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The paradox of scored tablets: a cost-saving risk

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One of the cornerstones of pharmacotherapy is the proper dose of medicine, which should ideally be tailored to the individual patient. However, even if clinically possible, this is economically not feasible as a too large number of different dosage strengths would be required. Therefore, a balance is required between the patient's benefit/risk and the cost to the individual and society on the other hand. Scored or splitted tablets were, and still are, often used strategies to these opposite interests, enabling more dose-flexibility, but also at the same time increasing the dose-variability as a consequence of the breaking process. The question of how to deal with this paradox was investigated by exploring the prevalence and classification of scored tablets as well as the cost-benefits. A strategy for clinical pharmacologists is presented to improve the outcome of this paradox.

1. Introduction

Currently, the production and distribution costs-of-goods of drug are to an important extent determined by the current Good Manufacturing Practice (GMP) and regulatory-maintenance expenditures. Consequently, for a same active pharmaceutical ingredient and form, it is economically justified to limit the number of different dosage strengths, as increasing this number will clearly increase the final drug cost. Moreover, there is a continual price pressure exerted by government and healthcare authorities, patients and their pressure groups, to reduce the prices of newly introduced and existing drugs. On the other hand, these different stakeholders also demand a clear evidence of efficacy without a corresponding increase in side-effects; a situation which is only attained when an appropriate dose is applied in clinical practice (Peck and Cross 2007). Indeed, the study by Poeta et al. (2007) and other recent investigations suggest that we are entering the era of individually tailored medicine. All these considerations of efficacy-risk balance and its regulation versus cost and reimbursement challenges have resulted in the much debated but even frequently applied use of scored tablets (Quinzler et al. 2006; De Spiegeleer et al. 2005; Rodenhuis et al. 2004; Barends et al. 2005; Van Santen et al. 2002; Bachynsky et al. 2002; Quinzler et al. 2008). Although patients have other reasons to split tablets, such as to facilitate swallowing, these are only minor reasons (Rodenhuis et al. 2004). Until recently, pharmaceutical guidelines and pharmacopoeial texts, there was very little, if any, attention of drug developers and manufacturers towards the scoring of tablets as its variability was considered negligible and/or easily solved. However, since the unit dose was clearly defined as the smallest part of a scored tablet, it became clear that breaking a tablet undoubtedly may significantly increase unit dose variability (Van Vooren et al. 2002). The question then arises what the existing situation is, i.e. what is the prevalence of scored tablets in the different therapeutic classes and especially their relationship with narrow therapeutic index (NTI) drugs? This current situation is the result of an evolution process, with different players each having influenced in a rather undetermined way the decision for a scored or unscored tablet. A second question is if there is an explicit relationship between the reimbursement classification and the prevalence of scored tablets, and what are the potential savings of scored tablets (Stafford and Randell 2002)? The findings presented here call for a scientific, risk-evaluating strategy in the scored tablet decision where pharmacists are expected to give added value to the patients, insurance organizations, regulatory authorities and industry.

2. Investigations, results and discussion

2.1. Prevalence of scored tablets according to ATC

In total, 1060 drugs are available as tablets in Belgium in 2005. These include different strengths, originator as well as generic drugs. In contrast to the general belief, we observed that tablets of different suppliers with identical active ingredient and strength, like in the situation of originator and its generic counterparts, do not always have identical score-properties. Apart from the observation that the excipients in these tablets might well be different, and thus also the breaking behavior of the tablets, the presence or absence of scores thus makes the practical exchange of these tablets in clinical settings rather difficult.

Figure 1 gives the percentage distribution of scored versus unscored tablets according to their ATC classification.

In total, 415 tablets have scores. Classes S and V have a too low number of tablets for any conclusion to be drawn. Four major ATC-classes are falling outside the 20–80%

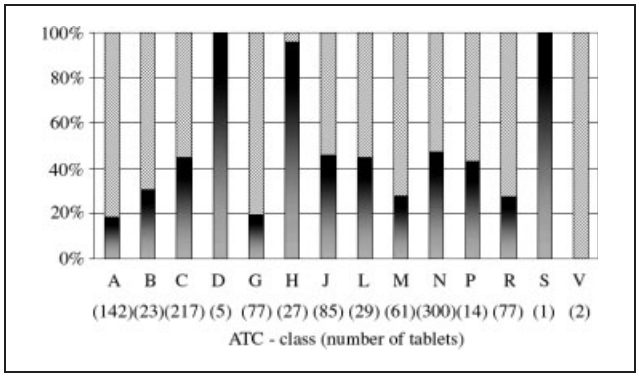

Fig. 1: Percentage scored tablets for the different ATC-classes. The total number of tablets in each ATC-class is given between brackets under the ATC-class. The lower bars in gradient are the scored percentages, while the upper bars in diagonals indicate the unscored percentages

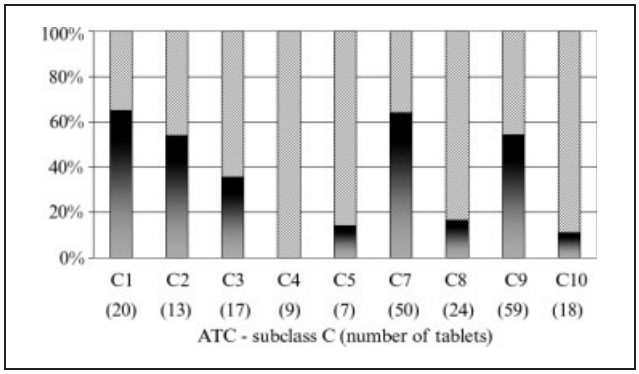

Fig. 2: Percentage scored tablets for the different subgroups in ATC-class C (cardio-vascular drugs)

interval, considered to be significant: dermatology (D) and systemic hormonal drugs (H) show a high proportion of scored tablets (>80%), while conversely the GI-drugs (A) and urogenital/sex-hormones (G) show a low proportion of scored tablets (<20%).

2.2. Health economics of scored tablets

The reimbursement system in Belgium classifies drugs in several groups, with decreasing financial support from the government: a defined reimbursement category (A, B, C) or non-reimbursed. The drugs in category A are completely paid by the government, category B for 85% to 75%, while category C is supported for only 50% to 20% by the government, and no reimbursement is given for the non-reimbursed drugs. The reimbursement classification decision is based on the life-saving aspects of the drug, but also on political and socio-economical considerations. This reimbursement principle is quite general, although variants and different operational systems are present on a national basis.

Figure 3 clearly shows that the highest proportion of scored tablets can be found in categories A and B, while the lowest proportion of scores are found in category C and the non-reimbursed drugs.

Overall, combining the reimbursed drugs (all categories A, B and C taken together; n = 998), 48% of the reimbursed drug tablets have scores, while this is only 28% for the non-reimbursed drugs (n = 577). Certain correlations between the reimbursement status, life-saving character and the therapeutic index of drugs cannot be excluded, which will partly explain the observed prevalence of scored tablets within the different reimbursement categories. However, it remains to be seen if this is the only explanation for these findings.

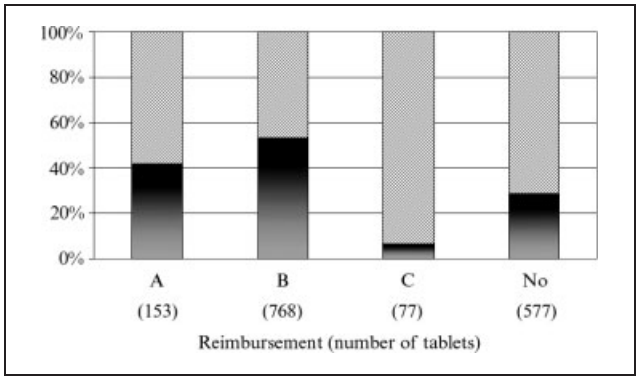

Fig. 3: Percentage scored tablets according to their reimbursement category

To have an estimation of the possible cost-savings using scored tablets, we selected the top 20 drugs with the highest total yearly cost (Inami-Riziv 2005: ⟨http://www.riziv.be⟩). Fourteen of these 20 drugs are formulated as tablets: atorvastatin, omeprazole, simvastatin, clopidogrel, pravastatin, molsidomin, paroxetin, alendronic acid, venlafaxin, pantoprazol, amoxicillin, olanzapin, sertralin and escitalopram. For each of the drugs and available dosage strengths, the price per defined daily dose (DDD, as defined by the WHO ⟨http://www.who.no⟩) was calculated. The difference between the lowest price per DDD and the mean price per DDD was considered as the estimated potential proportional cost-gain per drug. Using the total yearly expenditures per drug and the calculated potential proportional cost-gain, the total potential cost-gain per drug was deduced. Summing these for the 14 drugs considered, a potential cost-saving of 29% on the total budget was obtained: the yearly cost could potentially be reduced from 526 Mio Euro to 369 Mio Euro.

While the economic reasons for tablet splitting may be compelling, the more clinical risks other than incorrect dosing should be considered as well, as outlined in the literature (Bachynsky et al. 2002; Weissman et al. 2007; Quinzler et al. 2007), e.g. more complex medication regimens leading to patient confusion and noncompliance, which is aggravated by a lack of clear information communication. The physico-chemical problems of difficult splitting leading to incorrect dose and waste should be minimized by appropriately scored tablets which are designed for easy, correct and consistent dividing.

2.3. Conclusion

Considering the top 20 drugs with the highest yearly costs, the use of scored tablets which can be split into several dose-units can present a potential significant cost-saving estimated as 29%. Although the current regulatory reluctance and consequentially scrupulous data-supported justification for scoring tablets during the development of new drugs, existing tablets frequently exhibit scores. The scored tablets present a paradox: the benefit is that they allow a cost-efficient fine-tuning of the dose to the individual patient, while the draw-back is an unavoidable increase of the variability in unit dose. This paradox can also be stated as that NTI drugs show unexpectedly high prevalence of scored tablets compared to relatively low score prevalence for the non-NTI drugs in less life-threat-

ening ATC classes. This simultaneous increase in cost-efficient individualization of drug therapy and risk at the same time calls for a case-by-case evaluation instead of a uniform, standardized approach neglecting the specific pharmacological characteristics of each drug.

3. Experimental

The pharmaceutical compendium 2005 comprising the approved SPCs (summary of product characteristics) of all drugs registered and marketed in Belgium was the primary data-source. If the SPC did mention the presence of a score-line, it was given the attribute "yes". If the SPC did explicitly mention the absence of a score-line in the tablet description, the product was given the attribute "no". However, if nothing was explicitly mentioned in the SPC, the hypothesis of "no" was assumed, which was verified, and if required corrected, by a second source, i.e. the BCFI Commented Drug Repertorium (Belgian Centre for Farmacotherapeutical Information). This does not give the SPC, but gives the strengths of the tablets, their price as well as if they are dividable. A relational data-base program was written in Microsoft Access, and data of each tablet filled in the data-base.

The Anatomical Therapeutic Chemical (ATC) classification is maintained by the WHO Collaborating Centre for Drug Statistics, and structures all drugs in a convenient hierarchical system. Within clinical pharmacology, the term narrow therapeutic range or index (NTI) drugs is used for compounds with little difference between toxic and therapeutic doses. Formally, NTI drugs are defined as drugs with less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or drugs with less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood. Often, these NTI drugs require careful titration and patient monitoring. A working list of so called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research (CDER 1995). A quantitative value of therapeutic index was almost never given in the SPCs and hence could not be used for a more quantitative stratification.

The GI-group A tablets consist of drugs with a large therapeutic window, e.g. antacids, gastroprokinetics, vitamins, etc. . . . These drugs are considered to be not dose-critical, and thus the use of scores will not significantly increase the dose-variability risk. Nevertheless, the majority of these tablets do not contain scores. The systemic hormonal drugs (group H) in tablet form contain corticosteroids and drugs used in thyroid therapy, and are considered to be rather dose-critical. Nevertheless, almost all of these tablets contain scores. From these observations, the paradox becomes apparent: dose-critical tablet-drugs have scores, while this undoubtedly increases the dose-variability-risk. On the other hand, not-dose-critical tablet-drugs do not have scores, while here the use of scores is not a significant risk. A plausible explanation is that the rationale historically followed was that individual dose-fine-tuning if required could be more accomplished by using scored tablets, these by neglecting the dose-variability risk. As for not-dose-critical tablets, a gross dose deviation is not a risk, and hence, no scores were applied.

The above observations and related possible explanation is also seen in other groups. The blood group (class B) does contain important NTI drugs, like warfarin, containing scores. The paradox is thus again exemplified: on the one hand, no scores are expected to be present because the dose-variability in broken parts of the tablets increases the risk that the drug plasma concentration falls outside the therapeutic range. On the other hand, the presence of scores allows a fine-tuned individualization of the dose. Achieving effective and safe administration of these NTI drugs like warfarin has been both an urgent concern for clinicians and for researchers i.a. to explore the potential of pharmacogenomics. The administration of warfarin is tricky because of the drug's narrow therapeutic range and the large variations in dose requirements from one patient to another. The Food and Drug Administration (FDA) and researchers have acknowledges this: in August 2007, FDA deemed that the accumulation of information was sufficient to warrant a modification in the labeling of warfarin to highlight not only the potential relevance of genetic information to prescribing decisions, but also stating that "it cannot be emphasized too strongly that treatment of each patient is a highly individualized matter" (FDA 2007; Schwarz et al. 2008).

Also, when looking within the ATC-subgroups, the same remarkable observations are made. For example, in the cardiovascular group C, with a mean of 45% scored tablets, there is a high percentage (65%) of scored tablets in group C1, containing also NTI drugs with scores (procainamide, quinidine), while the lipid-lowering drugs of the C10 subgroup do contain a low percentage (11%) of scored tablets. Similar, as another example, in the CNS drugs of class N, the analgetics (N2) contain only 27% scores, while the psycholeptics (N5) containing the NTI drug lithium show scores very frequently (68%). It should be noted that specific properties of the galenic formulation (e.g. certain modified release preparations) or of the active pharmaceutical ingredient (e.g. light sensitivity) preclude splitting and this may confound to some extent our observations of low numbers for scored tablets in certain ATC-classes, e.g. C08 or R.

The paradox is thus encountered over all ATC-groups: drugs which are not dose-critical do not contain scores, while scoring these tablets could just be cost-effective and risk/efficacy-beneficial.

References

Bachynsky J, Wiens C, Melnychuk K (2002) The practice of splitting tablets: cost and therapeutic aspects. Pharmacoeconomics 20: 339–345.

Barends DM, Groot DW, Frijlink HW, Rodenhuis N, van der Steen JC (2005) Development of an in vivo test procedure for the ease of breaking of scored tablets. Pharm Eur Sci Notes 1: 27–30.

CDER (Center for Drug Evaluation and Research). "Scale-Up and Post-Approval Changes for Intermediate Release Products" (SUPAC-IR), Appendix A, November 1995.

De Spiegeleer B et al. (2005) Mass uniformity: influence of operational compression conditions on breakability of scored tablets as part of manufacturing robustness evaluation. J Food Drug Analysis 13: 22–29.

FDA, FDA-approved labeling for warfarin (Coumadin) NDA 9-218/5-105. Press release of the Food and Drug Administration, Rockville, MD, August 16, 2007. (http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html.)

Peck CC, Cross JT (2007) Getting the dose right: facts, a blueprint, and encouragements. Clin Pharmacol Ther 82: 12–14.

Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N, Califano JA, Ridge JA, Goodwin J, Kenady D, Saunders J, Westra W, Sidransky D, Koch WM (2007) TP53 Mutations and Survival in Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 357: 2552–2561.

Quinzler R, Bertsche T, Szecsenyi J, Haefeli WE (2008) Teilung von Tabletten: Welchen Einfluss haben die Rabattverträge auf die Verordnungsqualität? Med Klinik 103: 569–574.

Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE (2006) The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol 62: 1065–1073.

Quinzler R, Szecsenyi J, Haefeli W (2007) Tablet splitting: patients and physicians need better support. Eur J Clin Pharmacol 63: 1203–1204.

Rodenhuis N, De Smet P, Barends D (2004) The rationale of scored tablets as dosage form. Eur J Pharm Sci 21: 305–308.

Schwarz UI, Ritchie, MD, Bradford Y, Li C, Dudek SM, Frye-Anderson, Kim RB, Roden DM, Stein CM (2008) Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 358: 999–1008.

Stafford S, Randell S (2002) The potential of pill splitting to achieve cost savings. The American Journal of Managed Care 8: 706–712.

van Santen E, Barends DM, Frijlink HW (2002) Breaking of scored tablets: a review. Eur J Pharm Biopharm 53: 139–45.

Van Vooren L, De Spiegeleer B, Thonissen T, Joye P, Van Durme J, Slegers G (2002) Statistical analysis of tablet breakability methods. J Pharm Pharmaceut Sci 5: 190–198.

Weissman E, Dellenbaugh C (2007) Impact of splitting risperidone tablets on medication adherence and on clinical outcomes for patients with schizophrenia. Psychiatric Services 58: 201–206.