KER UNIT - PROTOCOL OF REVIEW

TITLE

Time of onset and predictors of biphasic anaphylactic reactions: A systematic review and meta-analysis of the literature

REVIEW QUESTION

A. To describe the time frame where biphasic reactions can occur.
B. To investigate risk factors and predictors of biphasic reactions in patients with anaphylaxis.
C. To investigate and describe therapeutic interventions of steroid, epinephrine and its effect on preventing biphasic reactions.

BACKGROUND:

1. Biphasic anaphylactic reactions are defined as the recurrence of anaphylaxis symptoms within 72 hours of the initial anaphylactic event, without re-exposure to the trigger[1].
2. The reported incidence of biphasic reactions is 4-20% of overall
anaphylaxis evaluated in the emergency department (ED) [1] [2] [3] [4] [5].

3. Relatively few studies have reported risk factors for biphasic reactions [1] [2] [3] [4] [5]. In addition, both protective and risk factors are not consistently found among study populations. Thus, biphasic reactions are poorly understood.

4. Usually the symptoms of biphasic reactions are less severe than the initial symptoms and do not require higher level of care including intubation, vasopressor infusion, or ICU admission compared to anaphylaxis without biphasicity [1] [3] [6] [7]. However on rare occasion biphasic reactions are fatal or severe [8] and requires monitoring.

5. Large proportion of biphasic reactions can occur beyond 6 hours [3]. Current guidelines [9] [10] [11] are recommending 6 hours of observation, however, some studies suggested 24 hours of observation [2] [12].

6. Therapeutic interventions such as steroid, antihistamines and epinephrine [3, 6] are possibly able to prevent biphasic reaction and subsequent airway compromise or shock, however evidence is not strong [1] [2] [4] [5] [12] [13].
ELIGIBILITY CRITERIA

INCLUSION

Study designs: Case series, retrospective, prospective, RCT

Participants: human, patients with anaphylaxis

Interventions: a discrete set of risk factors thought to be (not proven) associated with biphasic reaction

Control interventions: those without such risk factors

Outcomes of interest: biphasic reactions

Other criteria: any study that provides data sufficient to estimate a relative risk or odds ratio for this risk factor.

EXCLUSION

Minimal follow-up: NA

Minimal exposure: NA

Other criteria: Case series with less than 2 cases, review, editorials, animal studies

SEARCH STRATEGY (Pat Erwin to provide detailed strategy)

Years: Please refer to database

Databases: MEDLINE (1946 to January 2014), EMBASE (1988 to January 2014), Web of Science (to January 2014), Scopus (to January 2014)
Search terms: (biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR resurg* OR “late phase”) AND anaphyla*
((biphasic OR phasic OR multiphasic OR protracted OR (recur* AND hours) OR reactivat* OR resurg* OR “late phase”) AND anaphyla*) NOT MEDLINE[sb] 27
*remove mice,rats,guinea pigs

In addition, we will review the reference sections of eligible studies and available reviews. We will also request potentially eligible studies from content experts.

SELECTION

Two reviewers will consider the potential eligibility of each of the abstracts and titles that result from executing the search strategy. Reviewers will request the full text versions of all potentially eligible studies. Disagreements will also be retrieved in full text for evaluation.

Two reviewers working independently and blindly will consider the full text reports (all available versions of each study) for eligibility. The reviewers will calibrate their judgments using a smaller set of reports. Subsequently, disagreements will be harmonized by consensus; if not possible, by arbitration. Agreement will be measured using the kappa or phi statistics, as appropriate (the latter is appropriate when the distribution of agreement is extreme).

EXTRACTION
Data extraction will include full description of participants enrolled, the symptoms they developed, the symptoms in the control group, past history and inciting allergens, the measure of outcome (specifically defined as event or measure and time frame for the ascertainment of this outcome; the outcomes of interest are: Biphasic reactions).

QUALITY

For assessing the quality of non-randomized studies, we will assess blinding of the outcome assessors to arm assignment in relation to the outcome of biphasic reactions, comparability of outcome assessment, completeness of follow-up. The latter criteria follow the Newscastle–Ottawa quality assessment tool for observational studies.[2]

POOLING

When possible, we will generate meta-analytic estimates of treatment effect (relative risks preferred over odds ratios). As a rule we will use random-effects meta-analyses (some caveats apply for sparse events). If crossover and parallel group trials are included, we will pool together. The outcomes we will pool include: Biphasic reactions. We will measure inconsistency for each outcome by estimating the $I^2$ test and its associated confidence interval.[3] We will use RevMan and StatsDirect software to conduct the analyses.
SUBGROUPS

To explore causes of inconsistency and subgroup-treatment interactions, we will construct the following subgroup analyses defined by:

- Patients: emergency department, inpatient setting, pediatric population
- Study quality measure: Newcastle-Ottawa Scale showing low risk of bias

We will measure the difference in effect sizes between subgroups (univariate analyses). When possible we will construct meta-regression analyses with subgroups as the dependent variables and outcome as the dependent variable.

SENSITIVITY ANALYSES

When relevant we will explore how results of the meta-analyses changes when using fixed effects models, when borderline eligible articles are included/excluded. We will use the inverse variance method to incorporate the crossover results without making assumptions that inflate the variance of these trials.

REPORTING BIAS

We will contact all authors with a completed form including all their data for verification and missing data for their completion. The protocol for author contact includes: (1) email to the corresponding author (if incorrect or unavailable to the first or second authors; if no response, phone contact with office to obtain email address – brief conversation with the investigator about the upcoming task) with
statement of purpose, data collected and missing, and opportunity to email or fax back the results; (2) if unable or unwilling, letter of waiver to indicate that they will not be offering data for the review.

We will circulate the list of included articles to the content experts to judge completeness of the list and identified completed but unpublished studies.