Risk : benefit assessment of old medicines

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Any meaningful discussion about the present value of old drugs requires appropriate comparisons with new drugs. While there is noisy propaganda claiming the superiority of new drugs, the evidence supporting these claims is often scanty and poor. Therefore, the database utilizable to evaluate old and new drugs is incomplete and fragile. There are several reasons, including the poor dossiers presented for the approval of new drugs, the lack of comparisons aimed at showing superiority of new drugs, the bias frequently involved in clinical trials and the conflict of interests. This brief discussion reviews these questions and gives some examples by comparing diuretics and new antihypertensive agents, ticlopidine and clopidogrel, and atypical and classical antipsychotic agents.

The quality of new medicinal products

The new products offer little innovation. Some analyses indicate that only 10–20% of the products reaching the market offer substantial advantages over existing ones [1]. Specific analyses for drugs approved by the European Medicine Agency (EMA) have been made for anticancer, cardiovascular and CNS agents [2–4].

In addition, the quality of the dossiers is frequently inadequate to permit any meaningful assessment. As an exercise, we evaluated the clinical documentation of biotechnology drugs that must be approved by a central procedure and therefore account for all the products available to the 15 member states of the European market. As reported in Figure 1, excluding vaccines and

Figure 1

Biotech products approved by the EMEA and documentation underlying these approvals

insulins, between January 1995 and June 2003, 61 new active principles were approved. According to the EPAR (European Public Assessment Reports, available at the EMEA web site) only 36 (59.0%) were tested in formal clinical trials; 17 (27.9%) had a comparison with placebo; 19 (31.1%) were compared with active comparators, but only nine (14.8%) with the aim of demonstrating their superiority and only two (3.3%) considered a hard endpoint. In conclusion, only two drugs (etanercept and desirudine) were approved according to a randomized clinical trial, with a superiority design and hard endpoints. In addition, 14 out of 61 active principles were approved 'under exceptional circumstances', implying the obligation to complete their dossier.

Bias in clinical trials

The fragility of the database is further amplified by the bias that frequently arises in planning, conducting and analysing controlled clinical trials.

Despite the ethical principles set out in the Declara-

tion of Helsinki [5], it is not unusual for the design of the clinical trials to include an arm treated with placebo even when active treatments are available. This is done obviously with the intention of showing an effect, which is easier to demonstrate in comparison with placebo than an active comparator. But using a placebo means one cannot position the new drug in relation to the therapeutic tools already available.

When a comparator is used it is usually inadequate, in order to favour the new drug in relation to the old reference drug. For instance, the comparator for atypical antipsychotics has usually been haloperidol [6, 7], whereas it would have been more appropriate to select a phenothiazine. Furthermore, relatively high doses of haloperidol have been used [8], making for an accentuation of the extrapyramidal effects.

Another example is the comparison of tacrolimus with cyclosporin, where the comparator was utilized at lower than optimal doses in order to favour the new drug [9, 10]. In other trials the new drug was used at different doses, against a single dose of the comparator [11, 12].

The size of the study population is another fundamental point, particularly when equivalence or non-inferiority hypotheses are addressed. One analysis of the literature indicated that in 64% of 383 studies equivalence was defined as a difference of up to 50% from the comparator, but the acceptable difference was more than 25% in 84% of the cases [13].

The use of surrogate endpoints, particularly frequent in the area of antihypertensive and lipid-lowering agents, is not always paralleled by equivalent therapeutic endpoints and/or adverse events. Similarly, the use of combined endpoints poses frequent problems in the evaluation of single endpoints, as discussed below with regard to the CAPRIE trial of clopidogrel. Furthermore, the add-on design is unjustified in several cases, because it compares, for example, two drugs against one, when combined treatments are already available.

Another source of bias lies in the 'selection of the publications' since it is easier to publish positive than negative findings. A survey of the clinical trials of five antidepressants [selective serotonin uptake inhibitors (SSRIs)] considered 42 studies [14]: 21 positive and 21 negative. The positive studies generated 19 primary articles, but the negative studies only six. It is obvious that the perception of the efficacy of SSRI does not reflect these results.

Finally, conflict of interest is an important source of bias. Authors with a personal financial interest in the clinical trial or in the company producing the new drug tend to look more benignly on a new treatment than authors without any such interest [15]. Clinical trials reports are often written up by employees of pharmaceutical companies so the stated authorship does not reflect the real authors. This situation has become so heated that the editors of the main medical journals have been obliged to issue new rules on authorship [16].

In conclusion, the bias in favour of new drugs tends to overestimate the value of new ones compared with the old ones and this is further amplified by the imbalanced propaganda to physicians. It is worth recalling that old drugs, usually, have lower prices than new ones and are often generics, which does not leave large margins for promotion.

Some examples

We have selected three examples to support the view that new drugs do not always offer significant advantages over old ones: clopidogrel *vs.* ticlopidine; atypical antipsychotics *vs.* classical antipsychotics; and diuretics *vs.* new antihypertensive drugs.

Clopidogrel is an analogue of ticlopidine, differing only in the esterification with an ethyl group (Figure 2).

Figure 2

Structures of ticlopidine and clopidogrel

The main clinical study is known as CAPRIE and was done in comparison with aspirin [17]. The conclusion that clopidogrel was better than aspirin was challenged on several grounds. The study recruited a heterogeneous population under the hypothesis that all the patients had an atherosclerotic process in common. The primary endpoint was a combination of ischaemic stroke, myocardial infarction, or vascular death. On this endpoint clopidogrel was statistically better than aspirin, but when leg amputation was included in the combined endpoint as an obvious outcome measure of the peripheral disease, the slight advantage was no longer statistically significant. Furthermore, when the combined endpoint was disaggregated, it became clear that the overall results were mostly due to clopidogrel's effect on peripheral arterial disease, casting doubts on its real protection in the coronary and cerebrovascular areas [17]. It is also very strange that a comparison was made only with aspirin when the aim of developing clopidogrel was in fact to find a better and less toxic drug than ticlopidine.

A meta-analysis of small, heterogeneous studies where clopidogrel was compared with ticlopidine indicated a superiority of clopidogrel, but the comparison was made at 30 days [18]. Another study with a follow-up of several years indicated more cumulative deaths in the clopidogrel arm than with ticlopidine [19]. A further study published as an abstract [20] shows, at odds with other studies, that regimens using clopidogrel in stent implantation resulted in more occlusions than regimens containing ticlopidine. Clearly, therefore, the superiority of clopidogrel over ticlopidine remains to be demonstrated but it is worth noting the large difference in price (see Table 1) between ticlopidine and aspirin. An obvious question is: if clopidogrel is better than ticlopidine, why does the company keep both drugs on the market?

Atypical antipsychotics are used for the treatment of schizophrenia; this class includes drugs such as clozapine – already on the market for several years – risperi-

Table 1

Monthly cost of secondary prevention of cardiovascular events with antiplatelet drugs

	Cost of 30-day therapy
Clopidogrel 75 mg day ⁻¹	€70.0
Ticlopidine 25 mg × 2/day	€14.0
Aspirin 100 mg day ⁻¹	€2.3

done, olanzapine, and quetiapine. It is difficult to find their common characteristics except for the action on 5HT receptors, inhibition of dopaminergic receptors, and a smaller tendency to induce extrapyramidal adverse reactions. However, these activities are all present in the phenothiazines too. The purported better tolerability and a small effect on the negative symptoms of schizophrenia has enabled these drugs to acquire a place for first-line treatment, with a consequent large and profitable market due to their high price. In Italy sales in 2003 reached the 168 million Euro compared with 14 million Euro for the classical antipsychotic agents. The 46% of prescriptions caused 92% of the expense (personal communication of Dr Antonio Addis, OsMed, Osservatorio Nazionale sull'Impiego dei Medicinali, Italian Ministry of Health).

A number of clinical trials comparing atypical antipsychotics and – mainly – haloperidol are not very convincing for a number of reasons, including small numbers of patients; use of psychometric scales rather than hard endpoints for the function and social relations of schizophrenic patients; relatively low efficacy; short treatments; and relatively high doses of haloperidol. Geddes concluded in his meta-analysis that atypical antipsychotics may have some advantage only when haloperidol is employed at doses exceeding 12 mg, essentially less effect on the extrapyramidal system [8]. Another meta-analysis indicates that the number of drop-outs is not different for the atypical and classic antipsychotic drugs and that the superior therapeutic effect of the atypical antipsychotics is evident only when clozapine – certainly not a new drug – is included [21]. In another study olanzapine did not appear to be consistently superior to chlorpromazine [22]. The purported action of these agents in patients resistant to classical antipsychotics is also poorly demonstrated and not consistent in all the studies [6, 23–25].

In a recent randomized controlled trial, comparing olanzapine and haloperidol for their effectiveness and cost in the treatment of schizophrenia [26], 309 patients

were treated for 1 year with 5–20 mg of olanzapine or 5–20 mg of haloperidol, with benzotropine prophylaxis. The authors concluded that olanzapine offered no advantages over haloperidol in compliance, symptoms, extrapyramidal symptoms or overall quality of life, and its benefits in reducing akathisia (5.8% vs. 9.6% with no severe rating and only a small difference in magnitude) and improving cognition must be balanced against problems of weight gain and higher cost (US\$3000–9000 per year).

The emphasis on extrapyramidal effects has distracted the attention from the substantial body-weight gain (4–10 kg after 10 years) induced by the atypical antipsychotics. This is an important risk factor for cardiovascular diseases and for TYPE 2 diabetes.

Fontaine *et al.* calculated that if the four million US schizophrenics were treated with atypical antipsychotics, there would be an excess of 24 560 deaths, 120 760 cases of hypertension, and 92 720 cases of glucose intolerance [27]. Koro *et al.* confirmed that patients treated with atypical antipsychotics, particularly olanzapine, were more prone to diabetes than those using haloperidol [28]. It is evident from this quick overview that classical antipsychotics should not be relegated to second-line treatment for schizophrenia.

Diuretics, particularly hydrochlorothiazide and chlorthalidone, together with β -adrenergic blockers, have long been the reference treatment for uncomplicated hypertension – that is, until the advent of new antihypertensive agents, including α -adrenergic inhibitors, calcium channel blockers, angiotensin II-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists. The purported superiority of the new agents has for a long time rested largely on surrogate endpoints, but a recent study named ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) has cast considerable doubts on this view [29]. This was an independent trial supported by UK NIH funds, and recruited over 40 000 patients with hypertension and at least one risk factor for congestive heart disease (CHD), which were reduced to 33 357 when the arm of doxazosin (an α -adrenergic inhibitor) was interrupted because its outcome (occurrence of fatal CHD or nonfatal myocardial infarction) was superior to the diuretic arm (chlorthalidone).

Briefly, the other three arms were chlorthalidone (12.5–25 mg day⁻¹), lisinopril as an ACE inhibitor (10–40 mg day⁻¹) and amlodipine as a calcium blocking agent (2.5–10 mg day⁻¹) for a mean follow-up of 4.9 years. The primary outcome (fatal CHD + nonfatal myocardial infarction) was not different in the three arms. The secondary outcome showed that systolic

blood pressure was higher for amlodipine and lisinopril than with chlorthalidone, while diastolic blood pressure was lower with amlodipine than chlorthalidone and lisinopril. The arm treated with amlodipine had more heart failures than chlorthalidone; lisinopril had higher 6-year rates of combined cardiovascular diseases and stroke than chlorthalidone. These differences were quite consistent in the various subgroups, including factors such as sex, age and race.

The conclusions are quite straightforward: 'thiazide-type diuretics should be preferred for first-step antihypertensive therapy'. If physicians follow this advice in their prescriptions there will be very important financial consequences considering that in Italy the cost of diuretic treatment per month is 30–35 times less than with the newer antihypertensive agents, and that in 2002 the NHS spent 1136 million Euro for ACE inhibitors, 815 million Euro for angiotensin-receptor agents, and 713 million Euro for calcium channel blockers, as opposed to 61 million Euro for diuretics.

Concluding remarks

It is very difficult to compare the value of old and new drugs for the reasons described. The fact that European legislation does not make it obligatory to demonstrate added value for recently approved drugs, and the sources of bias in clinical trials, contrast with the need for an evaluation based on evidence. Therefore, the perception of the advantages of new drugs is frequently a result of promotion by pharmaceutical companies more than objective data.

When adequate studies are available, such as for the antihypertensive drugs, the old drugs, such as diuretics, fully retain their primary therapeutic role. In other cases, such as for antiplatelet agents, the data are contradictory and insufficient to establish an improvement with clopidogrel over ticlopidine. In the case of atypical antipsychotic agents the advantage in terms of reduced extrapyramidal toxicity is counterbalanced by the increased cardiovascular and diabetic risk due to weight gain, without significant differences in efficacy.

In these three examples the only objective finding is the markedly higher cost, which poses a burden on national health services with no evidence of increased therapeutic benefits.

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