Medical therapeutics: mortality effects, uncertainty, and informed consent

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ABSTRACT Many drugs used in medical therapeutics are able to save human lives. Unfortunately, many such drugs have also led to the death of patients. This fact raises important issues discussed in light of a number of cases taken from cardiovascular therapeutics. Medical therapeutics currently includes a vast number of different types of interventions, including drugs, devices, surgery, and diets. In what regards drugs, we currently use molecules with profound influences on the human body — some of which leading occasionally to negative outcomes or even to patient death. A reasonable degree of statistical certainty goes along with a large degree of individual uncertainty — a phenomenon is seen in a group of patients but a quite different phenomenon may be seen in a particular case. When treating an individual patient, it is his/her interest and personal preferences that must be taken into consideration, not the interests of society or of science. The choice of medical therapy with a definite intrinsic mortality risk must imply strict accordance from the part of the patient. Since many therapeutic modalities do carry a definite mortality risk, an overall change in medical practice is necessary. Informed consent should be the rule, and should be the starting point for medical therapeutics.

Keywords: informed consent, mortality, patients, therapeutics, uncertainty

Introduction

Many drugs used in medical therapeutics are able to save human lives. Other drugs improve symptoms, and therefore decrease human suffering. Unfortunately, many such drugs have also led to the death of patients. This fact raises important issues discussed in the present text.

Although other sources of information are frequently available and of interest, randomized controlled trials offer the only source of information which is likely to be unspoiled by both identified and unidentified sources of bias. Clinical trials, however, use aggregate data obtained from a large number of patients, meaning that the statistical conclusions that apply to the whole group do not necessarily apply to a single individual. If an overall favorable effect is seen in a group of patients, for each individual patient a favorable, a neutral or even an unfavorable effect may be seen.

In what concerns patient mortality, different scenarios may be considered. A first case would be one in which a given drug is able to save some but not all patient lives, with very little mortality (if any) caused by the drug itself. We can think of some antibiotics as an example. They were most probably caused by tuberculosis and not by the antibiotic. In the 1948 Medical Research Council streptomycin study, the observed fatalities observed in either arm of the trial were most probably caused by tuberculosis and not by the antibiotic.

Case studies

Case study 1 — implantable cardioverter–defibrillator therapy, DINAMIT study

In the Defibrillator in Acute Myocardial Infarction Trial study, implantable cardioverter defibrillator (ICD) therapy was studied in patients with a reduced left ventricular function, 6 to 40 days after a myocardial infarction. ICD therapy did not decrease overall mortality. Fewer deaths due to arrhythmia (hazard ratio 0.42, 95% confidence interval 0.22–0.83), but more deaths from nonarrhythmic causes (hazard ratio 1.75, 95% confidence interval 1.11–2.76) were seen in the ICD group of patients, compared to the control group. The authors suggested that the patients who did not die due to arrhythmia, died due to other cardiac causes.

In this first case, an explanation was put forward to explain the lack of beneficial effect of therapy—patients had a cardiac context of pneumonia or bacterial meningitis, some patients will survive with the help of antibiotics, whereas other patients will not; however, in the vast majority of cases the observed mortality will be essentially caused by the infectious agent and not by the antibiotic.
condition too serious to allow survival, only the mechanism of death would vary. Most fatalities would therefore be caused by the disease and not by therapy.

**Case study 2—aspirin in cardiovascular prevention**

According to a meta-analysis carried out by the Antithrombotic Trialists’ Collaboration, acetyl salicylic acid (aspirin) in primary cardiovascular prevention caused a 12% reduction in serious vascular events, including a reduction in nonfatal myocardial infarction (rate ratio 0.77, 95% confidence interval 0.69–0.86), but with increased major gastrointestinal and extracranial bleeds.6 The overall impact on mortality was nonsignificant (rate ratio of 0.95, 95% confidence interval 0.88–1.02). In secondary prevention, aspirin therapy yielded a 10% reduction in total mortality (rate ratio 0.90, 95% confidence interval 0.82–0.99).4

In the A Study of Cardiovascular Events in Diabetes randomized trial, aspirin was shown to decrease serious vascular events, while increasing the incidence of major bleeding, with no significant change in overall mortality (15,480 participants; mean follow-up of 7.4 years).5 In the Aspirin in Reducing Events in the Elderly study (19,114 persons enrolled), increased all-cause mortality was seen in healthy older adults treated with 100 mg aspirin each day, when compared to placebo (hazard ratio, 1.14; 95% confidence interval 1.01–1.29).5 Cancer-related death was increased in aspirin-treated patients.6 Disability-free survival was not enhanced by aspirin use (over a median of 4.7 years of follow-up), whereas major hemorrhage was increased with aspirin.7

In the Aspirin to Reduce Risk of Initial Vascular Events study, involving 12,546 patients, aspirin failed to change overall mortality,8 after a median follow-up of 60 months (hazard ratio 0.99, 95% confidence interval 0.80–1.24). The primary endpoint was not significantly changed, but aspirin increased gastrointestinal bleeding.

In this second case, aspirin therapy in primary prevention shows us that a decrease in cardiac events, seen in some studies, does not imply a favorable impact on overall prognosis (mortality). It is clear that an increase in bleeding took place—providing an explanation for the phenomenon that patients do not die less even if less cardiac disease (with the potential to cause some fatalities) was seen. An increase in mortality, in cancer-related death and in major hemorrhage was seen in the Aspirin in Reducing Events in the Elderly study.

In secondary prevention, a beneficial effect was seen in overall prognosis, but bleeding still occurred in some patients.

**Case study 3—Diabetes mellitus, action to control cardiovascular risk in diabetes study**

Concerning the therapy of Diabetes mellitus, in the Action to Control Cardiovascular Risk in Diabetes Study, reported in 2008, an increased mortality was seen with intensive therapy (hazard ratio 1.22, 95% confidence interval 1.01–1.46), and an increased cardiovascular mortality (hazard ratio 1.35, 1.04–1.76).9 However, a decrease in nonfatal myocardial infarction was also seen with intensive therapy (hazard ratio 0.76, 0.62–0.92). In this case, a glycated hemoglobin of 6.4% (intensive therapy) yielded a worse survival rate than the 7.3% value seen in the standard therapy group of patients.

In the Action to Control Cardiovascular Risk in Diabetes Study trial, increased mortality was seen with intensive therapy, in the presence of a decrease in nonfatal myocardial infarction. Hypoglycemia was more common in the intensive therapy group, as it happened with fluid retention and with weight gain >10 kg—thus providing at least a partial explanation for the increased mortality that was observed.

Decreased mortality was observed, however, in other trials in patients with Diabetes mellitus, involving the use of metformin, liraglutide, or empagliflozin.

**Case study 4—canakinumab in patients with previous myocardial infarction**

Canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, was studied in 10,061 patients with previous myocardial infarction and elevated C-reactive protein.10

Canakinumab therapy led to a lower rate of cardiovascular events than placebo, but also to a higher incidence of neutropenia, thrombocytopenia, and fatal infection.10 Overall mortality was not significantly changed (hazard ratio 0.94, 95% confidence interval 0.83–1.06).

This case also shows us that following the pharmacological effects of the drug, part of the observed mortality seems to have been due to therapy, although total mortality showed a nonsignificant trend in the good direction.

**Case study 5—metoprolol in noncardiac surgery, POISE study**

In noncardiac surgery, the effects of metoprolol succinate were studied in the Perioperative Ischemic Evaluation study.11 Metoprolol therapy was associated to a decreased incidence of myocardial infarction (hazard ratio 0.73, 95% confidence interval 0.60–0.89), with a greater mortality rate (1.33, 1.03–1.74) and a higher incidence of stroke (2.17, 1.26–3.74), when compared to placebo.

In this case, the increased incidence of clinically significant hypotension and of clinically significant bradycardia, seen in patients treated with metoprolol,11 could justify the mortality findings. Here also, some patients appear to have died due to drug therapy.

**Case study 6—high-intensity lipid-lowering therapy**

In 1978, clofibrate use, in the World Health Organization cooperative trial of primary prevention in ischemic heart disease, led to decreased cholesterol levels but also to an increased mortality.12 A reduction of 25% in nonfatal myocardial infarction cases was seen with clofibrate therapy.

Statins (inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase) have been shown to reduce mortality when compared to placebo in secondary cardiovascular prevention,13 and in at least 1 context of primary prevention.14

However, under the “lower is better” concept, concerning low-density lipoprotein cholesterol (LDL-C) values, high-intensity statin therapy, compared with lower-intensity statin therapy, has failed to decrease overall mortality; however, a decreased incidence of cardiovascular events was seen. Essentially the same type of findings was seen with ezetimibe (an inhibitor of cholesterol absorption, by inhibiting the Niemann Pick C1L1 protein)15 and with evolocumab (a proprotein convertase subtilisin-kexin type 9 inhibitor).16 This phenomenon has been termed the mortality paradox,17 and it could be due either to the prevention of nonlethal cardiovascular disease by high-intensity therapy or by some deaths being caused by high-intensity therapy compensated by the decreased incidence of cardiovascular events.
Effects of drugs on individual living organisms can be known. The primary prevention, in which a clear problem is identified who can represent a mortality risk (or another type of serious cause), requires informed consent. Informed consent in medical therapeutics is able to profoundly change prognosis. The examples previously presented show us that some drugs used in medical therapeutics are able to profoundly change prognosis. In some cases, a better overall prognosis is seen, in other cases a neutral effect is observed and, in yet other cases, mortality was increased.

In many if not all cases, the effect on prognosis seen in the aggregate group of patients studied in a given clinical trial (or group of trials) represents the sum of differential outcomes seen in different patients. In some cases, a clear negative outcome associated to therapy is identified—increased bleeding with aspirin therapy, increased incidence of hypoglycemic episodes with intensive antidiabetic therapy. In other cases, the situation is less clear, with documented changes in important outcomes, considered as likely to change the distribution of mortality due to different causes.

Data from different sources, obtained from subgroup analysis and from other statistical methods, can indicate a greater or lesser probability of either a favorable or an unfavorable outcome to occur in any given context. For instance, concerning aspirin therapy in primary prevention, the incidence of serious vascular events may depend on current smoking habits (lack of protection in smokers) but not on sex.4 However, up to the present moment, no method exists to predict with full certainty the effects of many drugs in any individual patient. Moreover, a change in the natural history of disease happens with the use of many such drugs, in such a way that it is not possible to establish in a particular patient what would have been the spontaneous evolution of the disease without the therapeutic intervention (should this latter have already taken place).

An uncertainty principle can therefore be postulated to exist in medical therapeutics—a limit to the precision with which the effects of drugs on individual living organisms can be known. The degree of uncertainty is likely to decrease in the next decades as further information is obtained.

Informed consent

A case can be made in favor of demanding that informed consent be obtained in every case that a drug is prescribed to a patient who can represent a mortality risk (or another type of serious risk). This concept should apply to cases such as aspirin in primary prevention, in which a clear problem is identified (bleeding), but also to situations in which a “mortality paradox” is observed, as it happens with some types of high-intensity lipid-lowering therapy.

Patient autonomy should be the rule, but for autonomy to be effective, relevant information should be provided to the patient. In any given case, the patient may or may not be interested in accepting the exchange between the odds of natural disease and the odds of therapy-treated disease.

For instance, in acute stroke patients, more patients treated with alteplase died with intracerebral hemorrhage, when compared to the placebo treated group, in the 1995 National Institute of Neurological Disorders and Stroke rt-PA Stroke study.18 In that study, at 36 hours, 9 patients in the plasminogen activator group died of intracranial hemorrhage, to be compared to 1 patient in the placebo group. At 90 days, there were no significant differences in mortality between the 2 groups, although beneficial effects in clinical neurologic outcomes were seen in patients under thrombolysis. It is clear from this case that, unless the patient is unable to make decisions for him/herself, this type of decisions should not be taken solely by physicians.

Nonmaleficence—not to be the cause of harm—in the context of thrombolysis for acute stroke, as in other cases, clearly becomes a statistical concept (the same happening, in fact, with the concept of beneficence). Even utility—to promote more good than harm—remains in the same realm. At the individual patient level, it is clear that if a patient dies of intracerebral bleeding shortly after thrombolysis, no utility of therapy whatsoever exists for him/her. To deny this idea would correspond to say that one is better off dead than with neurological sequelae of a stroke episode—something that common sense indicates us to be false.

There is only one way to ensure that physicians respect the nonmaleficence principle, and it consists in removing the decision from the hands of the physician, leaving the decision in better hands—those of the patient him/herself. The physician may suggest a given therapy, but only the patient may choose to follow a path that statistically improves outcomes but that in some cases may lead to his/her death. In this situation, the patient being able to take decisions, a relatively broad range of therapeutic solutions may in some cases be available to be chosen by the patient and the physician.

In a different setting, the patient being unable to take decisions, the physician must decide, namely in emergency conditions. In this latter case, it is adequate to choose a relatively standardized therapeutic solution, even if it entails a mortality risk—a solution that one can reasonably presume that the patient might chose (a form of presumed consent).

As in the case of solid organ transplantation, for presumed consent to be correctly implemented, every (adult) person should have the opportunity to express and have recorded his/her consent or refusal of a given therapy. Thrombolysis as stroke therapy would appear as a suitable candidate for such a type of advance directive (currently, thrombectomy is being increasingly used in this context).19

It must be recognized that in some cases, there may nevertheless exist a difficulty in choosing what might be called a reasonable standardized therapeutic solution, since clinical practice guidelines are sometimes presented in close parallelism with the interests of the pharmaceutical industry. A problem may exist if the views of a given physician are different from the guidelines.

The golden rule—to treat other people as one would like to be treated—should not apply to most decisions in medical therapeutics.1 The preferences of the physician should be relatively unimportant—the preferences that count are those of the patient (as it has been said: “while I do not wish others to impose on me, I also wish not to impose on others”). Decisions are necessary, and therefore suspension of judgment is not to be considered as a standard procedure.1

Alirocumab (also a proprotein convertase subtilisin-kexin type 9 inhibitor), however, did show a decrease in mortality of patients after acute coronary syndrome, but this effect was limited to patients with a baseline LDL-C of 100mg/dL or more.17 In any given case, the patient may or may not be interested in accepting the exchange between the odds of natural disease and the odds of therapy-treated disease.

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Important as the criticism of research cases without consent presented by Beecher in 1966 was, we must take into consideration the question of the number of patients currently involved in medical therapeutics. In the global economy in which we currently live, many drugs are used by tens of millions of people. This numerical aspect raises the importance of informed consent required. When treating an individual patient, it is his/her interest and personal preferences that must be taken into consideration, not the interests of society or of science.

The choice of medical therapy with a degree of uncertainty exists concerning effects of drugs on complex systems such as mammalian organisms. The structure and function of human beings surely depend on genes, but a considerable influence of the environment, both in physical and in cultural aspects, is at play. Epigenetics is one example of a source of considerable degree of variation of a nonpurely deterministic nature seen in biologic phenotypes. The principle of patient autonomy entails viewing human beings as entities endowed with free will, and therefore rejecting purely deterministic views, old and new.

Medical therapeutics currently includes a vast number of different types of interventions, including drugs, devices, surgery, and diets. In what regards drugs, we currently use molecules with profound influences on the human body—some of which leading occasionally to negative outcomes or even to patient death. A reasonable degree of statistical certainty goes along with a large degree of individual uncertainty—a phenomenon is seen in a group of patients but a quite different phenomenon may be seen in a particular case.

When treating an individual patient, it is his/her interest and personal preferences that must be taken into consideration, not the interests of society or of science.

The choice of medical therapy with a definite mortality risk must imply strict accordance from the part of the patient. Since many therapeutic modalities do imply a definite mortality risk, an overall change in medical practice is necessary. Informed consent should be the rule, and should be the starting point for medical therapeutics.

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Conflicts of interest

The author reports no conflicts of interest.

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