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Bias in Benefit-Risk Appraisal in Older Products

The Case of Buflomedil for Intermittent Claudication

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Abstract

Benefit-risk assessment should be ongoing during the life cycle of a pharmaceutical agent. New products are subjected to rigorous registration laws and rules, which attempt to assure the availability and validity of evidence. For older products, bias in benefit-risk assessment is more likely, as a number of safeguards were not in place at the time these products were registered.

This issue of bias in benefit-risk assessment of older products is illustrated here with an example: buflomedil in intermittent claudication. Data on efficacy were retrieved from a Cochrane systematic review. Data on safety were obtained by comparing the number of reports of serious adverse events and fatalities published in the literature with those reported in postmarketing surveillance databases.

In the case of efficacy, the slim basis of evidence for the benefit of buflomedil is undermined by documented publication bias. In the case of safety, bias in reporting to international safety databases is illustrated by the discrepancy between the number of drug-related deaths published in the literature (20), the potentially drug-related deaths in the WHO database (20) and deaths attributed to buflomedil in the database of the international marketing authorization holder (11).

In older products, efficacy cannot be evaluated without a thorough search for publication bias. For safety, case reporting of drug-related serious events and deaths in the literature remains a necessary instrument for risk appraisal of older medicines, despite the existence of postmarketing safety databases. The enforcement of efficient communication between healthcare workers, drug companies, national centres of pharmacovigilance, national poison centers and the WHO is necessary to ensure the validity of postmarketing surveillance reporting systems. Drugs considered obsolete because of unfavourable benefit-risk assessment should not be allowed to stay on the market.

Benefit-risk assessment should be ongoing during the life cycle of every drug. New drugs are continuously subjected to a thorough review procedure of all effects, beneficial as well as adverse.

On the contrary, older products, on the market for several decades, may never have been subjected to a formal benefit-risk analysis. These agents were registered before the era of rigorous

regulatory review. It is hard to retrieve the pivotal trials performed before the implementation of Good Clinical Practice.[1]

Comprehensive trial registration procedures were not in place before the late 1990s, therefore negative results were easy to hide. Often, the collection of new evidence stopped after registration. The safety control aspect can also be worrisome. The WHO safety programme was started in 1968 with ten countries participating on a voluntary basis. Now, 84 countries have a national pharmacovigilance centre (NPC), reporting regularly to the WHO. In addition, in some countries legislation is in place to enforce the drug companies to communicate all serious events from trials and spontaneous reporting systems to the national pharmacovigilance centres and vice versa. With passing time, the tendency to report well known adverse effects diminishes when their incidence and pathophysiological mechanisms become established. Over time, more potent or safer products become available within the therapeutic area, and the scientific interest in the older products subsides. Nevertheless, the utilization of such products in terms of market share may remain substantial. As a result, the life cycle of obsolete products may become protracted, without formal benefit-risk assessment being either initiated or repeated. The decision to end the life cycle is often taken very late, and not by the regulatory authorities but by the company, only after the product has become no longer economically viable.

To illustrate these points about bias in the benefit and risk assessment of older drugs compared with newer drugs, we discuss one of these older products, buflomedil, marketed since 1976 in many European countries, predominantly for use in intermittent claudication. Abbott Company is the international market authorization holder (MAH), but there are many licensed brands and generics in its main market (France) and in Europe.

A risk assessment at the country level was performed in 1999, by the French regulatory authority, after an overview of toxicity reports reported by local pharmacovigilance centres.[2,3] The product was kept on the market, without restrictions, after the LIMB (Limbs International Medicinal Buflomedil) trial[4] (discussed in more detail in section 1.1) was initiated at the request of the French authorities. In 2006, a new risk assessment was performed at the national level, after a new overview of reports on deaths and toxicity with buflomedil, presented at the 10th Annual Meeting of the French Society of Pharmacology, Montpellier, 2006.[5] The conclusion was that buflomedil was a product with a narrow therapeutic margin, safe to use in normal doses (600 mg/day) in appropriate indications, but dangerous at doses as low as 3–6 g in suicide and involuntary overdose, and in patients with renal insufficiency at doses as low as 300 mg/day, with predominantly cardiac and neurological complications. Dosage restrictions and label changes were imposed in 2006 in France, and in 2007 in Belgium. No decision at the European level was taken.

The objective of this article is to clarify the issue of bias in benefit-risk assessment of older products using the evidence on buflomedil as an example. For bias in efficacy, we describe a systematic review[6] of the randomized controlled efficacy trials. For bias in safety, we performed a comparative description of adverse reaction case series from different sources, to investigate the flow of information to international safety databases.

1. Search Strategies and Findings

1.1 Data on Efficacy

To examine the evidence for efficacy of buflomedil, we refer to our Cochrane systematic review of the efficacy of buflomedil for the symptomatic treatment (prolonging the walking distance) of intermittent claudication.[6] This review was first published in 2001, and updated three times, with only minor changes, as very little new information on efficacy became available.

In this review, we concluded that the evidence for efficacy is slim and undermined by publication bias. Of the six retrievable trials,[7-12] only two[7,8] rather small and short trials, both conducted before 1992, were considered to be of

more or less acceptable quality and accepted for inclusion in the review. Their results were statistically significant, but with wide confidence intervals and limited clinical relevance. However, these results are undermined by publication bias, discovered after a thorough search in the classical bibliographic databases in the Cochrane Library trial registers, in specific journals not referenced by these indexes (hand searching) and in the reference list of all relevant articles and reviews (snowballing). This led to the detection of at least another four unpublished studies. From the scarce description in the signalling review,[13] we were able to document the existence of these trials from the references and ascertain their inconclusive results. We were not able to retrieve the full text. Therefore, the evaluation of the quality of these trials and the integration of their data in a meta-analysis was not possible. This is a rare example of publication bias, actually proven and documented, and not just inferred from graphical or statistical methods.

At the beginning of 2008, a new large trial with a long follow-up (the LIMB trial[4]) was published in *Circulation*. The results were critiqued in the concomitant editorial[14] and in our opinion did not change our conclusion, as the effect on the walking distance was not measured with an objective method in this study.[15]

1.2 Data on Safety

We used four methods to collect data on the safety of buflomedil. First, we extracted the safety sections from all relevant published clinical trials[7-12] Second, we consulted the WHO international database (last consultation April 2008) at the Uppsala Monitoring Centre (UMC) in Sweden. Third, we consulted the Periodic Safety Update Reports (PSURs) based on the safety databases of the international MAH (last report April 2007). Finally, we searched the literature (Pubmed, International Pharmaceutical Abstracts and EMBASE) for reports on toxicity and adverse reactions with the following search strategy: ('Pyrrolidines/adverse effects' [Mesh] OR 'Pyrrolidines/poisoning'[Mesh] OR 'Pyrrolidines/toxicity'[Mesh]) AND 'buflomedil' [Substance Name] (last consultation, March 2008). We studied the temporal distribution of case reports in the WHO-UMC database and in the literature in periods of 5 years.

We contacted experts at the French and Portuguese NPCs, at the WHO-UMC and at the European Medicines Agency. These experts were contacted to clarify the temporal distribution to resolve the discrepancy between the literature and their data. In addition, their possible intervention in this matter was requested.

In the published clinical trials on buflomedil, only general statements were made, such as "the drug was well tolerated."[7,8] Also, in the publication of the LIMB trial,[4] the safety issue was not discussed. Hence, the information from randomized clinical trials was not suitable for numerical appraisal.

The WHO-UMC database[16] contains 797 reports (1359 events) from April 1984 to February 2007 (with the highest number of reports recorded per year in 2006) coming from 14 different countries, mostly from Europe (99%) with France delivering most cases. There were 25 deaths of which 3 were considered by the reporter to be related to the drug, 14 were considered likely to be related to the drug and 5 were considered unrelated to the drug. Three had no listed causality assessment (table I). 315 reports contained critical terms, i.e. adverse reaction terms referring to, or possibly indicative of, serious disease states that have been regarded as particularly important to follow-up. Reporting of seriousness to the WHO-UMC is done in line with the International Conference on Harmonisation's (ICH) E2B standard definition.[18] However, in these buflomedil reports, neither the concepts 'seriousness' (related to the consequences of the event) nor 'severity' (related to the intensity of the symptoms of the event) as internationally defined could be used in this study, due to the fact that the standard reporting format for these older reports did not require this information.[17,19-21]

The information coming from the WHO-UMC data is not homogeneous, at least with respect to the origin of the report or likelihood that the pharmaceutical product caused the adverse reaction, and this information does not represent the opinion of the WHO.

Table I. Safety data with reported number of deaths and drug relationship

Source	Case reports with serious events	Drug-related deaths
RCTs	0	0
WHO reports	315[a]	20[b]
Company safety report	65[c]	11[d]
Cases published in the literature	69[e]	20[e]

a Reports with critical terms (all critical and mixed) with no specification of relation to drug in the WHO safety database. Deaths are included in this number.

b In total there were 25 deaths: 3 related to, 14 likely related and 5 unrelated to buflomedil, and 3 without listed causality assessment (retrieved by considering in the search 'reaction outcome' in addition to 'patient outcome').

c Reports with one or more 'event of interest' not categorized into drug-related or non-drug-related event in the company safety database. Deaths are included in this number.

d In total there were 19 deaths: 11 were attributed to buflomedil.

e In the published case reports, all reported events were considered as serious adverse reactions with a 'reasonable causal relationship'[17] to the drug under study by the report authors and by the authors of this study.

RCTs = randomized controlled trials

In the safety report of the MAH (covering the period from 23 May 1979 to 7 December 2006), 65 reports containing 102 events (drug-related and not drug-related not always specified) were identified. Nineteen deaths were registered, of which 11 were reported as related to buflomedil, with a calculated rate of reported fatalities of 0.48 deaths per 100 000 patient treatment years, based on the number of fatalities and an exposure of 2.9 million patient treatment years between 1995 and 2006.[22]

In both the WHO-UMC report and the PSUR of the company, France was the main contributor of reports (in line with the consumption data).

The results of our literature search indicated that at least 69 drug-related serious adverse reactions have been published, of which 20 resulted in a fatal outcome.[23-39]

Next, we looked at the longitudinal time trends of reporting in the literature and in the safety databases. This was only possible because of the availability of reports in the WHO-UMC database (table II). Abbott Company answered they could not provide more detailed information. In the literature, a higher initial rate of cases was found in the 1980s, followed by a somewhat lower rate in the 1990s and a decline since 2000. The WHO database showed a reporting rate growing with time, with a dip between 2000 and 2004, again followed by a surge between 2005 and 2007 (table II).

We went back to a specific congress abstract of the 2006 Annual Meeting of the French Society of Pharmacology[5] and analysed the number and timeframe of those reports. The French local pharmacovigilance centres and the manufacturer collected 188 reports of severe adverse effects between January 1998 and March 2005, mainly reports of cardiac and neurological toxicity, with 16 deaths, of which 8 were considered to be drug related. In addition, the French poison centres recorded 223 acute self-poisonings with 24 deaths, of which 12 were definitely drug related and 10 were strongly suspected as being drug related, over the time period 1998–2004.[5] Forty-five percent of the cases comprised criteria of clinical severity. However, the toxicovigilance data from the French poison centres are not communicated to the NPC.

Table II. Time periods and adverse drug event[a] reporting

Time period	Cases published in the literature (no. of publications)	Cases in the WHO database
1980–4	28 (3)	3
1985–9	12 (4)	82
1990–4	10 (6)	180
1995–9	12 (7)	238
2000–4	6 (6)	85[b]
2005–7	1 (1)	209
Total	**69 (27)**	**797**

a Serious adverse events are not categorized into drug-related or non-drug-related events in the WHO safety database, while serious adverse events reported in the literature are published because the relationship with the drug is presumed.

b Between January 1998 and March 2005,[5] 188 cases were reported to the French National Pharmacovigilance Centre (NPC). However, the WHO-Uppsala monitoring Centre did not receive new reports from the French NPC between April 2001 and November 2005 because of necessary upgrading of ADR transmission processes in line with emerging international standards.[18] The backlog of reports was received at the WHO-UMC from December 2005, with the date of entry in the database (and not the date of occurrence) as the time stamp.

The WHO-UMC did not receive new reports from the French NPC between April 2001 and November 2005 because of necessary upgrading of ADR transmission processes in line with emerging international standards.[18] The backlog of reports was received at the WHO-UMC from December 2005, with the date of entry in the database (and not the date of occurrence) as the time stamp.

The French NPC confirmed that, according to the French law, the French MAHs are to report all serious events in France reported to them to the NPC. In addition, the MAHs need to report all other French cases published in the literature or accessible in published databases. On the other hand, the French NPCs need to report all serious cases to the MAH.

We were not able to match the cases from the different databases and the literature, to confirm or refute overlap between databases.

2. Discussion

The example of buflomedil in intermittent claudication presented here illustrates that the effort to conduct a formal benefit-risk assessment in older products is useful in the evaluation of both efficacy and safety.

For efficacy, there is only a slim basis of evidence, further undermined by proven publication bias. Indeed, we demonstrated the existence of at least four unpublished trials with inconclusive results, but not retrievable for formal meta-analysis.

For the safety sections of the reports of published randomized controlled trials, the information was insufficient for numerical analysis.

We demonstrated the presence of reporting bias in the safety databases of both the WHO-UMC and the MAH, as there is evidence that not all formally reported cases (in the literature or in the French pharmacovigilance and toxicovigilance systems) made their way into these databases.

Indeed, there was the surprising finding that the number of drug-related deaths in the literature was similar to the number of deaths attributed to the product in the safety database of the WHO-UMC, and higher than the number of drug-related deaths in the database of the company. In addition, the number of serious adverse reactions in the literature was higher than the number of 'events of interest' in the company database.

It is known from pharmacovigilance research that there is a lot of under-reporting by clinicians and that the use of the number of published case reports over a given time generally leads to an underestimation of the true incidence.[40] That is precisely the reason why the systems of post-marketing surveillance with reporting to safety databases of the company and the regulatory authorities were installed.

However, our findings in comparing the numbers of deaths and serious events between published case reports and safety databases for the older product buflomedil demonstrates that in this case this goal was not achieved, as not all cases in the literature were reported in the safety databases.

It is important that regulatory authorities should quickly be made aware of potential adverse drug reactions. Impact analysis might be a valuable method of prioritizing signals[41,42] of potential adverse drug reactions coming from spontaneous reports.

During our investigations, we found a number of possible causes of under-reporting in the international databases, as the data flow (or do not flow) from the clinicians to the local company and the headquarters or to the NPC and the International Database of the WHO (figure 1).

First, there are problems in the flow of reports to the NPC. There is no formal obligation for medical practitioners to report to the local or national pharmacovigilance centres. Also when a drug gets older, interest fades. At least in France, reports from the toxicovigilance centres do not get forwarded to the NPC. It is not known to what extent all local companies comply with the regulation (in place since 1995 in France) that marketing registration holders of pharmaceutical products have the obligation to report all serious adverse reactions to the NPC.

Second, in the flow of information to the international database of the company, it is unknown how many (verbal) reports made by clinicians to

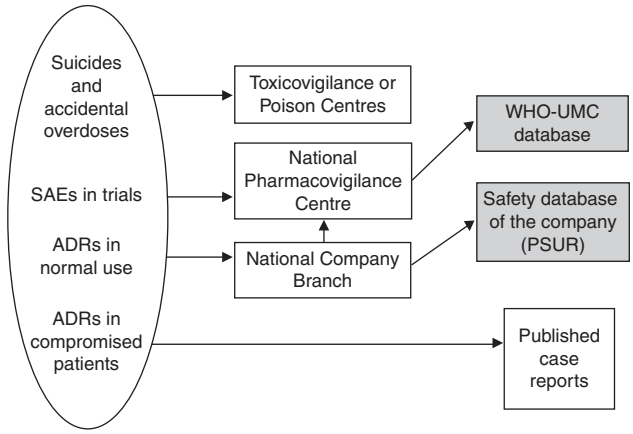

Fig. 1. Data flow between the different databases. **ADRs** = adverse drug reactions; **PSUR** = Periodic Safety Update Reports; **SAEs** = serious adverse events; **UMC** = Uppsala Monitoring Centre.

a company representative about a possible drug-related case do make it into the system. There are several speculative reasons for the lower number of deaths and serious cases reported. Although the French law imposes on the NPC to communicate reports of serious events to the local company, it may not be put into practice in this case. Reports from the local French company may not have been communicated to the international mother company (Abbott Company). Reports from generic companies may not reach the international MAH. Also, theoretically, a combination of all these reasons is possible.

Third, with regard to the flow of information to the WHO database, this is a voluntary system based exclusively on reporting from NPCs.

The WHO-UMC database primarily is intended to be a compilation of suspected spontaneous ADR reports and the NPCs are not actively requested to forward literature reports to the WHO-UMC.

The WHO-UMC never receives reports directly from a reporter, regardless of whether they are published in the literature; reports are always received via a NPC.

In the early blockbuster years of the product, there may have been under-reporting in the WHO safety database, as the cooperation between France (the country where the product was most intensively used) and the WHO started in 1986, 10 years after the first marketing of buflomedil.

Procedures in the NPCs are sometimes heterogeneous with respect to origin and likelihood that the pharmaceutical agent caused the event. The causal relationship is not always specified on the report, since not all countries include this information. Companies do not directly report to the WHO. Duplicate reports in the WHO database case series are possible, although techniques for detection are applied. There are non-random variations in the WHO database by year due to delays of reporting to the WHO due to database changes either at the WHO centre or the NPC. Indeed, we discovered that in France, there was an almost 5-year delay in the transfer of cases starting in 2001. In the case of buflomedil this had a visible impact on the time trends in the international database, as France is the main market for the product.

We want to stress the effort made by all safety data institutes to assemble the data and the wealth of data each of them possesses. However, communication and transfer of data should run more smoothly, and more transparency and insight in overlapping cases is desirable. The EU has recently taken an initiative specially directed to older products on its market, authorized in the procedures

of mutual and decentralized registration.[43] Three vital improvements have been made. First, for every older drug, one member state (Portugal for buflomedil) is chosen as the reference state for this product, collecting and appraising all safety information from states and all MAHs in Europe. Second, every product was assigned a European Harmonized Birthdate (23 May 1979 for buflomedil), to synchronize the five annual cycles of periodic assessment in all European countries (new PSUR for buflomedil to be expected 2 months after May 2008) In a personal e-mail communication on 5 February 2009, Professor Vasco Maria of the National Authority of Medicines and Health Products in Portugal (the reference member state for buflomedil) stated that the PSUR on buflomedil was submitted in due time in July 2008 and that the assessment is ongoing. Third, the reference member state will decide whether the update of the safety report necessitates changes in the labelling or the initiation of a risk management plan and notify all other European Competent Authorities and MAHs.

This new system has the potential to greatly enhance the quality of benefit-risk assessment of older products in Europe, if also case validation and overlap control could be incorporated.

In this study we used buflomedil as an example of an older product to illustrate difficulties in the collection of data on efficacy and safety. Comparisons with other similar products can only be made if a similar approach is made for these products. Also, it is not ruled out that some of the biases illustrated here for older products are also relevant for newer products.

In the case of buflomedil, the postmarketing safety databases did not raise the alarm to the safety concerns. The early warnings were not raised based on information in the databases, but based on information in the literature.[44,45] Regulatory action in France was taken on the basis of reports from the NPC and from the toxicovigilance centres.

3. Conclusion

Thorough benefit-risk appraisal is also possible for older products, and should also be performed on a regular, ongoing basis in these older drugs.

Evidence of efficacy based on trials performed decades ago should be carefully examined for publication bias.

Despite the existence of safety databases, case reporting of serious events and deaths in the literature remains a necessary instrument for risk appraisal of older medicines. A procedure to match fatal cases and drug-related serious adverse events published in the literature with those in the WHO database and the safety database of the company should be implemented. The enforcement of efficient communication between healthcare workers, drug companies, national safety committees and the WHO is necessary to assure the validity of postmarketing surveillance reporting systems. Drugs considered obsolete because of unfavourable benefit-risk assessment should not be allowed to stay on the market.

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