The Thai Anesthesia Incident Monitoring Study of Perioperative Allergic Reactions: An Analysis of 1996 Incidents Reports

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Objectives: *Analyze the clinical course, management, outcome, and contributing factors of perioperative allergic reactions in the Thai Anesthesia Incident Monitoring Study (Thai AIMS).*
Material and Method: *A prospective descriptive multicenter study was conducted in 51 hospitals across Thailand. Voluntary, anonymous reports of any adverse or undesirable events during the first 24 hours of anesthesia were sent to the Thai AIMS data management unit. Possible perioperative allergic reactions were extracted and examined independently by three peer reviewers.*
Results: *Forty-three reports of possible perioperative allergic reactions from the 2,537 incidents reported to the Thai AIMS (1.6%) were reviewed. There was a female predominance (1.9:1). The most common features were cutaneous manifestations (93%), arterial hypotension (20.1%), and bronchospasm (11.6%) respectively. The severity grades were 69.8% in grade I, 4.7% in grade II, and 25.6% in grade III. The three most suspected causative agents were neuromuscular blocking agents (39.5%, 30.2%-succinylcholine), antibiotics (27.9%), and opioids (18.6%) respectively. All but one responded well to treatment with complete recovery. One patient suffered acute myocardial infarction and had to stay at the hospital for longer than one week. None had further allergic reaction.*
Conclusion: *Perioperative allergic reactions accounted for 1.6% of anesthetic adverse events. The most common features were cutaneous manifestations. A quarter of these were life-threatening but responded well to treatment. The most common suspected causative agent was succinylcholine.*

Keywords: *Allergic reactions, Anesthetics, Perioperaive, Multicenter study, Anaphylaxis, Anaphylactoid reaction*

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Anaphylaxis is a cluster of signs and symptoms related to the release of histamine and other mediators following administration of a drug. Anaphylactic reaction in patients under general anesthesia may involve any combination of signs and symptoms originating from cardiovascular, respiratory or integumentary system. Some of these signs and symptoms can be life-threatening.

Histamine, as well as many other mediators, releases from mast cells following the administration of a drug that is either an anaphylactoid (non-immunological or pharmacological) or an anaphylactic (immunological or IgE mediated) reaction. Anaphylactoid and

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anaphylactic reactions are clinically indistinguishable, hence the term 'allergic reactions' is implied in the present report.

The incidence of anaphylaxis was between 1 in 3,500 and 1 in 20,000 anesthetics[1,2]. In fact, the incidence should be much higher since less severe reactions have been missed. From THAI Study, the incidence of perioperative allergic reactions in Thailand was 1 in 5,500 anesthetics[3]. Although rare, these reactions may lead to death, even when appropriately treated. Prompt and correct diagnosis is vital for early optimal management of life-threatening anaphylaxis regardless of etiology or mechanism.

The purpose of the present study was to identify possible perioperative allergic reactions from the expected 2,000 incidents reported to the Thai Anesthesia Incident Monitoring Study (Thai AIMS), and to examine and classify them with respect to clinical course, management, outcome and some contributing factors for possible future preventive strategy.

Material and Method

Thai AIMS is a multicenter study conducted in 51 hospitals across Thailand. The study is a prospective descriptive design and has been approved by each institutional ethical committee. Thai AIMS involves the voluntary, anonymous reporting of any adverse or undesirable events, during the first 24 hours of anesthesia that reduced or could reduce the safety margin for the patient. For this initial phase, 2,000 incident reports are expected for the analysis. Thai AIMS's detailed methods and overall results have been described elsewhere[4,5].

Forty-six completed records of possible perioperative allergic reactions were extracted from 2,537 incidents reported in 1,996 patients for detailed examination. The records were reviewed independently by three peer reviewers with a consensus to exclude the doubtful cases; and then to identify the incident's mechanism, contributing factors, clinical course, appropriate management and possible preventive strategy. Cases with 'allergy score' lower than 3 were considered doubtful and would be excluded. 'Allergy score', reported by Currie M. et al[6] is scored on the basis of clinical indicators and severity of the reactions. Descriptive statistics was used to summarize the data.

Results

Forty-three possible perioperative allergic reactions accounted for 1.6% of all cases reviewed. Forty-one incidents (95.3%) occurred in the operating rooms and the other two in the recovery rooms. General anesthesia was involved in 34 cases (79.1%) and regional anesthesia in eight cases (20.9%). In one case, the surgery was postponed before the anesthesia was started. The proportion of female and male was 1.9:1. The patients' data are shown in Table 1.

Clinical manifestations

Cutaneous manifestations including angioedema were present in 40 cases (93%), arterial hypotension in nine cases (20.1%), and bronchospasm in five cases (11.6%). No incident of cardiac arrest and death was reported (Table 2).

Thirty patients (69.8%) were considered as severity grade I (n = 30), while grade II and III accounted for 4.7% (n = 2) and 25.6% (n = 11) respectively. No severity grade IV was documented (Table 3).

Allergic reactions were suspicious when there were cutaneous manifestations. Monitors (NIBP, pulse oximeter, ECG and airway pressure) would help detect the more severe cases when there were arterial hypotension, desaturation, dysrhythmia, and bronchospasm (n = 11, 25.6%).

Table 1. Demographic characteristics and history of allergy

Patient data	Number (n = 43)	Percentage
Sex		
Female	28	65.1
Male	15	34.9
Age (yrs)		
Mean $\pm$ SD	37.8 $\pm$ 16.5	
Range	2-82	
History of allergy		
Yes	3	7.0
No	9	20.9
Not known	31	72.1

Table 2. Clinical features of patients with perioperative allergic reaction

Clinical symptoms	Number (n = 43)	Percentage
Cutaneous manifestation:		
Flush, rash, wheal, angioedma	40	93.0
Arterial hypotension	9	20.1
Bronchospasm	5	11.6

Table 3. Classification of patients on the basis of clinical severity (n = 43)

Grade	Skin	Respiratory	Cardiovascular	Percentage
Mild				
I (30)	Flush	None	None	69.8
II (2)	Urticaria, flush	Increased pulmonary resistance	Marked tachycardia, hypotension (≥ 20 mmHg systolic)	4.7
Life-threatening				
III (11)	Urticaria, flush	Bronchospasm, cyanosis	Gross hypotension (> 60 mmHg systolic), shock	25.6
IV	Urticaria, flush	Respiratory arrest	Shock, cardiac arrest	None

Causative agents

The suspected causative agents are demonstrated in Table 4. Neuromuscular blocking agents (NMBAs) were involved in 17 cases (39.5%), 13 (30.2%) of which were succinylcholine. All but one (succinylcholine) occurred in combination with induction agents, hence, the implication of the induction agents could not be ruled out.

The other agents involved were antibiotics (n = 12, 27.9%), followed by opioids (n = 8, 18.6%), blood components (n = 4, 9.3%), and colloid (n = 2, 4.7%). Neither local anesthetics nor latex allergy was documented.

Management and outcomes

As the majority of cases were classified as severity grade I; 15 patients (34.9%) had been closely observed without any treatment. The two most common drugs used were antihistamine (n = 21, 48.8%) and corticosteroid (n = 11, 25.6%) (Table 5). In more severe cases, inotrope, vasopressor, bronchodilator, and volume expander intervened as therapeutic and resuscitative measures. Mechanical ventilation was applied in most cases as a part of general anesthesia, hence not documented in the management.

Most patients (n = 31, 72.1%) recovered completely while 12 cases (27.9%) encountered mild to severe hypotension, bronchospasm and desaturation. Three of these were to be admitted at the intensive care unit; one of which had acute myocardial infarction and had to stay at the hospital longer than 1 week. There was no report of further allergic work-up in all patients. According to the attending anesthetists, all allergic reactions involved patient factors i.e., drug hypersensitivity, background, and rather unpreventable. There were six incidents (14%) that might have occurred from

Table 4. Suspected causative agents

Drugs or agents	Number (n = 43)	Percentage
Neuromuscular blocking agent (NMBAs) [n = 17 (39.5)]		
Succinylcholine	13	30.2
Vecuronium	2	4.7
Rocuronium	1	2.3
Atracurium	1	2.3
NMBAs + induction agent [n = 16 (37.2)]		
Thiopentone	11	25.6
Propofol	5	11.6
Antibiotics [n = 12 (27.9)]		
Cephalosporins	8	18.6
Cloxacillin	2	4.7
Metronidazole	1	2.3
Not specified	1	2.3
Opioids [n = 8 (18.6)]		
Pethidine	4	9.3
Morphine	3	7.0
Fentanyl	1	2.3
Blood components [(n = 4 (9.3)]		
Packed red cell	3	7.0
Fresh frozen plasma	1	2.3
Colloid (gelatin) [n = 2 (4.7)]	2	4.7

Table 5. Drugs used in the management of allergic reactions

Drug	Number (n = 43)	Percentage
Antihistamine	21	48.8
Corticosteroid	11	25.6
Inotrope, vasopressor	8	18.6
Bronchodilator	3	7.0
Volume expander	3	7.0
No treatment	15	34.9

human errors i.e., no testing of antibiotics (n = 3, 7%), drug dosage error (n = 1), known allergen given (n = 1), and too many drugs (4) given during induction of anesthesia (n = 1).

Discussion

In 2003, the Royal College of Anesthesiologists of Thailand initiated the Thai Anesthesia Incidents Study (THAI Study) of anesthetic adverse outcomes, as a registry of all consecutive anesthetics in 20 hospitals, to study incidences of anesthesia related complication[7,8]. Therefore, the THAI Study provided the baseline incidences of adverse outcomes and some contributory factors for quality improvement. However, the occurrence of anaphylactic/anaphylactoid reaction in the Thai Study was considered underestimated. The present study used the method of incident reporting in anesthesia from 51 hospitals to identify and analyze incidents.

According to 'allergy score', a combination of any of the major clinical indicators i.e., arterial hypotension, cutaneous manifestations, bronchospasm and severity grade III would make the likelihood of allergic reactions. On this basis, some of these 43 incidents would have been considered doubtful (allergy score = 2). However, in anaphylactic patients, a history of previous drug allergy could be as high as 29%[9]. In the present study, such a history was positive in only 3 patients (7%), whereas 'unknown' in the majority of patients (72.1%). If there had been a thorough history taking, the allergy score could have been added up and some patients would be included in the suggestive group. This was the reason why some doubtful cases were still included in the present study.

It is no wonder that the majority of allergic reactions occur in patients under general anesthesia particularly during induction of anesthesia, when many different drugs are administered intravenously in a short time frame. This also makes it difficult to identify the specific causative agent when allergic reactions occur. Regional anesthesia were involved in eight cases (18.6%) but local anesthetics was not likely to be the causative agents[10]. It is noteworthy that the female predominance of allergic reactions in the present study was (1.9 females/1 male), which confirms the results of other studies[11].

Major risk factors related to anaphylaxis include, but not limited to, prior history of such reactions, concomitant beta-adrenergic blocker therapy, or atopic background. In anaphylactic patients, a history of previous drug allergy ranges from 13.5%[12] to 29%[9], a rate comparable that reported in normal subjects[13]. Therefore, its value as a predictor of anaphylaxis is still questionable. However, avoidance of the known allergen in the future is mandatory. Laxenaire et al[11] reported that 25.4% of anaphylactic cases were atopic. The presence of atopy was significantly more frequent in cases of latex allergy than in allergy to neuromuscular blocking agents (NMBAs)[14].

The most common clinical features in the present study were cutaneous manifestations (93%), followed by arterial hypotension (20.1%) and bronchospasm (11.6%) which correlated well with severity grades. Arterial hypotension and bronchospasm, especially when they do not occur together, are usually due to more common causes. However, isolated bronchospasm may be anaphylactic reactions where the lung is the sole or predominant shock organ rather than the cardiovascular system. These include the reactions with etomidate, propofol, vecuronium, rapacuronium, and rocuronium. Coincidence of obvious cutaneous manifestations would help make the diagnosis. In the present study, the large fraction of cutaneous manifestations could be due to the inclusion of some doubtful cases.

Regarding the severity, the majority of reactions were grade I (69.8%) while 4.7% were grade II and 25.6% were life-threatening grade III. This may imply that there was a larger fraction of anaphylactoid reactions, the reactions of which were normally less serious.

The major suspect causative agents were NMBAs (39.5%), antibiotics (27.9%) and opioids (18.6%). The concurrent administration of an induction agent and NMBAs in conjunction with no further allergic work-up, make it unable to exclude the could-be implication of such induction agent. These results are different from the study by Mertes P. et al[15] that the 3 most frequent causes of anaphylaxis were NMBAs (69.2%), latex (12.1%), and antibiotics (8%). In the present study, succinylcholine remained the most frequently involved in allergic reactions, followed by small fractions of vecuronium, rocuronium, and atracurium.When the true anaphylactic incidence of one particular drug is considered, the actual clinical use or market share of which should be taken into account. By this means, rocuronium and succinylcholine appeared to be involved most frequently, followed by pancuronium, vecuronium and atracurium respectively[11]. This should raise the anesthesiologist's awareness of possible adverse reactions to rocuronium, which might resemble those of rapacuronium[16].

Anaphylaxis can occur even in patients who have had no previous anesthesia or exposure to NMBAs, since it can develop following previous contact with similar epitopes (i.e., ammonium molecule) of different drugs or substances in environment i.e., cosmetics[17]. Since all NMBAs possess tertiary or quaternary ammonium ions, cross-reactivity between the different NMBAs is a common phenomenon[18]. The highest rate of cross-reactivity was observed with rocuronium (89.4%) and vecuronium (92.7%); it was 72.6% for succinylcholine.

Allergic reactions to antibiotics were observed in 27.9% of cases, most to cephalosporins (18.6%). In fact, penicillin remains the most common cause of drug-induced anaphylaxis. However, the increased actual clinical use of cephalosporins has made a higher fraction of anaphylaxis compared with penicillin. Since the extent of allergy cross-reactivity between penicillin and cephalosporins appears to be low (1-4%), patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. Those who have positive penicillin skin test responses might receive an alternative antibiotic (non-beta-lactam) or receive cephalosporins through graded challenge. In Thailand, antibiotics still remains the major drug group that skin testing is compulsory. The 'test dose' technique for prophylactic antibiotics is widely applied by most anesthesiologists. However, a negative result is no guarantee that a reaction will not occur. It is probably more useful to allow some time between giving induction agents and antibiotics as reactions usually occur within a few minutes. Reactions to drugs given at induction will then occur before the antibiotic is given, ruling this out as a cause.

Allergic action to opioids is usually mild. The main mechanism is anaphylactoid reaction, the same as those frequently occur after thiopentone and benzylisoquinoline NMBAs. However, if non-immunological histamine release occurs due to more than one drug administered at the same time, during anesthetic induction for example, the total histamine release is likely to be higher and their clinical effects may increase.

Fewer allergic reactions incidents were observed in patients who received blood components and colloid solution. The allergic reactions in this group might be underreported as a substantial number of patients were in the situation where acute blood loss should be considered rather than allergic reactions. It is note-worthy that the two cases of allergic reactions to colloid were both gelatin; and there was no report of allergic reactions to latex in the present study.

Management of anaphylaxis depends on the clinical severity, which usually yields good outcome. Even severe reactions are often symptomatically well managed by anesthesiologists, leading to a low morbidity. In fact, death may simply represent mismanaged severe reactions. In the present study, the two most frequently administered drugs were antihistamine (48.8%) and corticosteroid (25.6%); and 'no treatment' in 34.9%. Actually, severity grade I presents only cutaneous manifestations, thus, no action is necessary. In severity grade II, which is more severe histaminoid and manifests in mild hypotension and marked tachycardia, the patient may require intervention but this will be largely cosmetic (e.g. antihistamine and corticosteroid). In such a case, the reactions should be noted in the patient's record. Severity grade III and IV are truly life-threatening and immediate action is necessary. Furthermore, laboratory investigation should be initiated. It is noteworthy that there was no mention about further allergic work-up in all 43 reports.

Apart from some human errors (14%), most allergic reactions seemed to be unpreventable due to patient's drug hypersensitivity background. However, thorough history taking of atopy, asthma, particular drug allergy, and previous anesthesia may, in part, help decrease the occurrence of perioperative allergic reactions. Correct and prompt diagnosis is vital for early optimal management of life-threatening allergic reactions to reduce the morbidity and mortality. It is, therefore, essential that guidelines for the identification and/or management of high-risk groups should be initiated. Furthermore, an anesthesia-related allergy clinic should be set up. All patients who have encountered severity grade III and IV allergic reactions must have allergic work-up so as to confirm the diagnosis and, if possible, identify the causative agents. Patient education might be the most important preventive strategy. They must be informed about the causative agents and possible cross-reactivity to other agents, and the risk of future anaphylaxis. Avoiding the same allergen in the future is crucial since the reactions could be more severe.

Conclusion

Perioperative allergic reactions accounted for 1.6% of the adverse events reported to Thai AIMS. NMBAs and antibiotics were 2 predominant possible causative agents. Succinylcholine remained the major causative agent, hence, its routine use must be reconsidered. A quarter of incidents were life-threatening reactions but responded well to treatment. There was

no report of further allergic work-up. An anesthesia-related allergy clinic should be set up for rational approach to patients with perioperative allergic reactions to reduce future risk of anaphylaxis.

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โครงการเฝ้าระวังภาวะแทรกซ้อนทางวิสัญญีในประเทศไทยโดยการรายงานอุบัติการณ์: การวิเคราะห์อาการแพ้จากรายงานผู้ป่วย 1996 ราย

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วัตถุประสงค์: *เพื่อวิเคราะห์อาการ อาการแสดง วิธีการจัดการและผลการรักษา รวมถึงปัจจัยเสี่ยงของปฏิกิริยาการแพ้ในโครงการเฝ้าระวังภาวะแทรกซ้อน จากการให้ยาระงับความรู้สึกในประเทศไทย โดยการรายงานอุบัติการณ์ (Thai AIMS)*

วัสดุและวิธีการ: *เป็นการศึกษาแบบพรรณนา โดยเก็บข้อมูลแบบไปข้างหน้าในโรงพยาบาล 51 แห่งทั่วทุกภูมิภาคของประเทศไทย อุบัติการณ์ภาวะแทรกซ้อนในระหว่างการให้ยาระงับความรู้สึกจนถึงหลังผ่าตัด 24 ชั่วโมง จะถูกบันทึกในแบบฟอร์มมาตรฐานและส่งมายังศูนย์จัดการข้อมูล Thai AIMS เพื่อคัดกรองรายที่สงสัยว่าจะเกิดปฏิกิริยาการแพ้ เพื่อนำมาวิเคราะห์โดยผู้เชี่ยวชาญ 3 คน*

ผลการศึกษา: *พบอุบัติการณ์ที่สงสัยว่าจะเป็นปฏิกิริยาการแพ้ระหว่างการให้ยาระงับความรู้สึก 43 ราย จากจำนวน 2,537 อุบัติการณ์ในผู้ป่วย 1996 คน คิดเป็นร้อยละ 1.6 เป็นผู้ป่วยหญิงมากกว่าชายในอัตราส่วน 1.9:1 อาการแสดงที่พบบ่อยได้แก่ มีผื่นตามตัว (ร้อยละ 93) ความดันเลือดตก (ร้อยละ 20.1) และหลอดลมตีบ (ร้อยละ 11.6) ระดับความรุนแรงที่พบแบ่งเป็น ระดับ 1 เล็กน้อย ร้อยละ 69.8 ระดับ 2 ปานกลาง ร้อยละ 4.7 และ ระดับ 3 รุนแรง ร้อยละ 25.6 ยา หรือ สารเคมีที่สงสัยว่าจะเป็นสาเหตุของปฏิกิริยาการแพ้ 3 อันดับแรกได้แก่ ยาหย่อนกล้ามเนื้อ (ร้อยละ 39.5 โดยร้อยละ 30.2 เป็น succinylcholine) ยาปฏิชีวนะ (ร้อยละ 27.9) และยาอนุพันธ์ฝิ่น (ร้อยละ 18.6) ผู้ป่วยเกือบทั้งหมดได้รับการดูแลที่เหมาะสมและปลอดภัย มีเพียง 1 รายที่เกิดภาวะกล้ามเนื้อหัวใจขาดเลือดแบบเฉียบพลัน ทำให้ต้องพักรักษาในโรงพยาบาลนานกว่า 1 สัปดาห์ ในผู้ป่วยทุกรายไม่พบรายงานการติดตามเพื่อวิเคราะห์สาเหตุของปฏิกิริยาการแพ้ที่เกิดขึ้น*

สรุป: *ปฏิกิริยาการแพ้ระหว่างการให้ยาระงับความรู้สึกพบได้ร้อยละ 1.6 ของภาวะแทรกซ้อนทั้งหมด อาการแสดงที่พบได้บ่อยที่สุดได้แก่ มีผื่นขึ้นตามตัว ร้อยละ 25 มีอาการรุนแรง ผู้ป่วยเกือบทั้งหมดได้รับการดูแลที่เหมาะสมและปลอดภัย ยาที่สงสัยว่าจะเป็นสาเหตุของปฏิกิริยาการแพ้บ่อยที่สุด ได้แก่ ยาหย่อนกล้ามเนื้อ succinylcholine*