

Serious Anaphylactic Reactions due to Protamine Sulfate: A Systematic Literature Review

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Abstract: Anaphylactic reactions caused by injection of protamine sulfate during cardiac surgery are a well-known complication. A systematic literature review was therefore conducted to gather evidence of the knowledge concerning these side effects, and to see if any prospective randomized studies supported this. Studies investigating the effect of protamine sulfate in human beings were extracted from MEDLINE, Embase and the Cochrane Library, retrieving 487 articles. Abstracts were evaluated by both authors, and referred articles not found in the primary search were furthermore extracted from reviews and case reports, resulting in a total of 272 relevant articles. Of these, 9 retrospective studies and 16 prospective studies were performed in an evidence-based manner. However, only 3 of the 16 prospective articles had an optimal design as far as inclusion criteria, randomization, and description of symptoms were concerned. Incidence of anaphylactic reactions in the prospective studies was 0.69% compared to 0.19% in the retrospective studies, but caution should be taken due to a pronounced heterogeneity of those studies. One study found heparinase I unsuitable as replacement for protamine sulfate. Overall, our findings support the low incidence of anaphylactic reactions reported in previous studies, but of note only few prospective investigations was conducted on the subject. Our study also emphasizes the need for critical appraisal of many routine procedures: in all aspects of medical care, systematic literature review conducted in a well-structured, repeated manner should be given high priority.

Protamine sulfate is a strongly alkaline polypeptide, mainly used to reverse anticoagulant effects of heparin. When injected intravenously, the alkaline protamine combines with the acidic heparin to form a neutral salt, thereby eliminating the anticoagulating properties of heparin. Another major use of protamine sulfate occurs in neutral protamine Hagedorn (NPH) insulin, where complexation with insulin delay absorption and prolong the duration of action. Although being a relatively safe drug, it can cause severe systemic reactions with pronounced morbidity and mortality [1], and protamine sulfate is reported as one of the most common causes of life-threatening adverse reactions during cardiac surgery when used for rapid neutralization of heparin. Anaphylactic reactions to protamine sulfate have been known for many years, but the incidence reported varies from 0.06% to 10.6% [2] and range from minor haemodynamic instability to fatal cardiovascular collapse. The incidence of catastrophic reactions to protamine sulfate during cardiovascular surgery is reported to be 0.13% [3], and a recent study has confirmed the relation between protamine sulfate reactions and mortality risk [4]. The protamine–heparin complexes are thought to be responsible for the adverse effects observed, including allergic reactions, systemic hypotension and increased pulmonary arterial pressure, but most articles

gathering this knowledge have been either case reports, review articles, or of a retrospective, epidemiologic kind. To disclose the evidence-based knowledge concerning the anaphylactic reactions caused by this drug, a systematic literature review was therefore conducted.

Materials and Methods

Search strategy. Reports of studies investigating the effect of protamine sulfate in human beings were extracted from MEDLINE, Embase and the Cochrane Library. The search period ended August 2007.

The search strategy for PubMed was: (('pharmaceutical preparations' [TIAB] not MEDLINE [SB]) or 'pharmaceutical preparations' [MeSH Terms] or drug [Text Word]) and induced [All Fields] and ('hypersensitivity' [MeSH Terms] or hypersensitivity [Text Word]) or (('hypersensitivity' [TIAB] not MEDLINE [SB]) or 'hypersensitivity' [MeSH Terms] or allergic reaction [Text Word]) or ('anaphylaxis' [MeSH Terms] or anaphylaxis [Text Word]) or (Anaphyl*) and ('protamines' [MeSH Terms] or protamines [Text Word]).

The search strategy for Embase was: (pub-date > 1973 and protamines and (hypersensitivity or allergic reaction or anaphylactic or anaphylaxis)) or (pub-date > 1973 and TITLE-ABSTR-Key (protamines) and TITLE-ABSTR-KEY (hypersensitivity)) or (pub-date > 1973 and TITLE-ABSTR-KEY (protamines) and TITLE-ABSTR-KEY (allergic reaction)) or (pub-date > 1973 and TITLE-ABSTR-KEY (protamines) and TITLE-ABSTR-KEY (anaphylactic)) or (TITLE-ABSTR-KEY(protamines) and TITLE-ABSTR-KEY (anaphylaxis)) or (pub-date > 1822 and protamines and (hypersensitivity or allergic reaction or anaphylactic or anaphylaxis)).

The search strategy for the Cochrane Library was: protamine or protamines and MeSH descriptor anaphylaxis explode all trees or MeSH descriptor allergy and immunology explode all trees or

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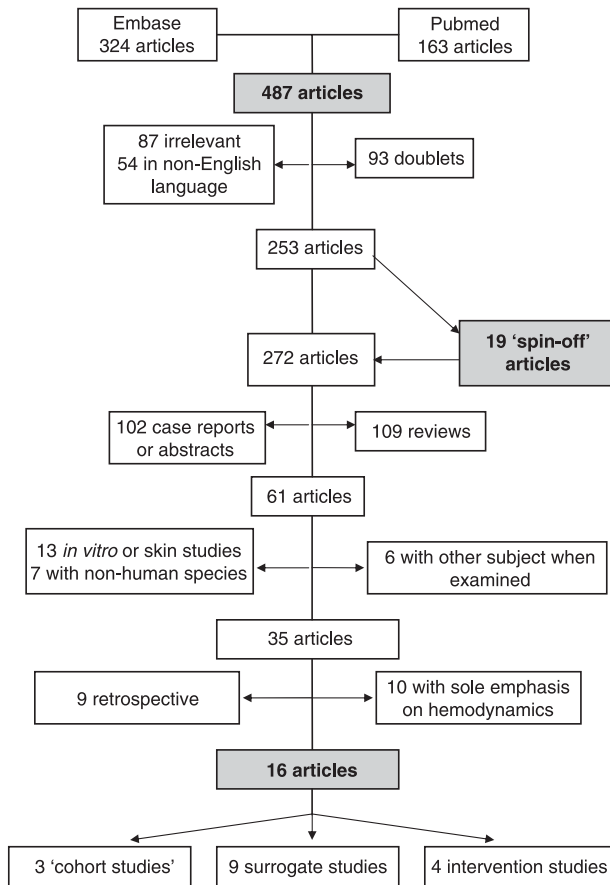


Fig. 1. Flow chart of retrieved, excluded and analysed articles.

MeSH descriptor abnormalities, drug-induced explode all trees or (reaction or reactions). All those articles were also listed in PubMed and are therefore contained in this box in fig. 1.

Data extraction. The entire search resulted in 487 articles. Both investigators took part in the further selection of the articles, diminishing the amount of articles from the initial 487 to 253 (fig. 1). Reviews and case reports were all read in order to extract referred articles not found in the primary search, resulting in 19 extra 'spin-off' articles and thus a total of 272 articles. Abstracts from those were read by both investigators, excluding articles concerning other subjects, animal studies, *in vitro* or skin studies as well as reviews and case reports. In the end, 35 articles were eligible for the study (fig. 1). The quality of the study design (i.e. inclusion criteria, randomization and description of symptoms) was assessed independently by both investigators: 10 articles were sorted out as they focused only on the haemodynamic influence of protamine sulfate administration. Nine articles of retrospective design were dealt with separately. Sixteen articles had a prospective design, but had very different settings, why they were further subdivided. At first, the predefined quality criteria's given by Centre for Evidence-Based Medicine in their harm/aetiology worksheet was used to score the studies selected, but this turned out to be problematic due to their diverse character. To allow comparison of the results, it was therefore chosen to categorize the studies according to the aim stated in the articles. Furthermore, some studies [5] had both a prospective and a retrospective part and were classified in both groups. As the studies identified were very heterogeneous with for example some studies including predisposed patients, it seemed irrelevant to report confidence intervals, why an overall incidence proportion of anaphylactic reactions and range of incidence proportions was calculated.

Table 1.

Selected prospective studies. For selection, please see text and fig. 1. The adverse reaction requested in the table requires a thorough description of symptoms (e.g. a mild hypotensive period is not sufficient).

Author and reference data	Design	No.	Adverse reactions
Reed and Gascho [5]	Retrospective cohort + case-control	24/50	0
Weiler <i>et al.</i> [2]	Cohort study	243	4
Stafford-Smith <i>et al.</i> [6]	Controlled randomized study	87/80	40/44
Baraka <i>et al.</i> [7]	Intervention study	20/20	0
Kambam <i>et al.</i> [8]		15/15	0
Levy <i>et al.</i> [3]		50	1
Mayumi <i>et al.</i> [9]		126	0
Chiu and Samson [15]	Surrogate marker study	31	0
Click <i>et al.</i> [16]		46	0
Ellerhorst <i>et al.</i> [17]		30	ND
Horrow <i>et al.</i> [18]		32	0
Lee <i>et al.</i> [19]		11	3
Loubser [20]		16	ND
Nell and Thomas [21]		358	ND
Nyhan <i>et al.</i> [22]		93	ND
Weiss <i>et al.</i> [23]		70	ND

ND, not described.

Results

Prospective studies.

The 16 articles fulfilling the criteria for a prospectively designed study were subdivided as follows: three randomized studies, four intervention studies and nine surrogate marker studies (table 1).

- The study by Reed and Gascho [5] was a case-control study where 24 diabetic patients were compared to 50 non-diabetic patients when administering protamine sulfate. None developed anaphylactic reactions.

- Weiler *et al.* [2] prospectively examined 243 patients, and found 10.7% to have an objective reaction, while 1.6% (four patients) had a precipitous drop in blood pressure immediately after protamine sulfate administration.

- Stafford-Smith *et al.* [6] compared the efficacy and safety of protamine sulfate with heparinase I in order to evaluate whether the latter favourably could replace protamine sulfate. One hundred and sixty-seven patients were randomized to either protamine sulfate or heparinase I, and with a very profound clinical scoring 40 versus 44 patients were found to have increased morbidity. As heparinase I demonstrated an inferior safety profile, it was not found suitable as a replacement for protamine sulfate.

Intervention studies.

- Baraka *et al.* [7] investigated the effect of hydrocortisone in 20 patients prior to protamine sulfate administration compared to 20 patients without pre-treatment. No patients developed genuine anaphylaxis, but a higher degree of

hypotension was noted in the group without pre-treatment. The article did not contain information on blinding or randomization.

- Kambam *et al.* [8] studied the effect of pre-treatment with histamine blockers in 15 patients and compared to 15 patients without pre-treatment. A drop in blood pressure was noted in the group without pre-treatment, but no actual anaphylactic reaction was registered.

- In the study by Levy *et al.* [3], a prospective evaluation of protamine sulfate reaction risk was made for patients taking NPH insulin. Fifty patients were randomized to a prophylactic dose of corticosteroid and/or antihistamine prior to protamine sulfate administration. One pre-treated patient had severe pulmonary hypertension, while one other pre-treated released histamine, but developed no anaphylactoid symptoms.

- Mayumi *et al.* [9] described the effect of histamine blockers on protamine sulfate reaction, and changes in blood pressure were noted. Histamine pre-treatment were shown to have a small positive effect on hypotension produced by protamine sulfate administration.

Surrogate marker studies.

Those studies merely described measurement of inflammation or allergy markers (e.g. complement components or histamine). The design in general did not include thorough inclusion criteria, randomization or blinding. Furthermore, signs of anaphylaxis were only described at random.

Altogether, the prospective studies included 1252 patients, of which 48 had an anaphylactic reaction, that is, an overall incidence of 3.8% (range 0–46%). However, the study by Stafford-Smith *et al.* [6] identified many adverse reactions compared to the other studies, and when excluded, the incidence was 0.69% (8 out of 1165) (range 0–27%).

Retrospective studies.

The nine retrospective articles (table 2) altogether comprehended 17,573 patients, of which 34 had an anaphylactic reaction, that is, an overall incidence of 0.19% (range 0–27%).

Wakefield *et al.* [10] made a questionnaire study in 1994 to elucidate differences in administration of heparin and

protamine sulfate in North America and Europe, respectively. However, this implied self-reporting of complications and a thereby indirect measurement of incidence, why the study was excluded.

Discussion

This systematic review shows that of 487 articles retrieved (+19 extra provided from the articles themselves), 9 retrospective and 16 prospective articles were found relevant. For retrospective studies, the incidence of an anaphylactic reaction was 0.19% consistent with the incidence reported elsewhere [3]. However, due to their nature, those retrospective studies do not contribute to a physiological disclosure of the problem. Only 3 of the 16 prospective studies had an optimal design as far as inclusion criteria, randomization, blinding and description of symptoms were concerned. However, as prospective investigations are difficult to conduct on low-incidence phenomena, the general insistence on prospective randomized studies could perhaps be a reflex response, as this technique can only be used if there is an alternative approach: as one would need an efficacious alternative to protamine to conduct such a trial, the low number of prospective comparison trials is not necessarily surprising. The only credible alternative to protamine reversal of heparin today is heparinase I as described by Stafford-Smith *et al.* [6]: this was, however, found inferior to protamine sulfate and could not be recommended as an alternative drug in general. Of note, alternatives do exist that can replace the use of heparin and protamine sulfate (e.g. the thrombin inhibitor bivalirudin) [11]. It seems to have several advantages, for example, safe to use in patients with heparin-induced thrombocytopenia [12], and evidence gathered so far seems very promising.

Another well-known reason for a low number of evidence-based studies is if the subject investigated is potentially mortal, as it would be highly unethical to conduct a prospective randomized study with increased mortality as outcome. A good example on this is appendicitis: the benefit of postoperative antibiotics to prevent infection has been elicited in a Cochrane review [13], but a blinded, randomized

Table 2.

Selected studies of retrospective design. For selection, please see text and fig. 1.

Author and reference data	No.	Focus	Incidence
Ford <i>et al.</i> [24]	1346	AR related to heart surgery	3/1346
Gupta <i>et al.</i> [25]	1150	Vascular surgery with AR due to PS	11/1150
Laxenaire <i>et al.</i> [26]	477	Referred to allergy clinic due to AR to PS	1/477
Levy <i>et al.</i> [27]	1743	Heart surgery with AR due to PS	4/1743
Levy <i>et al.</i> [28]	3225	Heart surgery with AR due to PS	NPH: 1/160; others: 2/3065
Mertes <i>et al.</i> [29]	789	Referred to allergy clinic due to AR to PS	1/789
Reed and Gascho [5] (retrospective part)	5131	Heart catheterization	DM: 0/206; others: 0/4925
Stewart <i>et al.</i> [30]	651	Heart catheterization with AR due to PS	NPH: 4/15; others: 3/636 (one with fish allergy)
Vincent <i>et al.</i> [31]	3341	Heart catheterization	NPH: 2/171; others: 2/3170

AR, anaphylactic reaction; DM, diabetes mellitus; NPH, neutral protamine Hagedorn; PS, protamine sulfate.

outcome study of antibiotic treatment instead of appendectomy has to the knowledge of these authors not been conducted although evidence-based knowledge within this area has been requested from time to time [14]. This empiric way of acting could in the long run leave us with unsubstantiated routines that in the worst case could be harmful. However, the role of randomized controlled trials can certainly be discussed when exploring adverse reactions, and, for example, the use of database analyses could prove helpful as well. This approach has always been a source of important information when investigating outcome of certain procedures and was also used in some of the articles found in this study (e.g. Laxenaire *et al.* in table 2). In addition, to reach a sufficient level of evidence, the knowledge gained through these studies will often need confirmation through, for example, a randomized trial, why these studies generally are given higher weight.

The most common factor predisposing to an anaphylactic reaction to protamine sulfate is prior treatment with NPH insulin. Thus, consideration of such a reaction perhaps should be limited to those individuals as in most studies from the mid-80s. However, many of the later studies have been conducted on diabetes patients disregarding their treatment or in a general population which contributes to the common idea of protamine sulfate causing adverse reactions in a general population without substantial evidence. In this context, a systematic literature review is a powerful tool that provides a well-structured insight into the evidence lying behind different 'manners', and in order to gain insight into a certain area, the literature must be profoundly scrutinized. To our knowledge, this is the first systematic literature review of studies addressing adverse reactions to protamine sulfate. Earlier studies have mainly been of a reviewing kind or have been case reports supported by a literature summary. Therefore, there is no conflict with earlier reports, but our findings does question the profoundness of reviews and literature summaries in general: often, these are performed by a specialist in the field, why the literature will be viewed in a subjective way. In order to assure that the 'common knowledge' is evidence-based, a thorough, systematic literature review of the matter in question should be performed. Of note, this should be considered even for illustrious routines that go a long way back: certainly, many traditions has an empiric sound nature and should be preserved, but evidence-based knowledge could from time to time add new, important aspects.

Our study has some limitations concerning the retrieval of literature and evaluation of symptoms described: composition of the literature search is critical, why a broad search strategy was applied to assure high sensitivity in the search to retrieve all relevant studies. Furthermore, the literature retrieved was thoroughly read by both authors to assure a valid evaluation, and reviews and case report literature was evaluated to extract 'spin-off' articles not found in the primary search. As 19 articles emerged from this, it indicates that even the most vivid literature search does not guarantee extraction of all existing literature on a certain topic. As far

as evaluation of symptoms is concerned, we have relied solely on statements in the articles to distinguish between anaphylactic/anaphylactoid reactions and other types of haemodynamic instability, as no crude data were available for interpretation.

In conclusion, the retrospective studies support the general opinion concerning adverse reactions due to protamine sulfate, but evidence for the magnitude and physiological background for an actual anaphylactic reaction caused by protamine sulfate is very limited. Our findings support the low incidence of anaphylactic reactions reported in other studies (<1%), but caution should be taken due to a pronounced heterogeneity of the studies. Furthermore, a straightforward clinical implication of this work is the recommendation of a more critical appraisal of many daily routine procedures: a systematic literature review of such issues should be performed in a well-structured, repeated manner in order to accumulate new-gained insight in the task at quest. This approach should be given higher priority in all aspects of medical care, and could beneficially be included in the medical education programme and used as a tool in this context.

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