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COCHRANE CORNER

Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock

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Clinical Question: What are the benefits and harms of adrenaline in the treatment of anaphylaxis with and without shock?

Context: Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Most anaphylactic episodes involve an immediate hypersensitivity reaction following allergen interaction with cell bound immunoglobulin E (IgE). This involves release of histamine and other mediators from mast cells and basophils.

The diagnosis of anaphylaxis is a clinical one based largely on history and physical findings. Anaphylaxis is not a reportable disease and the true incidence is unknown. An estimate of the incidence in the general population is influenced by definitions, which differ from one investigator to another, as well as by coding issues and misclassification errors. A population based study calculated an annual incidence of 30 per 100,000 person years, which raised concern that anaphylaxis was frequently not recognized. Other studies suggest the true incidence may be up to 590 per 100,000 person years. Anaphylaxis from the four most common triggers (foods, insect stings, medications, and natural rubber latex) may affect more than 1% of the general population with considerable variations in age and in age-specific aetiology.

Adrenaline (epinephrine) is widely advocated as the initial treatment of choice for anaphylaxis. This initial emergency management is supervised by a physician or other healthcare professional when anaphylaxis occurs in a healthcare setting. In this setting intramuscular (i.m.) or intravenous (i.v.) infusion, or both, routes for adrenaline are preferred. When anaphylaxis occurs in the community, the standard of first-aid treatment is the administration of self-injectable adrenaline into the anterolateral thigh using an EpiPen, Anapen, AnaHelp, Fastject, Twinject, or other adrenaline formulation.

Adrenaline is an alpha- and beta-adrenergic agonist with bidirectional cyclic adenosine monophosphate-mediated pharmacologic effects on target organs and a narrow therapeutic index. It results in vasoconstriction, increased peripheral vascular resistance, decreased

mucosal oedema, inotropic and chronotropic effects, bronchodilation, and decreased mediator release from mast cells and basophils. The plasma and tissue concentrations of adrenaline needed for recovery from anaphylaxis have not yet been defined in humans.

The evidence base in support of the use of adrenaline is unclear.

Intervention: Any systemic (intravenous infusion or bolus injection, intramuscular, subcutaneous, or inhaled from a metered-dose inhaler or a nebulizer) administration of adrenaline by the individual, a lay caregiver (of a child), or a medical professional. Adrenaline could have been administered anywhere in the community. The comparative treatments of interest were no intervention, placebo, other adrenergic agonists; and different treatment approaches to the administration of adrenaline.

Bottom line:

Searching yielded 382 citations, but no studies fulfilled the inclusion criteria. This review failed to uncover any evidence from prospective, randomized or quasi-randomized trials on the effectiveness of adrenaline for the emergency management of anaphylaxis. The authors found no relevant evidence for adrenaline use in the treatment of anaphylaxis. They were therefore unable to make any new recommendations based on the findings of this review. In the absence of appropriate trials, the authors recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular (i.m.) injection should still be regarded as first-line treatment for the management of anaphylaxis.

Caveat: In summary, the use of adrenaline in anaphylaxis appears to be based largely on extrapolation from first principles, expert opinion, and tradition. The evidence for the use of adrenaline in anaphylaxis is based on fatality series in which most individuals dying from anaphylaxis had not received prompt adrenaline treatment. Adrenaline appears to be life saving when injected promptly; however, there is no evidence from randomized controlled trials for or against the use of adrenaline in the emergency treatment of anaphylaxis.

Although there is a need for randomized, double-blind, placebo-controlled clinical trials of high methodological quality in order to define the true extent of benefits from the administration of adrenaline in anaphylaxis, such trials are unlikely to be performed in individuals with anaphylaxis. Indeed, they might be unethical because prompt treatment with adrenaline is deemed to be critically important for survival in anaphylaxis.

Guidelines on the management of anaphylaxis need to be more explicit about the basis of their recommendations regarding the use of adrenaline.

Cochrane Systematic Review:

Sheikh A, Shehata YA, Brown SGA, Simons FER. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006312. DOI: 10.1002/14651858.CD006312.pub2.