Double-blind studies in allergy

Moral limitations

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Summary

In allergy, like in other fields of medicine, double-blind placebo-controlled studies are regarded as the gold standard of clinical trials for therapeutic as well as diagnostic purposes. The technical aspects, the strict requirements, the weaknesses and limitations of the studies are underlined. They also raise ethical issues and often put the physicians in a perplexing dilemma.

The Declaration of Helsinki, the creation of national ethical committees, morally limit these trials but do not prevent controversies about the use of placebo, the informed consent of the patients and the investigator's responsibility. – To solve the present and future problems in the field of allergy, we have to rely on the good sense and intelligence of the scientific and medical community.

Zusammenfassung

Wie in allen anderen medizinischen Disziplinen gelten auch in der Allergologie sowohl für Diagnostik als auch Therapie placebokontrollierte Doppelblind-Studien als „Goldstandard“ klinischer Prüfungen. Es werden die technischen Aspekte, die strengen Kriterien sowie Schwächen und Grenzen dieser Studien herausgearbeitet. Es erheben sich auch ethische Fragen, die die Ärzte oft in erhebliches Dilemma bringen.

Die Erklärung von Helsinki und die Einrichtung nationaler Ethikkomitees setzen den Doppelblind-Studien moralisch Grenzen, ohne jedoch Kontroversen über den Einsatz von Placebos, die Zustimmung der Patienten und die Verantwortung der klinischen Forscher verhindern zu können.

Um aktuelle und künftige Probleme in der Allergologie lösen zu können,

müssen wir auf Einsicht und Klugheit der Wissenschaftler- wie der Medizinergemeinschaft vertrauen.

Introduction

In allergy, like in other fields of medicine, randomized double-blind studies are often regarded as the “gold standard” of clinical trials for the assessment of drug effectiveness.

It is particularly important in the field of allergen immunotherapy which has been the subject of considerable controversy despite the recent progress in purification and standardization of allergens, the identification of specific epitopes, the use of recombinant allergens and the use of different routes of administration of allergens ranging from injection to sublingual, to ophthalmic, to intra-nasal.

In the case of challenge testing where the role of an allergen must be defined as related to the disease under study, the double-blind study becomes essential particularly in food allergy. It is obvious that properly controlled trials are of critical importance in the progress of medical science and require the caution of scientific rigor. So, since the eighties, and in spite of many ethical problems, it has become the norm to require placebo-controlled double-blind studies in medical experimentation.

Justification of the procedure

The blinding procedure is aimed to avoid the bias of “open trials”. This may be due to the investigator with the risk of a non-objective assessment of the results in case of preferential treatment, a wrong judgement on the therapeutic or side-effects, or by positive suggestion of the medical group.

Bias may be due to the patient who may be more indulgent in the assess-

ment of symptoms and in the therapeutic outcomes, since he believes in a new drug or procedure. He may also minimize its side effects.

Thus, the objective appreciation of a new drug or a provocation test has lead statisticians, physicians and administrative authorities to condemn these open trials and require controlled studies for the quality of the investigation, the benefit of the patient, and as a general point of view, for the benefit of society.

For the patient, even if, in the short term, the use of a placebo gives rise to an ethical issue, in the long term an efficient new drug such as immunotherapy may improve his symptoms and his quality of life. We must remember that in the seventies it has been shown that whole-body extracts used as immunotherapy in Hymenoptera allergy were not superior to placebo and that only extracts of venom could bring an efficient protection against stinging insect hypersensitivity. This was also the beginning of rush- immunotherapy trials and a general re-evaluation of hyposensitization.

Moreover, the indisputable positivity of a provocation test, utilizing the technique of double-blind challenge, may have medico-legal implications such as recognition of an occupational allergy.

But the blinding procedure itself is not free from bias or false negative results. It also generates conflicts between the Hippocratic tradition of the therapist and obligations of scientific research.

Technical aspects of double-blind procedures

There are three main different designs of double-blind studies for *therapeutic purposes*:

First, the patient and all the members of the medical group are not aware of the drug, allergen, or placebo, which is given, until the end of the trial. This implies that a third person, usually a representative of the sponsor which is often a pharmaceutical company or a government agency, delivers the drug or the placebo, in individual numbered lots, according to a list prepared earlier. The patients are then assigned to one or other product according to their inclusion in the study and randomly divided into two groups. In one group the subjects are given the study drug; in the control group the placebo is given for the duration of the trial in a double-blind cross-over fashion. Further, there is a strict randomization and absolute secrecy as to which product is given to avoid all risks of leaks. There are well described inclusion criteria including diagnosis, severity of the disease, previous treatment, and duration of the trial. There is a sufficient sample size for a new drug compared to a placebo. Statisticians require at least 50 patients per group in order to provide assurance that the study has the desired power to detect a minimally meaningful difference between the treatment groups.

There are criteria of effectiveness which include clinical and laboratory examinations and diary cards, with, whenever possible, objective measurements such as rhinomanometry and functional respiratory or biological tests. Accurate statistical methods including statistical significance and confidence intervals are essential. The trial may be relatively short, and in case of emergency, undesirable side effects, or when the masked treatment is thought to be unsatisfactory, as in a change to open label design, the code may be unblinded.

In some trials, the new drug studied is compared with an older, well-established one, the safety and efficacy of which has been largely documented. The results may be obvious that the new drug is superior to the older one; but in a number of cases the results may not be so clear-cut, the two drugs sometimes may be differentiated in terms of side effects, but have a similar efficacy. This may be due to an insuffi-

cient sample size, to relatively insensitive outcome measures, or poorly trained medical staff and may lead to long and larger studies, with several

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medical and financial constraints. In fact, for epidemiologists and physicians who do not approve the use of a placebo in such studies which may deprive patients of an efficient therapy, other factors such as unintended effects, interactions or routes of administration should be taken into account (3). We should therefore realize that some patients find advantages to a treatment which is not superior in terms of efficacy but better with respect to the quality of life, acceptability and cost.

A third design in double-blind placebo-controlled trials consists of cross-over studies, where the patient is his own control, and is successively given the new drug or placebo or vice versa, depending on the blinding technique.

More sophisticated techniques may compare 2 drugs of similar efficacy, or an association of drugs with placebo, in a double-blind parallel, double-dummy study, generally conducted over a short period. In any case, the use of placebo and adequate controls and statistics are prerequisites to validate such studies. (1, 6, 7).

Double-blind procedures are also undertaken for *diagnostic purposes*: for example, Double Blind Placebo Controlled Food Challenge (DBPCFC); other allergy provocation tests are rarely feasible with a double-blind design.

This procedure includes several phases: initially a medical and dietary history, including suspected food allergy or intolerance, intestinal symptoms and also other atopic diseases such as urticaria, angioedema, asthma, eczema, is essential.

Skin prick tests and IgE blood levels to a standard range of foods and additives and to offending foods mentioned in the history should be next. Exclusion criteria in the case of pregnancy, anaphylactic reactions to foods, or children (in whom open challenge is usually sufficient) are needed and elimination of the selected foods, during one or two weeks prior to challenge, should be done. The subjects are randomized, allocated to the order in which active and placebo challenge was administered, the interval between the second part of the design being at least one week. The food substance is then administered by a dietician, whenever possible, in freeze-dried form, packed in gelatine capsules or masked in a vehicle to make it indistinguishable from the placebo. The provocation test is carried out under strict medical monitoring, for at least two hours and preferably in hospital, with the patient and the investigator unaware of the product administered. The symptoms are recorded on diary cards, and there is confirmation of food allergy if the subject has clear symptoms after provocation. If the results are equivocal, a third single blind challenge may be performed to exclude or confirm the reaction (2, 9). During the provocation test, increased levels of plasma histamine suggest a positive reaction.

The majority of the studies performed according to this protocol confirm that there is a discrepancy between the perception of food intolerance and positive results of the DBPCFC. Such studies suggest that only 1.8% to 2.4% of the population in developed countries are affected while 20% to 33% complain of adverse reactions to foods. However, these tests are time-consuming and inconvenient; many patients are lost during the study. They are also potentially dangerous, they can trigger anaphylaxis and they are not always feasible. But in the absence of other validated tests, they are essential to confirm the diagnosis of food allergy with its public health implications in terms of nutritional and financial aspects.

It should be pointed out that such provocation tests fall into the compe-

tence and responsibility of the physician and under common law. They do not depend on an ethical committee, except for a clinical programmed research.

Technical limitations of the double-blind studies

If the DBPCC is regarded, by investigators, physicians and official agencies, as the hallmark of good science, it has, apart from ethical counterarguments, several weaknesses.

All protocols are not feasible and a too sophisticated design increases the risk of early withdrawal from the trial. More than 10% of drop-outs decreases the quality and the significance of the study. Clinician bias may occur. Apart from leaks or tricks from the medical team, the physician may rapidly identify the product which is administered to his patient, whether it be drug or placebo, as the result of therapeutic or side effects.

The placebo effect may be significant. The placebo itself may produce benefits for up to 40% of patients, regardless of their complaints. This is the "non-specific effect" and the informed consent procedure is also a part of this effect. It must be differentiated from the "specific effect" of the treatment by appropriate statistical analyses; however, there is often interaction between these factors and a too vigorous reliance on statistical validity may be harmful (5).

We must also take into account psychological factors such as the physician's verbal attitude, the pill color, and the impressiveness of the treatment. In the field of allergy, environmental factors such as the intensity of concomitant exposure to allergens also play an important role.

Finally, we must bear in mind the natural course of the disease with a presumable remission of the disease as well as the biological variability of individuals.

Moral limitations of double-blind studies

All the DBPCC studies raise ethical questions and put the investigator in a perplexing moral dilemma, highlighting the conflict between the indi-

vidual safeguard and health of his patient and his responsibility to the benefit of the society and its scientific progress.

First of all, we must remember the fundamental rule in medicine: "Do no harm" – "primum non nocere".

In 1947, when the atrocities of the Nazi "pseudo-investigators" were unveiled, these outrageous acts were condemned with severity by the Nuremberg Military Tribunal. The Nuremberg Code was the first international declaration concerning involvement of human subjects for the purpose of research. Indeed, in the sixties, violations of human rights were re-

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ported, even in the Western society, under the guise of medical experimentation. So in 1964, during the 18th World Medical Association Assembly, the Declaration of Helsinki, was developed and forms the best international code on human experimentation; It states that "every patient – including a control group, if any – should be assured of the best proven diagnostic and therapeutic method". The declaration was confirmed by the 29th Assembly in Tokyo in 1975.

One of the main recommendations among all the articles and guidelines is informed consent of the subject.

Since this time, a large number of national and international codes or laws have tried to solve the problems we physicians face in the development of the medical science and underline the role of the state in their solution.

In France, in 1984, a national ethical committee was created and includes eminent personalities who are in charge of these questions. Then, in 1988, a law known as "Loi Huriet", the name of a senator and doctor, was passed in order to protect subjects who agree to take part in biomedical research. Moreover, in all important French hospitals, a local ethical committee reviews all projects related to clinical trials and encourages the physi-

cian to adhere to fundamental conditions of scientific, ethical, and valid medical research. It also makes sure that the protocols do not threaten the delivery of optimal care and thus provides protection to the patient.

But, generally speaking, the French authorities consider that a project without validity risks steering patients to useless treatments or leads to wrong conclusions for future patient studies or treatments. A large number of international scientists are in agreement with these rules, guidelines and codes.

Areas of concern in such studies include: the investigator, most often the physician (mandated by an official agency or a drug company), the patient, and the Ethics Committee.

Regarding the investigator, the DBPCC studies are contrary to the traditions of practitioner autonomy and do not comply with his duty to treat and guard the patient health. Some physicians risk acting in violation of their moral obligations and the precepts of the Declaration of Helsinki, in order to further their career or glorify their positions.

Obviously, there is a lack of consensus about the use of placebo groups in drug trials. For some scientists this use is unethical, even if the patient gives his consent and placebos must be proscribed when a proven therapeutic method exists. They argue that when a placebo is given instead of an effective treatment, the effect of a new drug may appear obvious and statistically significant, even in small studies. The essential medical question is "how does the new treatment compare with the old one, not whether it is better than nothing". This procedure may be beneficial for the pharmaceutical company, but not for the patient who receives the placebo.

For the majority of investigators, placebo controls are necessary to ascertain a drug's effectiveness, provided that ethical rules are respected. So a human experiment should be preceded by laboratory and animal testing, should avoid unnecessary physical and mental suffering, and expose the minimal number of people to the minimal possible risks. Most impor-

tantly, the experiment should be conducted by a qualified physician, able to resist the pressure of sponsors, and in agreement with the ethical committee.

Regarding the patient, the "informed consent" is mandatory. This principle is required in all designs of drug trials and by all ethical committees. Its aim is to avoid any coercive or cruel experiments. The patient must be told that he is to participate in an experimental procedure and is advised of the risks involved, including a randomized design and the possibility of being treated by a placebo.

In a recent study, 54 of 79 patients (68%) strictly informed according to the ethical guidelines, agreed to participate in a trial, the two major motivations being altruism and good patient-physician relationship (4). These were mostly elderly patients who were long-term hospital residents. The 25 others (32%) refused, either through ill-feeling of the blind procedure, or because of anxiety about the placebo or adverse reactions to drugs.

Furthermore some individuals are legally or morally incompetent to give consent because of the lack of autonomy, the presence of psychiatric vulnerability, or as prisoners or low socioeconomic class.

Moreover the disclosure of the procedure of randomization may lead the patient to distrust the physician and to bias the final results. This is why the opponents to the use of placebo claimed that informed consent is an "escape clause", a "fiction" and that the patients are rarely, if ever, clearly informed of the research protocol. These are all the more reason to require a written informed consent or oral one given in the presence of a witness.

Regarding the *Ethics Committees*, their role is essential. They must make sure that the legitimate needs of society that they represent are met and must enhance the knowledge and

health of its members, that the study does not generate conflict with the rights of individuals and the subjects are protected against exploitation or abuse of power or ambition. The Committee must try to reconcile scientific research and medical practice.

These committees include wise, independent, multidisciplinary expert members, who must preserve integrity and credibility in either government or industry-sponsored trials, check all the steps of the study and give their agreement if there is no risk to the patient, a benefit for him and/or Society and if the study satisfies the unanimously accepted ethical requirements.

On a general point of view, the French laws consider that *all that is not scientific is not ethical*. In clinical research using a placebo, the trial is with or without individual benefit. The subjects who receive the placebo are in the second group. But if some of the participants benefit from the new drug, this is the category which prevails. In other words, a diagnostic or therapeutic innovation intended for only one patient does not fall into the competence of the French laws; it is the physician's responsibility.

In the field of allergy, where a majority of diseases are benign (except for anaphylaxis, angioedema, severe asthma), the drug trials or challenge tests are usually well accepted by patients and Ethics Committees if they comply with all the moral obligations of medical practice.

Although young women who do not use methods of contraception are generally excluded from all the trials, the problem of women who become pregnant during the study needs stringent guidelines due to the risk of teratogenicity or toxicity for the fetus.

In case of infants, interim analyses are often suggested as they allow discontinuation of the regimen as soon as it shows a toxicity/efficacy profile inferior to a well-established drug effect

on the disease. Among 401 protocols submitted to a French hospital Ethics Committee between 1989 and 1994, 343 dealt with adults and 190 (55.4%) were accepted. Fifty eight protocols concerned children of which 30 (51%) were accepted, 10 were double-blind and 9 used placebo. The pediatric protocols were more difficult to evaluate than trials in adults (8).

Finally, double-blind studies are recognized as essential for the progress of medical science. If the use of placebo remains controversial in the medical community, properly controlled trials with a formal informed consent and respect of good medical practice, fulfilling the guidelines of an independent ethical committee, are the precondition of modern human experimentation and of scientific progress.

However, many other problems have been uncovered regarding studies in allergy: Although gene therapy in allergic diseases is not planned today, the advances in gene identification of atopy, risk putting the clinicians in a difficult quandary in the future.

The cases of recombinant or modified allergens cause the same ethical issues as those of any new drug.

But the genetically engineered foods may represent a real concern for dieteticians, allergists and public health authorities in the near future.

In conclusion, we must rely on the wisdom of the scientific and medical community to solve these problems as they advance.

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