

Review article

H₁-antihistamines for the treatment of anaphylaxis: Cochrane systematic review

Background: Anaphylaxis is an acute systemic allergic reaction, which can be life-threatening. H₁-antihistamines are commonly used as an adjuvant therapy in the treatment of anaphylaxis. We sought to assess the benefits and harm of H₁-antihistamines in the treatment of anaphylaxis.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); MEDLINE (1966 to June 2006); EMBASE (1966 to June 2006); CINAHL (1982 to June 2006) and ISI Web of Science (1945 to July 2006). We also contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material. Randomized and quasi-randomized-controlled trials comparing H₁-antihistamines with placebo or no intervention were eligible for inclusion. Two authors independently assessed articles for inclusion.

Results: We found no studies that satisfied the inclusion criteria.

Conclusions: Based on this review, we are unable to make any recommendations for clinical practice. Randomized-controlled trials are needed, although these are likely to prove challenging to design and execute.

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Anaphylaxis is described as a potentially life-threatening, acute systemic allergic reaction with many possible trigger factors, including foods, insect venoms, medications, anaesthetics, latex rubber and exercise (1–6). It now occurs commonly in the community as well as in healthcare facilities (2). Progress is being made towards a universally acceptable clinical definition of anaphylaxis as ‘a serious allergic reaction that is rapid in onset and may cause death’ (7). Historically, it has been defined mechanistically as a hypersensitivity reaction involving the release of mediators from mast cells and basophils following allergen interaction with cell-bound immunoglobulin E (IgE) and has been distinguished from anaphylactoid reactions, which involve non-IgE-mediated or even nonimmune release of mediators. This mechanistic distinction is generally discouraged in clinical practice, as it is recognized that the clinical picture and the treatment of anaphylaxis are similar regardless of trigger factor or pathophysiological mechanisms (3, 4).

Cutaneous symptoms and signs, including generalized urticaria, angioedema, flushing and itching are the most

common manifestations of anaphylaxis, occurring in about 90% of individuals, followed by respiratory symptoms in up to 70%, and gastrointestinal symptoms in up to 40%. Hypotension, manifest as dizziness, shock and unconsciousness or both, occurs in only 10–30% of individuals with anaphylaxis (1–4, 6). Recognition of the wide spectrum of symptoms and signs in anaphylaxis and of the continuum of symptoms and signs has been emphasized (5).

The time course of anaphylaxis is usually rapid. Symptoms and signs often occur within 5–30 min of exposure to the trigger factor, although occasionally they do not develop for several hours. Anaphylaxis may be fatal within 5–30 min (8). Protracted and biphasic (delayed phase) reactions may occur, although the frequency with which such reactions occur is as yet unclear because of methodological concerns surrounding existent studies; those reporting high rates (up to 25%) are from highly selected groups with particularly severe reactions, whereas those reporting low rates (<2%) are retrospective, with potential for under-reporting (9–14).

Clinically, it may be difficult to distinguish true biphasic (recurrent) reactions from protracted severe reactions where an apparent recurrence in fact represents unmasking of an ongoing reaction when prior adrenaline treatment has worn off.

The diagnosis of anaphylaxis is based largely on history and physical findings at the time of the event. Laboratory tests available to support the diagnosis have proved to be somewhat disappointing in clinical practice. Transiently elevated plasma histamine levels of >10 nM correlate with the severity and persistence of cardiopulmonary manifestations or gastrointestinal manifestations. However, as histamine needs to be measured within 1 h of the onset of an anaphylaxis episode, and is not stable during routine handling, this test is seldom used. Identification of an elevated serum tryptase level (>11.4 ng/ml; Phadia AB, Uppsala, Sweden) within 12 h (preferably within 3 h) of the onset of an episode is more widely used as a confirmatory test. The assay for total serum tryptase available in hospital laboratories measures the alpha-tryptase that is constitutively secreted from mast cells, as well as the mature tryptase that is released after mast cell activation in anaphylaxis. Because of this additional 'noise' and because tryptase release into the circulation may not always occur, total serum tryptase levels may be within normal limits in patients with clinically confirmed anaphylaxis; serial total serum tryptase measurements may be more helpful than single measurements (15).

Anaphylaxis is under-recognized and under-diagnosed, both in those who survive and those who die. Half of all of those who do not survive an episode of anaphylaxis have no indicative findings at autopsy (8). Individuals aged >30 years are more likely to experience hypotensive anaphylaxis (16), and are thus at greatest risk of death from insect sting anaphylaxis, with cardiovascular collapse usually a prominent feature (8). In comparison, people who die from food-induced anaphylaxis tend to be younger, and fatality is predominantly due to upper and/or lower airway obstruction; moreover, poorly controlled asthma appears to be a major risk factor for death (8, 12, 17).

Adrenaline is the initial treatment of choice for anaphylaxis. The patient's airway, breathing and circulation need to be assessed, monitored and managed. In addition to adrenaline, oxygen and inhaled β_2 -agonists are used in the case of breathing difficulties and volume expanders are used in the case of hypotension (18, 19). As adjuvant therapies H_1 - and H_2 -antihistamines and steroids are also often given, although there is little data to support these uses and in the case of first-generation, potentially sedating H_1 -antihistamine preparations, there is potential to cause harm (20, 21).

During anaphylaxis, a number of inflammatory mediators are released from mast cells and basophils. Histamine plays a pivotal role in acute allergic inflammation, which is a complex network of events that involve redundant mediators and signals, including tryptase,

mast cell carboxypeptidase, platelet-activating factor, prostaglandins, leukotrienes and cytokines. In a systemic response, however, there may be sufficient redundancy and amplification such that reactions do not respond to a single mediator antagonist (21, 22).

In an attempt to downregulate the allergic response and minimize the clinical impact of histamine release, H_1 -antihistamines are often given. These medications act as inverse agonists, i.e. they combine with and stabilize the inactive form of the H_1 -receptor, shifting the equilibrium towards the inactive state (21). There are two main functional classes of H_1 -antihistamines: first-generation antihistamines, which are sedating, and second-generation antihistamines, which are relatively nonsedating.

Given the frequency with which H_1 -antihistamines are used in the emergency management of anaphylaxis, we searched systematically to assess the benefits and harm of H_1 -antihistamines in the treatment of anaphylaxis.

Methods

Criteria for considering studies for this review

We sought to include randomized-controlled trials and quasi-randomized-controlled trials comparing H_1 -antihistamines with placebo or no intervention. We were interested in all patients (infants, children and adults; community, hospital/medical setting) experiencing anaphylaxis caused by food, insect venom, medication, anaesthetics, latex, exercise or any other trigger.

We were also interested in studies involving any systemic (intravenous, intramuscular or oral) administration of H_1 -antihistamines by patient/lay carer (of a child) or medical professional. We intended to examine the use of H_1 -antihistamines when administered for the treatment of acute anaphylaxis. We specifically excluded any studies where the primary aim was to examine the use of H_1 -antihistamines for the prevention of anaphylaxis, where the drug under study was not an H_1 -antihistamine or where the purpose of administration was to prevent rebound or recurrence of anaphylaxis. We intend to examine the use of prophylactic H_1 -antihistamines in a separate review.

Our outcome measures of interest are detailed in Table 1.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); MEDLINE (1966 to June

Table 1. Outcome measures of interest

Primary
1. Clinical improvement by any objective measure
2. Mortality rate
Secondary
3. Hospitalization rate
4. Length of emergency department visit
5. Length of hospital stay
6. Representation rate to hospital
7. Iatrogenic adverse events
8. Rate of persistent/delayed/biphasic reactions
9. Costs to health services and patients

2006); EMBASE (1966 to June 2006); CINAHL (1982 to June 2006) and ISI Web of Science (1945 to July 2006).

We searched MEDLINE, using Ovid and the Cochrane randomized-controlled trial filter (23) and the following key words: anaphylaxis and H₁-antihistamines. Our full search strategy is detailed in Appendix 1. This was adapted for searching the other databases. We imposed no language restrictions in the literature search.

We attempted to uncover additional relevant published data, grey literature, unpublished data and research in progress by:

- 1 developing a database of first and last authors of potentially eligible studies. We searched The Science Citation Index Expanded (SCI-EXPANDED, 1945 to June 2006) using these names for additional studies;
- 2 searching the bibliographies of identified studies;
- 3 compiling a database of international experts in anaphylaxis (see Appendix 2);
- 4 contacting relevant pharmaceutical companies (see Appendix 2);
- 5 searching the UK's National Research Register;
- 6 searching websites listing ongoing trials (<http://clinicaltrials.gov/> and <http://www.controlled-trials.com>; accessed 16 May 2007).

Selection of trials

Two authors (VB, AS) independently reviewed titles and abstracts from literature searches and selected possibly relevant studies. These studies were reviewed in full and assessed using the inclusion criteria detailed above.

We had agreed that we would resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, a third author (ES) was to be involved, and if necessary, arbitrate, but this did not prove necessary.

Details of the proposed methods for data extraction, assessment of methodological quality of included studies, data analysis and synthesis are available in the full review (24). Proposed subgroup analyses are detailed in Table 2.

Results

Searching the four databases until June 2006 yielded 2070 citations. After scrutiny of the abstracts of these studies, only one article (25) was retrieved for full text analysis, but this did not fulfil the inclusion criteria on account of the allergic reactions being studied and the absence of a suitable control group. The search of the UK National Research Register, Current Controlled Trials and

ClinicalTrials.gov using anaphylaxis as a keyword identified no useful articles.

We contacted context editors and pharmaceutical companies (Appendix 2), but this did not contribute any published or unpublished studies.

Discussion

We found no high quality evidence either for or against the use of H₁-antihistamines in anaphylaxis.

Anaphylaxis is a medical emergency. To help ensure appropriate standards of care, guidelines have been developed in several countries. For example, the guideline on anaphylaxis used in the UK advises that, after oxygen and adrenaline are given, patients should receive an H₁-antihistamine and, if needed, additional treatments with fluids or hydrocortisone (26). H₁-antihistamines are seen to have a role in the treatment of anaphylaxis in this and other guidelines, although the evidence base in support of this position remains very weak.

H₁-antihistamines are effective in some localized and less severe systemic allergic reactions, for example, in allergic rhinitis they relieve sneezing, itching and rhinorrhea; in allergic conjunctivitis they relieve erythema, itching and lacrimation; and in urticaria they relieve itching, whealing and erythema, as documented in systematic literature reviews (27, 28). In other allergic disorders, they are of little clinical importance. The evidence-based UK guideline on asthma, for example, does not recommend treatment with H₁-antihistamines (29). Furthermore, a systematic literature review conducted on atopic dermatitis could not demonstrate a beneficial effect of H₁-antihistamines (30). Generalizations to anaphylaxis based on their effectiveness (or ineffectiveness) in other allergic disorders are therefore problematic.

Although H₁-antihistamines are expected to relieve itching, hives, other cutaneous symptoms and rhinorrhea in anaphylaxis, they are not expected to relieve airway obstruction, gastrointestinal symptoms, or neither shock, nor do they prevent ongoing mediator release from mast cells and basophils in doses used clinically (18). Moreover, after administration by mouth, H₁-antihistamine absorption and onset of action are slow, taking at least 1–2 h (18). Most medications in this large class cannot be administered by injection, with the exception of a few first-generation H₁-antihistamines such as chlorpheniramine, diphenhydramine, hydroxyzine and promethazine (18). In many episodes of anaphylaxis, improvement attributed to an orally administered H₁-antihistamine is likely to be due to spontaneous improvement or endogenous compensatory mechanisms such as increased adrenaline and angiotensin II secretion (31, 32).

It is also important to bear in mind that treatment with H₁-antihistamines may have side effects. The first-generation H₁-antihistamines cross the blood–brain barrier and in usual doses may cause drowsiness, fatigue,

Table 2. Proposed subgroup analysis for investigation of heterogeneity

Our subgroups of interest were:
1. Presence/absence of shock
2. Mild/more severe anaphylaxis
3. Class of H ₁ -antihistamine given (sedating/nonsedating and also traditional classification based on chemical structure, i.e. ethylenediamine, ethanolamine, alkylamine, phenothiazine, piperazine, piperidine and other)
4. Mode of administration of treatment (for example, intravenous vs intramuscular vs oral)
5. Time from onset of anaphylaxis to receiving treatment
6. Age (infant, child, adult)

somnolence, dizziness, confusion, impairment of cognitive function and other CNS symptoms. In infants and young children, paradoxical CNS stimulation, including seizures, can occur. Hypotension and dose-related cardiac toxic events have been reported (21). Overdose of first-generation H₁-antihistamines has led to fatalities. In contrast, second-generation H₁-antihistamines are relatively nontoxic (21, 22, 33); however, they are not available for parenteral use.

As the evidence suggests that H₁-antihistamines are effective only in some less severe allergic disorders; that administration of H₁-antihistamines may cause important side-effects, and that the existing studies investigating their role in anaphylaxis have used suboptimal study designs the research question. One may then, reasonably ask why there are as yet no randomized-controlled trials in this area? We hypothesize that one of the primary reasons there are no trials might be the fact that anaphylaxis represents a potentially life-threatening emergency. Executing a randomized-controlled trial in an emergency situation raises a number of ethical questions. For example, how can informed consent be obtained? How can one refuse a possible treatment option in an emergency? How can one get approval for the use of a placebo? We consider these important considerations below.

How should informed consent be obtained?

Paragraph 26 of the Declaration of Helsinki states that: ‘...in an emergency context, consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate’ (34). No direct consent is needed, which makes it, in principle, ethically feasible to conduct a randomized-controlled trial in this context; however, the Declaration of Helsinki is not a legal document. The European Union agreements do, however, have legal weight (35). Within these agreements, the patient or his/her legal representative should be informed about the purposes and risks of the trial, before entering it. To inform someone and to find a legal representative takes time; time which typically is not available in an emergency situation (36). Currently, an amendment has been proposed by the UK in which an exception for emergency situations has been proposed. This exception implies that before entering a trial no direct informed consent is needed; although consent must be given or obtained within 24 h (37). Approval of this amendment will facilitate the execution of randomized-controlled trials in medical emergency situations.

How can one refuse a possible treatment option in an emergency?

H₁-antihistamines are seen as a possible treatment option because a number of guidelines recommend their use. This recommendation has been incorporated into guidelines without a proven effect ever being demonstrated. There might be no effect, or the side effects might be

worse than the effect itself. It can therefore be argued that there is a state of clinical equipoise between H₁-antihistamines and placebo. However, to examine this in the presence of current guidelines may prove difficult.

How can approval for the use of a placebo be obtained?

The argument mentioned above can also be used here. When a state of clinical equipoise exists, a comparison between antihistamine treatment and placebo should be possible. Although uncommon, there are placebo-controlled trials done in emergency situations. Two that are of possible relevance will be described here. The first study (38) was a prospective, randomized, double-blind, placebo-controlled clinical trial, designed to evaluate the safety and efficacy of oral nicardipine for the treatment of urgent hypertension in the emergency department. The control group was treated with a placebo. Individuals who did not respond to their first treatment got a second tablet of open-label nicardipine. The study, however, excluded the hypertensive emergencies. Another study (39) examined the administration of benzodiazepines by paramedics for out-of-hospital status epilepticus. Patients were given intravenous diazepam, lorazepam or placebo. Two treatments: waiting or giving benzodiazepines were compared. An open-label diazepam was immediately available when the patient was at high risk for a life-threatening complication. While these randomized-controlled trials are not directly comparable to investigation of H₁-antihistamines in anaphylaxis, their existence may provide useful information relevant to the design of a future randomized-controlled trials of H₁-antihistamine treatment in anaphylaxis.

The second reason for the absence of randomized-controlled trials in anaphylaxis could be linked with the absence of a universally accepted definition on this topic. Many emergency departments work with their own definitions and this hinders standardized research and treatment (40). This issue has been repeatedly highlighted (2, 5, 7).

A third reason for their absence might be the perceived relevance of our research question. Why should we want to know what the effects are of H₁-antihistamine treatment in anaphylaxis? This might not be the most important question asked. But given that anaphylaxis is a life-threatening disease with potentially avoidable mortality, we have no hesitation in arguing for the need for robust data to guide clinical decision-making. Moreover, the administration of H₁-antihistamines potentially delays the use of other, perhaps more effective, treatment modalities.

Finally, designing trials for conditions with a low incidence/prevalence and interventions with likely modest effect sizes is challenging, as the studies need to be large in order to have adequate power. The number of patients required may thus be prohibitive.

Considering the above points, there are many challenges inherent in conducting a controlled trial in this

area. These challenges need to be weighed against the possible advantages of generating robust evidence. Given the lack of findings uncovered by this comprehensive review, we believe the ethics and feasibility of mounting and successfully executing a randomized-controlled trial of H₁-antihistamines now warrants broader discussion and debate.

Implications for practice

We found no relevant evidence. We are therefore unable to make recommendations about H₁-antihistamine use in the treatment of anaphylaxis. Guidelines on the management of anaphylaxis need to be much more explicit about the basis of their recommendations regarding the use of H₁-antihistamines.

Implications for research

Given the widespread use of H₁-antihistamines for anaphylaxis treatment (40), there is a case for randomized trials of high methodological rigour in order to define the true extent of benefit from the administration of H₁-antihistamines in anaphylaxis. Specifically, more information is required on the subset of patients most likely to benefit from this therapy and the most appropriate

preparations, route and dose of administration. Any future trials would need to consider in particular: appropriate sample sizes with power to detect expected differences; careful definition and selection of target patients; appropriate comparator therapy; appropriate outcome measures including all those listed in this review; careful elucidation of any adverse effects and the cost-utility of the therapy.

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Appendix 1. Search terms

-
- 1 randomized controlled trial.pt.
 - 2 controlled clinical trial.pt.
 - 3 randomized controlled trials.sh.
 - 4 random allocation.sh.
 - 5 double blind method.sh.
 - 6 single blind method.sh.
 - 7 1 or 2 or 3 or 4 or 5 or 6
 - 8 (ANIMALS not HUMAN).sh.
 - 9 7 not 8
 - 10 clinical trial.pt.
 - 11 exp clinical trials/
 - 12 (clin\$ adj25 trial\$.ti,ab.
 - 13 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
 - 14 placebos.sh.
 - 15 placebo\$.ti,ab.
 - 16 random\$.ti,ab.
 - 17 research design.sh.
 - 18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
 - 19 18 not 8
 - 20 19 not 9
 - 21 comparative study.sh.
 - 22 exp evaluation studies/
 - 23 follow up studies.sh.
 - 24 prospective studies.sh.
 - 25 (control\$ or prospectiv\$ or volunteer\$.ti,ab.
 - 26 21 or 22 or 23 or 24 or 25
 - 27 26 not 8
 - 28 27 not (9 or 20)
 - 29 9 or 20 or 28
 - 30 ANAPHYLAXIS/
 - 31 anaphylactic react\$.mp.
 - 32 anaphylactic shock\$.mp.
 - 33 anaphylactic syndrome\$.mp.
 - 34 anaphylactoid react\$.mp.
 - 35 anaphylactoid shock\$.mp.
 - 36 anaphylactoid syndrome\$.mp.
 - 37 acute systemic allergic react\$.mp.
 - 38 idiopathic anaphylaxis.mp.
 - 39 systemic anaphylaxis.mp.
 - 40 or/30–39
 - 41 exp Histamine H₁ Antagonists/
 - 42 antihistamin\$.mp.
 - 43 Chlorpheniramine.mp. or
CHLORPHENIRAMINE/
 - 44 brompheniramine.mp. or
BROMPHENIRAMINE/
 - 45 Dimethindene.mp. or DIMETHINDENE/
 - 46 Pheniramine.mp. or PHENIRAMINE/
 - 47 Tripolidine.mp. or TRIPROLIDINE/
 - 48 Buclizine.mp.
 - 49 Cyclizine.mp. or CYCLIZINE/
 - 50 Hydroxyzine.mp. or HYDROXYZINE/
 - 51 Meclizine.mp. or MECLIZINE/
 - 52 Oxatomide.mp.
 - 53 Azatadine.mp.
 - 54 Cyproheptadine.mp. or
CYPROHEPTADINE/
 - 55 Diphenylpyraline.mp.
 - 56 Ketotifen.mp. or KETOTIFEN/
 - 57 Carbinoxamine.mp.
 - 58 Clemastine.mp. or CLEMASTINE/
 - 59 Dimenhydrinate.mp. or
DIMENHYDRINATE/
 - 60 Diphenhydramine.mp. or
DIPHENHYDRAMINE/
 - 61 Doxylamine.mp. or DOXYLAMINE/
 - 62 Phenyltoloxamine.mp.
 - 63 Antazoline.mp. or ANTAZOLINE/
 - 64 Pyrilamine.mp. or PYRILAMINE/
 - 65 Tripeleennamine.mp. or
TRIPLENNAMINE/
 - 66 Methdilazine.mp.
 - 67 Promethazine.mp. or PROMETHAZINE/
 - 68 Doxepin.mp. or DOXEPIN/
 - 69 Alimemazine Tartrate.mp.
 - 70 Acrivastine.mp.
 - 71 Cetirizine.mp. or CETIRIZINE/
 - 72 Levocetirizine.mp.
 - 73 Astemizole.mp. or ASTEMIZOLE/
 - 74 Desloratadine.mp.
 - 75 Ebastine.mp.
 - 76 Fexofenadine.mp.
 - 77 Levocabastine.mp.
 - 78 (Loratadine or loratidine).mp. or
LORATADINE/
 - 79 Mizolastine.mp.
 - 80 Olopatadine.mp.
 - 81 Terfenadine.mp. or TERFENADINE/
 - 82 Azelastine.mp.
 - 83 Emedastine.mp.
 - 84 Epinastine.mp.
 - 85 Cinnarizine.mp. or CINNARIZINE/
 - 86 Flunarizine.mp. or FLUNARIZINE/
 - 87 Methapyrilene.mp. or METHAPYRILENE/
 - 88 Mianserin.mp. or MIANSERIN/
 - 89 Actifed.mp.
 - 90 carebastine.mp.
 - 91 chloropyramine.mp.
 - 92 dexchlorpheniramine.mp.
 - 93 Iodoxamide tromethamine.mp.
 - 94 mequitazine.mp.
 - 95 mirtazapine.mp.
 - 96 NCO 650.mp.
 - 97 picumast.mp.
 - 98 protopine.mp.
 - 99 proxicromil.mp.
 - 100 temelastine.mp.
 - 101 Tranilast.mp.
 - 102 tritoqualine.mp.
 - 103 Valoid.mp.
 - 104 Otrivine-Antistin.mp.
 - 105 Zaditen.mp.
 - 106 Phenergan.mp.
 - 107 Atarax.mp.
 - 108 Ucerax.mp.
 - 109 Tavegil.mp.
 - 110 Periactin.mp.
 - 111 Piriton.mp.
 - 112 Dimotane.mp.
 - 113 Vallergran.mp.
 - 114 Mizollen.mp.
 - 115 Xyzal.mp.
-

116 Telfast.mp.
 117 Neoclarityn.mp.
 118 (Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben or zyrtec or claritin or coricidin or soltara or allegra or alavert or tavist).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 119 or/43–118
 120 41 or 42 or 119
 121 29 and 40 and 120

Appendix 2. List of experts and pharmaceutical companies contacted

Dr A. Bock
 Prof. A. Brown
 Dr C. A. Camargo
 Dr S. Clark
 Dr P. W. Ewan
 Prof. M. Fisher
 Dr D. Golden
 Dr A. Helbling
 Dr S. Kemp
 Dr P. L. Lieberman
 Dr R. Y. Lin
 Dr R. Lockey
 Prof. D. A. Moneret-Vautrin
 Prof. U. Muller
 Prof. J. M. Negro-Alvarez
 Dr R. S. Pumphrey
 Prof. J. Ring
 Prof. H. A. Sampson

Amdipharm
 Aventis Pharma,
 Cambridge Healthcare Supplies
 GlaxoSmithKline Consumer Healthcare
 Novartis Consumer Health
 Rhone-Poulenc Rorer
 Schering-Plough
 Schwarz
 Viatris Pharmaceuticals
