Assessment of Cellular Antigen Stimulation Test in Diagnosis of Drug Allergy

Thesis

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﴿وَقُل رَّبِّ زِدْنِي عِلْماً﴾

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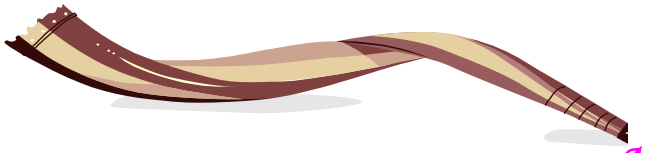

Aya Mohamed Elgendy

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List of Abbreviations

ACE	:	Angiotensin converting enzyme inhibitor
ADEs	:	Adverse drug events
ADR	:	Adverse drug reaction
AERD	:	Aspirin-exacerbated respiratory disease
AGEP	:	Acute generalized exanthematous pustulosis
ANA	:	Antinuclear antibody
ANCA	:	Antineutrophil cytoplasmic antibody
ASA	:	Acetylsalicylic acid
AX	:	Amoxicillin
BAT	:	Basophil activation test
BLs	:	Betalactams
Bp	:	Benzylpenicillin
Bpo	:	Benzylpenicilloyl determinant
BSA	:	Body surface area
BSACI	:	British Society for Allergy and Clinical Immunology
CFSE	:	Carboxyfluorescein N-succinimidyl ester
CLA	:	Cutaneous lymphocyte-associated antigen
COX	:	Cyclooxygenase
CXR	:	Chest X-ray
DAIG	:	Drug Allergy Interest Group
DBPCFC	:	Double-blind placebo-controlled food challenge
DHR	:	Drug hypersensitivity reactions
DILE	:	Drug-induced lupus erythematosus
DMARDS	:	Disease-Modifying Antirheumatic Drugs
DPT	:	Drug provocation test
DRESS	:	Drug rash with eosinophilia and systemic symptoms
DTDHR	:	Delayed-type drug hypersensitivity reactions

List of Abbreviations (Cont.)

EAACI	:	European Academy of Allergology and Clinical Immunology
EBV	:	Ebstein bar virus
ELISA	:	Enzyme-linked immunosorbent assay
ELISPOT	:	Enzyme-linked immunosorbent spot
EM	:	Erythema multiforme
ENDA	:	European Network of Drug Allergy
FACS	:	Fluorescence-activated cell sorting
FAST	:	flow-cytometric allergen stimulation test
FBC	:	Full blood count
FDE	:	Fixed drug eruption
FEIA	:	Fluorescent enzyme immunoassay
FESS	:	Functional endoscopic sinus surgery
GA2LEN	:	Global Allergy and Asthma Euroepan Network
HANNA	:	European Network on Hypersensitivity to Aspirin and Nonsteroidal Anti-Inflammatory Drugs
HAS	:	Human serum albumin
ICM	:	Iodinated contrast media
IDT	:	Intradermal test
IL	:	Interleukin
L-ASA	:	Lysine aspirin
LAT	:	Lymphocyte activation test.
LFT	:	Liver function test
LTT	:	Lymphocyte transformation test
MAPK	:	Mitogen-activated protein kinase
MDM	:	Minor determinant mixture
MPE	:	Morbilliform exanthemas
MPEs	:	Maculopapular eruptions
NECD	:	NSAIDs-exacerbated cutaneous disease
NERD	:	NSAIDs-exacerbated respiratory disease

List of Abbreviations (Cont.)

NIUA	:	NSAIDs-induced urticaria/angioedema
NMBA	:	Neuromuscular-blocking agents
NPV	:	Negative predictive value
NSAIDs	:	Non-steroidal anti-inflammatory drugs
NSF	:	Nephrogenic systemic fibrosis
OPT	:	Oral provocation test
PAMAM	:	Polyamidoamine
PPL	:	Penicilloyl-polylysine
RAST	:	Radio allegro sorbent test
RCM	:	Radiocontrast media
RIA	:	Radioimmunoassay
SCAR	:	Severe cutaneous adverse reactions.
sIgE	:	Specific IgE
SJS	:	Stevens-Johnson Syndrome
Slt	:	Sulfidoleukotrienes
SNIRD	:	Single-NSAID-induced delayed hypersensitivity reactions
SNIUAA	:	Single-NSAID-induced urticaria/angioedema or anaphylaxis
SPT	:	Skin prick test
STAT	:	Signal transducer and activation of transcription
TCR	:	T-cell receptors
TEN	:	Toxic epidermal necrolysis (TEN
TMPSMX	:	Trimethoprim-sulfamethoxazole
TNF	:	Tumor necrosis factor
U&E	:	Urea and electrolytes
WAO	:	World Allergy Organization

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Introduction

Adverse drug reactions (ADRs) result in major health problems in the both the inpatient and outpatient setting. ADRs are broadly categorized into predictable (type A and unpredictable (type B) reactions. Predictable reactions are usually dose dependent, are related to the known pharmacologic actions of the drug, and occur in otherwise healthy individuals, they are estimated to comprise approximately 80% of all ADRs. Unpredictable are generally dose independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible individuals. Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy (IgE mediated), and pseudo allergic reactions (non-IgE mediated). Both type A and B reactions may be influenced by genetic predisposition of the patient (**Solensky et al., 2010**).

Drug allergy encompasses a spectrum of immunologically-mediated hypersensitivity reactions with varying mechanisms and clinical presentations. This type of adverse drug reaction (ADR) not only affects patient quality of life, but may also lead to delayed treatment, unnecessary investigations, and even mortality. Given the myriad of symptoms associated with the condition, diagnosis is often challenging. Diagnosis of the etiology of drug hypersensitivity is a vital step in therapy, which is mainly done through patient history, as skin testing is not always reliable and oral provocation testing is life-threatening. Hence, evidence for an underlying IgE mediated mechanism is difficult to obtain **(Refaat and Attia 2011**). Also routine or validated tests are not available for the majority of drugs, considerable experience is required for the investigation of allergic drug reactions and to undertake specific drug challenge. A missed or incorrect diagnosis of drug

allergy can have serious consequences **(Mirakian et al., 2009).**

Some reactions closely resemble allergic reactions and are termed allergic-like or pseudo-allergic (non-IgE mediated). This includes anaphylactoid reactions that clinically resemble anaphylaxis, since in both situations chemical mediator release or activation is responsible for these symptoms **(Anderson et al., 2007).** Non-IgE-mediated reactions to drugs account for the majority of adverse reactions encountered in clinical practice. It is usually by careful history taking and keeping a diary of exposure in relation to clinical exacerbation that is identified as the possible culprit for the adverse reaction. Until recently, there was no laboratory test available to evaluate clinical sensitivity to non-IgE-mediated triggers of adverse reactions to drugs (**Potter 2006).**

The insight in the cellular immunological background of allergic diseases has increased tremendously the past 20 years, and this has spurred an interest in using cellular systems for in vitro diagnosis of allergic diseases. In spite of a vast literature on cellular aspects of allergy and immunology only a few tests have actually been introduced in the clinic **(*Poulsen et al., 2004)*.**

Some cellular tests, i.e. tests determining the reactivity of blood cells in vitro, particularly basophils, to allergens, have been available for many years. The determination of histamine release has been widely used in allergy pathophysiological research but its routine application in allergy diagnosis has been restricted to few groups. Basophil degranulation, as determined by microscopic examination, was promoted by some groups in the 1980's but has been largely abandoned since around 10 years ago; an alternative cellular test, based on the determination of

sulfidoleukotrienes (LTC4, LTD4, LTE4) produced by IL-3 primed basophils stimulated by allergens in vitro, has been proposed **(Weck and Sanz, 2003).**

The cellular antigen stimulation test (CAST) is useful for detecting non-IgE-mediatedsensitivity to drugs (**Potter 2006)**.

A large number of reports on CAST diagnostic value establish the value of this diagnostic test, particularly in instances where other in vitro or in vivo diagnostic tests are not reliable, such as food or drug allergies, as well as in non-IgE- mediated immediate hypersensitivity reactions**(Weck and Sanz, 2003)**.

The CAST-ELISA (Buhlmann Laboratories, Switzerland) has gained respectability as an important test in the allergy diagnostic arena, if properly selected and interpreted (**Potter 2006).**

However, a number of questions about the CAST diagnostic assay are still open or have not been systematically explored. This may explain, in addition to the practical limitations inherent to all allergy cellular tests, why CAST has not yet become a very widely used assay worldwide, having gained broad acceptance in some countries but not in others **(Weck and Sanz ,2003).**

Aim of the Work

The aim of this work is to evaluate the efficacy of CAST(cellular allergen stimulation test) in diagnosis of patients with history of allergy to drugs and compare values with healthy control.

Chapter (1)

Drug Allergy

Definition:

The WHO has defined an ADR as 'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product**(Edwards and Aronson , 2000).**

ADRs affect quality of life, may lead to unnecessary investigations or even death. Allergic reactions to drugs are ADRs and anaphylaxis to drugs is the commonest cause of fatal anaphylaxis in adults with a mean time to death of around five minutes **(Pumphrey, 2000)**. Antibiotics, NSAIDs, general anaesthetics and radiocontrast media are listed as the commonest culprit drugs in fatal anaphylaxis **(Mirakian *et al., 2009*)**.

Adverse drug reactions (ADRs) are broadly divided into predictable (related to pharmacologic actions of the drug in otherwise normal individuals) and unpredictable reactions (related to individual's immunological response and, on occasion, to genetic differences in susceptible patients). Drug allergy is a type of unpredictable reaction **(Johansson et al., 2003).**

ADRs should be differentiated from adverse drug events (ADEs) **(Morimoto et al., 2004)** as ADEs extend beyond ADRs to include harm related to medication errors and drug/food interactions.