immune CAP system to detect specific IgE to penicillin, namely CAP-FEIA (Phadia, Uppsala, Sweden) generally has lower sensitivity than ST, approximately 50%. When combining CAP-penicilloyl G and -amoxicillin to detect penicillin allergy, the high specificity is 96% to 100%[10]. Despite its overall lower sensitivity, it was positive in 42% of patients with negative ST but positive DPT, and would reduce the need of DPT in these patients. Another study found very low sensitivity of CAP-FIEA of 6.7% and specificity of 93% for BL allergy. This may be because of limited availability of CAP-FEIA to cephalosporin. Homemade radio-allergosorbent test had higher sensitivity of 46.7%, but lower specificity of 73.3%[11]. The sensitivity and specificity of both tests varied based on the initial clinical presentation of the patients.

BAT was developed by Sainte-Laudy et al in 1990, and the first study using this method was published in 1996[12]. Detection of the CD63 surface marker as a marker of basophil activation was performed using flow cytometry technique and fluorescent monoclonal antibodies[13]. In most of the results from previous studies, sensitivity of BAT was better compared to specific IgE[8,14,15]. The reports of BAT sensitivity using CD63 among patient with BL allergy ranged from 29% to 50% with specificity range from 89% to 97%[13,15-17]. However, when combined markers such as CD63 and CCR3 markers were used as parallel testing, the sensitivity increased to 55% with specificity of 100%[18]. In addition, a study of BAT using CD63 and CD203 among patient with moderate to severe anaphylaxis to culprit drugs such as cephalosporin, antihistamine, or insulin found positive rate of 73.7%. The strength of this test was quick result, safe and reliable[19]. BAT is recommended for diagnosis of immediate-type hypersensitivity to BL and can be used together with other in vitro tests[20].

The aim of the present study was to determine the usefulness of BAT including its diagnostic properties (sensitivity, specificity) and patients' perspective (co-operation of children and adult subjects) compared with standard ST and DPT.

Materials and Methods

Patients

All the pediatric and adult patients with a history of immediate-type HSR to common BL, including penicillin G sodium [PGS], amoxycillin [Amx], amoxicillin/clavulanate potassium [Aug], ampicillin [Amp], and ceftriaxone [Cef], at the Out-patient Department [OPD] or the In-patient/Ward, Ramathibodi Hospital during 2010 to 2012 were enrolled. The present study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (IRB No.02-54-06). The definition of immediate-type HSR was defined as the following signs and symptoms that occurred within 24 hours after taking suspected drugs: erythematous eruption/flushing, urticarial rash, angioedema, anaphylaxis, conjunctivitis, rhinitis, and bronchospasm/asthma. Written informed consent was obtained before demographic and allergy history information was collected. ST, DPT, and blood sample collection were

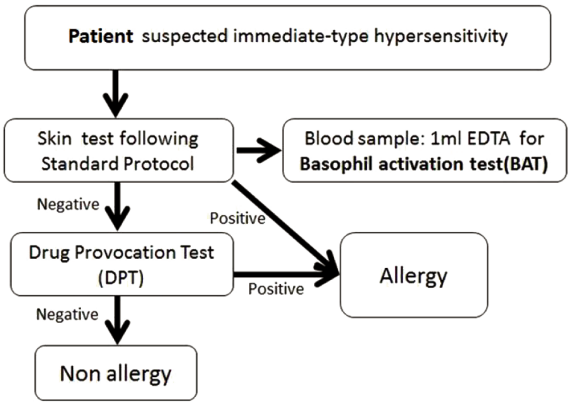

Figure 1. Flow chart of the diagnostic study.

scheduled after resolution of HSR, and all patients were in stable condition, see Figure 1.

Skin testing

ST or SPT or epicutaneous ST was performed using the Duotip-Test® (Lincoln Diagnostics, Decatur, IL, USA), with 1% histamine as a positive control and 0.9% NaCl as a negative control. A BL ST battery was used according to ENDA recommendations[8,21], comprising of PGS 25,000 U/ml, Amp 20 to 25 mg/ml, Aug 20 to 25 mg/ml, and Cef 2 mg/ml. SPT results were read after 15 minutes and considered positive result when the wheal diameter was greater than 3 mm. Patients with negative SPT proceeded to IDT by injection of a drug solution to produce a wheal of 4 to 5 mm, and the result was read after 20 minutes. Culprit drug concentrations were diluted from 1/10 to 1/100, according to severity of allergic history, and if negative, the concentration was incrementally increased, not exceeding irritating concentration. Positive IDT was considered when the wheal diameter was double or increased greater than 3 mm from the injection wheal, together with pruritus or flares. If the ST result was positive, a diagnosis of IgE-mediated immediate HSR was made and DPT was performed with an alternative drug which gave negative ST results.

Drug provocation test

Patients with negative ST results underwent DPT by oral or intravenous route, depending on the type of antibiotic. DPT began with the smallest dose and with incremental increases of dosage every 30 minutes to reach a cumulative dose as close as possible to the maximum daily dose, adjusted by weight. Protocols were as followed: PGS intramuscularly 1,000 U, 10,000 U, 50,000 U, 100,000 U, 500,000 U, 1 mU; Amx orally 5, 10, 50, 100, 250, 500 mg (for adults, a final dose of 1,500 mg was added); Aug orally 5, 10, 50, 100, 250, 500 mg of amoxicillin (for adults, a final dose of 1,000 mg of Amx was added); Cef intravenously 10, 50, 100, 300, 540 mg (for adults, a final dose of 1,000 mg was added). Objective signs and symptoms relevant to clinical history occurring within 24 hours after the last dosages was considered positive DPT.

Basophil activation test

Fifty µL of Ethylene-diamine-tetra-acetic acid [EDTA] blood was collected on the day of ST or DPT and BAT was immediately performed using Flow2CAST® technique, (BÜHLMANN Laboratories, Basel, Switzerland). Stimulation control reagents were anti-FcεRImAb and fMLP. Measured basophil activation markers were CCR3-PE and CD63-FITC. Drugs were reconstituted with injection-grade water in various concentrations according to a dose-response curve, and were prepared immediately before use as follows: PGS 200, 1,000, and 5,000 mcg/ml; Amp 100, 1,000 and 2,500 mg/ml; Aug 100, 1,000 and 2,500 mg/ml; Cef 100, 1,000, and 2,500 mg/ml. BAT was performed according to the protocol of the Flow2CAST, similar to a previous study using Flow2CAST[16]. Results were analyzed using a flow cytometer to calculate the percentage of CD63-positive cells compared with the total amount of basophilic cells. Results were obtained if the background was less than 5±1%. A positive result was confirmed when the stimulation index [SI] was 2 or greater (SI = ratio between CD63-positive cells activated by allergen and negative control). An example of positive BAT result is shown in Figure 2.

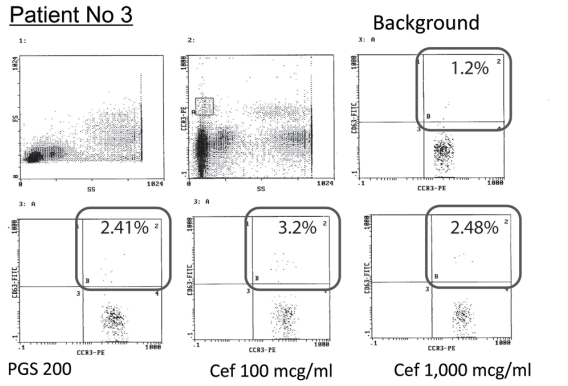

Figure 2. Example of positive BAT results in this study.

Statistical analysis

Descriptive statistics for population data were analyzed and reported. The descriptive data were presented as mean, standard deviation [SD], median, and ranges (min to max), frequency, and percentage were used. The Chi-squared (χ^2) and Fisher's exact test were used to analyze statistics. The diagnostic statistics consisted of sensitivity and specificity of BAT compared with DPT or ST was analyzed. A *p*-value smaller than 0.05 was considered as statistically significant. All of the analyses were performed using Stata 14.0 software (College Station, TX, USA).

Results

Fifteen patients (10 children and 5 adult), seven males and eight females, were definitely diagnosed as immediate-type HSR from all of the patients that met the inclusion criteria. Age of children group; mean ± SD (ranges) was 10.0±2.6 (5.0 to 13.0) years old, and adult group was 67.8±12.6 (51.0 to 82.0) years old, respectively. The median delay between the reaction and drug testing was 12 months (ranging from 1 month to 12 years, SD 37.7 months) and the median of the onset of reaction was 50 minutes (ranging from immediately to 180 minutes, SD 56.4 minutes). As shown in Table 1, eight patients were categorized as having definite drug allergy according to positive ST (patient numbers 1 to 4), and positive DPT (patient numbers 6 to 9). DPT showed equivocal results in two patients with negative ST (numbers 10 and 11). Patient number 10 had a history of nasopharyngeal carcinoma and gastrointestinal [GI] lymphoma post-chemotherapy and radiotherapy, and presented with septic shock from bacterial septic arthritis. He had a history of localized urticarial rash at the anterior of the neck after intravenous Cef. After completion of DPT with intravenous Cef, he had transient pruritus without any rash, which spontaneously resolved few minutes later. Patient number 11 had underlying intermittent idiopathic urticaria, and showed mild, transient, self-limited urticarial rash after a full therapeutic dose of Amx during DPT. Overall, these two equivocal results were considered as negative DPT because mild pruritus and mild transient urticarial reaction could be presentations of the patients' underlying skin disorders. Four patients (numbers 12 to 15) were negative for both ST and DPT. One patient (number 5) with negative ST, but DPT could not be performed because of uncontrolled underlying disease. Among the four patients who had ST positivity, one had a positive reaction by SPT to Amp and Aug, as well as IDT positive to PGS. The other three patients had positive IDT to Cef, Amp, and Aug. The sensitivity of ST in patients with immediate-type HSR to BL was 50%, estimated by calculation from four out of eight patients who were truly allergic. Baseline characteristics of patients and test results are presented in Table 1.

BAT was performed on all 15 patients, BAT was

Table 1. Baseline characteristics of patients and test results

Case No.	Sex/age	Onset (minute)'/reaction	Culprit drugs	Skin test	DPT result	Lag period before BAT	BAT result
1	F/60	20'/anaphylaxis	Cef	IDT+Cef	-	6 months	-
2	F/82	5'/anaphylaxis	Aug	IDT+PGS SPT+Amp, Aug	-	6 months	+PGS, Amp, Aug
3	M/11	20'/angioedema	Cef	IDT Amp	-	1 year	+PGS, Cef
4	M/10	60'/macular exanthema and pruritis	Aug	IDT+PGS, Aug	-	4 years	+PGS
5	F/77	Immediate/anaphylactic shock	Cef	Negative	ND	7 months	+Cef
6	F/51	120'/anaphylaxis	Cef	Negative	+Cef	2 years 9 months	-
7	M/11	120'/urticaria	Amx	Negative	+Amx	2 years 6 months	-
8	M/13	180'/angioedema	Amx	Negative	+Amx	12 years	-
9	M/6	30'/angioedema	Amx, Aug	Negative	+Aug	6 years	+Aug
10	M/69	45'/localized urticaria	Cef	Negative	Cef-negative	7 months	-
11	F/11	60'/urticaria	Aug, Amx	Negative	Amx-negative	2 months	-
12	F/13	60'/urticaria	Amx	Negative	Amx-negative	5 years	-
13	F/5	5'/erythematous patch and papule	Cef	Negative	Cef-negative	2 months	-
14	M/10	60'/urticaria	Aug	Negative	Aug-negative	2 years	-
15	F/10	60'/urticaria	Aug	Negative	Aug-negative	3 years	-

Amp = ampicillin; Amx = amoxicillin; Aug = amoxicillin/clavulanate potassium; BAT = basophil activation test; Cef = ceftriaxone; DPT = drug provocation test; F = female; IDT = intradermal test; M = male; ND = not done, PGS = penicillin G; SPT = skin prick test

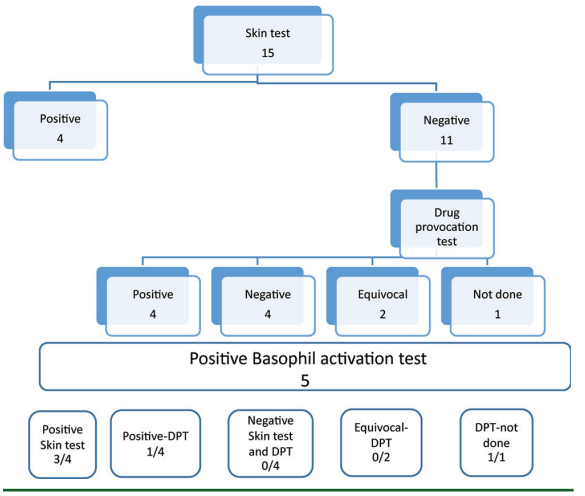

Figure 3. Results of skin test, drug provocation test and basophil activation test.

positive in four out of eight patients who were truly allergic (3 from positive ST, 1 from DPT). Drugs that resulted in a positive BAT were PGS, Amp, Aug, and Cef. Moreover, none of the patients with equivocal or negative DPT had positive BAT, as shown in Figure 3. BAT sensitivity among patients with immediate-type HSR to BL was 50%, with a specificity of 100%. When analyzing the four patients who had positive ST results, BAT sensitivity was 75% (positive in three out of four patients). Similarly, the sensitivity was 25% in patients with positive DPT (positive in one out of four patients). A combination of ST and BAT revealed sensitivity of 50% and preserved the specificity of 100%. In the present study, all patients cooperated well in performing BAT and no one had serious adverse reactions from drug testing.

Discussion

The present study revealed that the sensitivity of ST among patients with immediate-type HSR to BL was 50%, similar to that of BAT. When these two techniques were combined, the sensitivity increased to 62.5%, and BAT could prevent one out of four patients with negative ST from having reproducible allergic symptoms when undergoing DPT. Moreover, the diagnosis of one patient contraindicated to DPT could have been confirmed with a positive BAT test. If this patient was to be included in the allergic patient (n = 9), the sensitivity of BAT would be higher than ST, 55% compared to 44%, respectively, and the combined sensitivity would be 66%.

Torres et al (2004), BAT showed positivity of 50.9% in patients with ST positive[15]. When compared to the present study, the author demonstrated a higher sensitivity (75%). This could possibly be related to the use of CCR3 marker, which might have increased the sensitivity of BAT.

De Weck et al (2009)[16] conducted a similar study in 181 patients using the FlowCAST® method and sulfidoleukotriene release assay (CAST-ELISA). Five determinants were used, benzathine penicillin, benzylpenicilloyl poly-L-lysine, minor determinant mixture, Amx, and Amp. The sensitivity of FlowCAST was 50% when using all the determinants. In patients who were ST negative, FlowCAST positivity was 37%, with specificity of 89% to 97% for each determinant[16]. Similar to our study, they reported the BAT sensitivity in 25% of patients with positive DPT. Thus, BAT could be used as alternative test, and prevent severe allergic reaction in contraindicated patient with DPT in which one fourth of these patients had negative ST.

Conclusion

BAT has advantage over DPT in case of severe anaphylaxis or contraindication to DPT, because it can prevent 25% of patients from reproducing reactions they undergo DPT. The other advantages are good cooperation to do the test procedure, even in small children, and ex vivo challenge makes it a multifaceted and promising tool for the allergist. However, the cost of performing BAT is higher than other test modalities and might not practical for some hospitals. Finally, to diagnose drug allergy, multiple modalities of drug testing need to be performed. The authors suggest that if available, BAT could be considered because of patients' safety.

The present study still has limitation based on the low incidences and rare proven immediate-type HSR to BL allergy. The cross-sectional study design can demonstrate small amount of immediate-type allergic reaction patients. Therefore, further design study in a larger sample size should be explored for solid conclusion of diagnostic accuracy. The present study of penicillin ST reagent did not include major and minor determinant of penicillin, which were not available in Thailand, thus can reduce the sensitivity of ST when compare to other studies[22,23].

What is already known on this topic?

Patients suspected of immediate type allergy to BL should perform investigation to confirm diagnosis. The ENDA has devised a short diagnostic algorithm including in vitro test among patients with negative ST to increase the work-up sensitivity and screen patients

before undergoing DPT. In vitro testing is safe and would be appropriate for children as it requires a single blood sample. BAT is one of the recommended in vitro test with various sensitivity and specificity between different methods.

What this study adds?

After performing BAT with CD63 and CCR3 marker detection method, estimated sensitivity of ST was similar to BAT of 50%, while BAT specificity was 100%. Combined testing (ST and BAT) resulted in higher sensitivity of 62%. The authors observed BAT positive results in 75% of patients with positive ST, and 25% of patients with positive DPT. BAT has advantage in patients who contraindicated to perform DPT. Moreover, BAT can avoid risk of reproducible reactions from in vivo testing, especially in high-risk patients. When available, we suggested that BAT should be performed to maintain patients' safety.

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Potential conflicts of interest

None.

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การทดสอบการแพ้ยากลุ่มยาบีตาแลคแทมแบบเฉียบพลัน โดย basophil activation test โดยใช้ CD63 และ CCR3 ในประเทศไทย

ปองทอง ปูรานิธี, ทิชา ฤกษ์พัฒนาพิพัฒน์, วสุ กำชัยเสถียร, โสมรัชช์ วิไลยุค, วิภารัตน์ มนุญากร, ศักดา อาจองค์ วัลลิภากร, สุวัฒน์ เบญจพลพิทักษ์

วัตถุประสงค์: เพื่อศึกษาประโยชน์ของ basophil activation test [BAT] ในการวินิจฉัยการแพ้ยาบีตาแลคแทมแบบเฉียบพลัน และเปรียบเทียบ BAT กับการทดสอบการแพ้ยามาตรฐานที่ปฏิบัติทั่วไป เช่น การทดสอบความไวทางผิวหนัง การทดสอบโดยวิธี drug provocation test [DPT] ในผู้ป่วยที่สงสัยมีการแพ้ยาในประเทศไทย

วัสดุและวิธีการ: การศึกษาแบบตัดขวาง โดยรวบรวมผู้ป่วยที่มีการแพ้ยาบีตาแลคแทมที่ใช้กันทั่วไปแบบเฉียบพลัน 15 ราย ที่แผนกผู้ป่วยนอกเด็กและอายุรกรรม คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี ตั้งแต่ พ.ศ. 2553 ถึง พ.ศ. 2555 โดยผู้ป่วยทุกรายจะได้รับการทดสอบการแพ้ทางผิวหนัง (skin test) และการทดสอบการแพ้ยาด้วยวิธี DPT ในรายที่มีผลการทดสอบทางผิวหนังให้ผลเป็นลบ โดยทุกรายจะผ่านการทดสอบการแพ้ยาด้วยวิธี BAT

ผลการศึกษา: ผู้ป่วยทั้งสิ้น 15 ราย ที่มีประวัติสงสัยการแพ้ยาบีตาแลคแทม (เด็ก 10 ราย และผู้ใหญ่ 5 ราย) โดยแบ่งเป็นเพศชาย 7 ราย และหญิง 8 ราย พบว่า 5 ราย มีอาการนำด้วยอาการแพ้รุนแรงแบบ anaphylaxis 10 ราย มีอาการนำด้วยอาการผื่นลมพิษ หรือ อาการแพ้บวมรุนแรง (angioedema) จากผู้ป่วยทั้งสิ้น 15 ราย พบเพียง 8 ราย ที่ตรวจยืนยันแน่นอนว่ามีการแพ้ยากลุ่มบีตาแลคแทม 4 ราย พบให้ผลบวกต่อการทดสอบการแพ้ทางผิวหนัง และอีก 4 ราย ให้ผลบวกต่อการทดสอบด้วยวิธี DPT พบผู้ป่วยหนึ่งรายที่มีอาการแพ้รุนแรงแบบ anaphylaxis แต่ให้ผลทดสอบที่เป็นลบต่อการทดสอบการแพ้ทางผิวหนัง แต่ไม่สามารถส่งทำ DPT ได้ด้วยข้อจำกัดของโรคประจำตัว เมื่อเปลี่ยนไปส่งตรวจโดยวิธี BAT กลับพบผลที่เป็นบวก นอกจากนี้ผู้ป่วย 4 ราย จาก 8 ราย ที่ได้รับการยืนยันว่าแพ้ยาจริง ได้ผลบวกจากการทดสอบโดย BAT (ร้อยละ 50) ไม่พบว่าผู้ป่วยที่ให้ผลลบต่อการทดสอบการแพ้โดยวิธีมาตรฐาน กลับมาได้ผลการทดสอบเป็นบวกเมื่อทดสอบด้วย BAT (ร้อยละ 100) ผลที่ได้จากการศึกษาพบว่าได้ค่าความไวของการทดสอบของ BAT เพิ่มสูงขึ้นเท่ากับร้อยละ 62 เมื่อรวมการ BAT และการตรวจทดสอบการแพ้ทางผิวหนัง โดยสามารถสังเกตได้ว่าผล BAT จะให้ผลบวก ร้อยละ 75 ในผู้ป่วยที่ให้ผลบวกต่อการทดสอบการแพ้ทางผิวหนัง และผลทดสอบให้ผลบวกอีกร้อยละ 25 ในผู้ป่วยที่การทดสอบโดย DPT ให้ผลบวก

สรุป: การทดสอบการแพ้ยาบีตาแลคแทมแบบเฉียบพลัน โดย BAT มีประโยชน์ในผู้ป่วยที่มีข้อห้ามในการทดสอบโดย DPT และสามารถช่วยเลี่ยงความเสี่ยงจากการเกิดอาการแพ้ยาเมื่อทดสอบการแพ้ยาแบบ in vivo โดยเฉพาะอย่างยิ่งในผู้ป่วยที่มีความเสี่ยงสูง จึงแนะนำให้ทำการทดสอบการแพ้ยาโดย BAT ซึ่งเป็นอีกทางเลือกหนึ่งในการส่งทดสอบการแพ้ยา เพื่อป้องกันการเกิดอาการแพ้และเพื่อความปลอดภัยของตัวผู้ป่วยในสถานพยาบาลที่มีความพร้อม