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The Use and Abuse of Placebo in Clinical Trials

Key Words
Placebo · Clinical trials · Evaluation of new vs. standard drugs

Schlüsselwörter
Placebo · Klinische Studien · Vergleich von neuen mit Standardmedikamenten

Summary
This article particularly looks at the advantages and disadvantages of the use of placebos in the evaluation of new drugs when a standard drug is already available. Placebos make blinding possible and in that way help to control measurement bias when assessing the outcome of a trial. Several considerations need to be made when deciding whether to use a placebo. There are legal aspects, registration requirements, commercial interests, medical issues and scientific aspects. A placebo can and should be used in all research when the condition of the patient is not life-threatening and when there are no irreversible consequences of placebo treatment, even if a standard drug is available, but obviously only after informed consent. Insufficient evidence is provided if a placebo group is omitted when assessing a new drug versus standard drug. Obviously, this causes a conflict between the ethical aspects on one hand and the scientific aspects on the other, but if placebo groups are not used it will slow developments in medicine and reduce therapeutic possibilities.

Zusammenfasung
Sinn und Unsinn von Placebo-Kontrollen in klinischen Studien
Der vorliegende Artikel beschäftigt sich v. a. mit den Vor- und Nachteilen des Einsatzes von Placebo zur Beurteilung der Wirksamkeit neuer Medikamente, wenn ein Standardmedikament bereits auf dem Markt ist. Placebos ermöglichen eine Verblindung und dadurch die Kontrolle eines Bias bei der Bewertung von Studienergebnissen. Bei der Entscheidung für oder gegen den Einsatz eines Placebos müssen mehrere Faktoren berücksichtigt werden: rechtliche Aspekte, Zulassungsanforderungen, kommerzielle Interessen, medizinische Belange und wissenschaftliche Aspekte. In der Forschung kann und sollte ein Placebo immer dann eingesetzt werden, wenn der Zustand des Patienten nicht lebensbedrohlich ist und wenn die Behandlung mit Placebo keine irreversiblen Schäden verursacht – selbst wenn ein Standardmedikament bereits auf dem Markt ist, was natürlich die Einwilligung des Patienten erfordert. Ein zusätzlicher Placeboarm verleiht einer Studie zum Vergleich eines neuen Medikamentes mit einer Standardtherapie mehr Aussagekraft. Dies führt natürlich zu einem Konflikt zwischen ethischen und wissenschaftlichen Aspekten, ein Verzicht auf eine Placebogruppe würde jedoch therapeutische Fortschritte verzögern.

Placebo or Active Product as Controls?

In order to avoid the pitfalls and biases of uncontrolled treatment evaluations, randomised placebo-controlled trials, when possible, have become the standard method for evaluating treatment efficacy. Placebos make it possible to perform single- or double-blind trials in which co-interventions and measurement bias can be controlled. Here, we particularly look at the advantages and disadvantages of the use of placebos in the evaluation of new drugs when a standard drug is already available.

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The Role of Placebos

Placebos make blinding possible and in that way help to control measurement bias when assessing the outcome of a trial. Blinding also helps to ensure that co-interventions (aspects of treatment other than those being specifically tested in the trial) are comparable between groups. Placebos are particularly important if a trial is looking at a 'soft' or subjective endpoint. On the other hand, they are not appropriate in life-threatening situations, for example, bleeding from a carotid artery. When a placebo is needed it can be used in different trial settings, for example, to evaluate a new drug or to compare two drugs, but also in the evaluation of some other interventions such as ultrasound treatment or even a surgical procedure.

Several considerations need to be made when deciding whether to use a placebo. There is the legal aspect in that a doctor is duty-bound to treat a patient in the best possible way at any time or under any circumstance. There may be the registration requirements for a new drug that state that it must be evaluated against a placebo. From a commercial point of view a manufacturer might want to show that a drug is efficacious but not necessarily better than an existing drug. And, from a medical point of view a doctor will want to know the risk/benefit balance of a drug.

Generally there are two main questions to ask when evaluating a new drug: 'Is it better than placebo?' and 'How does it compare with the standard drug?'

Is a Placebo Always Necessary?

Should a new drug be compared with a standard drug but not a placebo? I do not believe so. Where possible a placebo should be used, and this is particularly so for studies which use subjective outcomes and when the design of the study may itself influence reports of efficacy and outcome. This is because blinded assessment in order to avoid measurement bias can be realized easiest by using a placebo control. One influence arises out of the need to obtain informed consent, which makes a clinical trial setting different from the daily practice setting. Typically, patients are told much more about the expected effects (wanted and unwanted) of a treatment in a trial and so then have different and more expectations themselves. In practice, some of the people in a treatment group would get better with no treatment, some would get better because of a placebo effect and some would get better because of the drug.

Consider the following hypothetical, but realistic situation: An existing standard drug that is taken twice daily for chronic pain has been tested against a placebo in the past and has obtained an analgesic score of 6 versus a score of 3 for placebo. A new drug is then evaluated against the standard drug without using a placebo because the medical ethical committee has disallowed it and the outcome is a score of 7 for both drugs. It is interesting to note that the standard drug has now scored 7 rather than 6, maybe because the placebo component of its effect has increased or because other interventions have been implemented in practice that are also effective. In a further trial, a placebo group is added for comparison with the standard drug and the placebo now scores 5 rather than 3 as earlier. So the specific effect, both absolute and relative, has changed compared with the earlier situation and this might indicate that it is difficult to compare existing drugs to old placebo groups. A placebo group is then included for comparison with the new drug and scores 6, maybe because the new drug needs to be taken three times daily and therefore has a better placebo effect than the treatment group. Which treatment is preferable now? The difference between 7 for the new drug and 6 for the placebo might not be significant but the difference between 7 and 5 for the standard drug and placebo might be. So, even though the two drugs were the same when compared to each other, the new drug would look less effective against placebo. Another scenario is that the new drug might be given as a once-daily dosage and have a smaller placebo effect, therefore looking more effective than the standard treatment in relation to placebo. Or, maybe the informed consent procedure contributed to some differences in the expectations of the patients, because the new drug has unknown unwanted effects or more unwanted effects than the standard one. Suppose that the new drug is even more effective than the standard one, but at the same time is no better than placebo. Or, there is a new drug that is not as effective as the standard drug but is relatively more effective when compared to placebo.

The Evidence

There is evidence that all these kinds of mechanisms may take place. In a randomised trial of naproxen versus placebo in cancer pain [1], half of the patients were treated with either naproxen or placebo but without informed consent, and half were treated with one or other of the same two products but with informed consent. In the informed consent groups, both placebo and naproxen produced better analgesia. In fact, informed consent was a far stronger determinant of the outcome of the treatment than the drug itself. On the other hand, the differences between the placebo and drug were much smaller in the informed group, so the efficacy of the drug appeared to be larger in the group that was not informed.

Further insight is gained from review of 31 trials of the effect of cimetidine in the treatment of duodenal and gastric ulcers [2]. The review revealed that some of the trials showed a statistically significant effect with cimetidine and others did not. In the trials where the result was of statistical significance, the cure rate with cimetidine was about 75%. In the trials without a significant difference the cure rate was also about 75%. So the significant difference was introduced by the placebo groups – 60% versus 40%.

Overall the placebo effect of the trials ranged between 10% and 90%. Interestingly, the trials that had been done in Germany had on average much higher placebo rates than the trials done in other countries.

What Kind of Placebo Group Is Needed?

Because of the requirement to give informed consent and so to tell volunteers or patients about unwanted effects, which may be different for the standard and the new treatments, it maybe preferable to compare each treatment group with a placebo group. In fact, whenever possible I would like to see at least a placebo group for both drugs, and possibly even a placebo group for the combined drugs.

Conclusion

A placebo can and should be used in all circumstances that are not life-threatening, even if a standard drug is available. Insufficient evidence is provided if a placebo group is omitted when assessing a new drug versus standard drug. Obviously, this causes a conflict between the ethical aspects on one hand and the scientific aspects on the other, but if placebo groups are not used it will slow developments in medicine and reduce therapeutic possibilities.

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