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ORIGINAL REPORT

Changes in prescribed drug doses after market introduction

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SUMMARY

Purpose The establishment of recommended dosing regimens has always been a difficult aspect of drug development. This paper examines the extent to which postmarketing prescribing deviates from initially recommended dosing regimens. We used the World Health Organization's (WHO) periodically updated compilation of the 'Defined Daily Dose' (DDD) to reflect prevailing patterns of prescribing in national markets. The aim of this study was to evaluate DDD changes over time (1982–2000) and to identify possible determinants of these changes.

Methods Data on DDD changes were obtained from the WHO's Oslo Collaborating Centre. We performed a case–control analysis in which we compared drugs with (cases) and without (controls) postmarketing changes in DDD on possible determinants associated with DDD change.

Results We found 115 instances of a change of DDD in the period 1982–2000 (45 (39.1%) increases and 70 (60.9%) decreases). Antibiotics showed the greatest number of changes in DDD: predominantly increases in the 1980s, while the 1990s were dominated by decreases in DDD of mostly cardiovascular drugs.

Conclusion Changes in DDD reflect the outcome of a melange of forces, including misconceptions of dose requirements during pre-market development of drug and postmarketing changes in pharmacotherapeutic knowledge, clinical concepts, economic forces, and, in the case of anti-infective agents, changing patterns of resistance/sensitivity of target microorganisms to the anti-infective agent(s) in question. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — dosing changes; pharmacoepidemiology; postmarketing; label changes; registration

INTRODUCTION

Optimal drug therapy requires appropriate dosing in order to obtain the desired therapeutic effects at minimal risk. It is apparent from available data on drug usage that the doses currently used in clinical practice sometimes differ from those initially recommended by the manufacturer at the time of the drug's registration and initial market entry.[1,2] This observation raises questions of how dose regimens and titration schedules are selected during drug development, why they change after market introduction, and how one may affect the other. The identification of optimal dosing regimens has long been a subject of debate in clinical pharmacology, with new elements now being added by developments in pharmacogenetics.[3–5]

The establishment of recommended dosing regimens has always been a difficult aspect of drug development. Great pressure is placed on arriving at the earliest possible definition of a recommended dose, so that definitive clinical trials can commence. Thus, recommended doses are often set at a very early point in the drug development process, when information about the drug and its actions is relatively sparse. Certain drug classes, e.g. anti-epileptics, psychotropics, antihypertensives, and antiretroviral drugs, are well known for problems in deriving the appropriate dose.[6–9]

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Ascertainment of the time-history of drug exposure is a major topic in pharmacoepidemiology. Sound assessment of both outcomes and hazards of drug use requires reliable data on drug exposure, ideally at the level of the individual patient. If that is not possible, then the next best approach is to have reliable data on drug dispensing. In a paper on patterns of drug usage, Leufkens and Urquhart recognized three phases in the research of drug exposure. In the first phase, drug exposure is regarded as a dichotomous 'yes/no'. In the second phase, information on dosing of the drugs is included to allow for dose–response studies. In the third phase, focus has shifted toward patient profiles and drug usage patterns over time.[10]

The second and third phases of drug exposure assessment benefit from a system of sound classification and standardization. Such a system is provided by the ATC/DDD (Anatomical-Therapeutic-Chemical/Defined Daily Dose) system, which was developed by the World Health Organization in the 1970s as a tool in drug utilization studies.[11,12] The use of the DDD as a measure of dosages actually prescribed offers possibilities for dose–response research in pharmacoepidemiology, for studies on the effects of dosage changes, and correlative information in the quest to identify optimal dosing regimens for widely-used drugs.

WHO defines the DDD as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'.[13] For newly marketed drugs, however, an average maintenance dose can only be derived from the label-recommended dosing regimen, which is based on pre-registration clinical studies that may not always reflect subsequent use in everyday clinical practice. For that reason, the WHO's Oslo Centre maintains ongoing surveillance to detect changes in the DDD of a drug after its initial designation. Analysis of these DDD changes reveal ways in which everyday clinical practice comes to deviate from initially recommended dosing regimens for newly marketed drugs. The aim of our study is to evaluate DDD changes over time (1982–2000) and to identify possible determinants of dosage increases or decreases.

METHODS

We used data available from the WHO Collaborating Centre for Drug Statistics and Methodology in Oslo, Norway, which is responsible for the assessment and designation of DDDs. As a result of discussion during the European Drug Utilization Group meeting at the Dead Sea in 1999, the Centre compiled and posted on its website a list of all drugs with one or more changes in DDD between 1982 and 2000. For these drugs the year of first registration anywhere in the world was obtained from various sources, including leading trade publications.[14,15] The company that first registered the drug was designated as the innovator company. We classified companies as US-based or non-US-based. The DDD system is inextricably tied to the Anatomical Chemical Therapeutic (ATC) classification system in which the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.[13] We used the ATC system to classify drugs.

We carried out a case–control analysis in which we compared drugs with (cases) and without (controls) postmarketing changes in DDD. For cases, we included all drugs mentioned in the WHO list and for controls we took a random sample from all drugs with an ATC code that was not on that list. We compared the two groups in a case–control analysis including only the first instance of a DDD change for each individual drug.

RESULTS

We found 115 instances of a change of DDD in the period 1982–2000. Of these changes, 45 (39.1%) were increases and 70 (60.9%) were decreases relative to the initially designated DDD. Figure 1 shows that while increases in the DDD predominated in the 1980s, the most common changes later on were decreases in DDD. Table 1 shows that this time-dependent change is also seen in relation to the registration date: drugs registered and marketed in the 1980s or earlier show more increases in their respective DDDs, while later-registered drugs more often

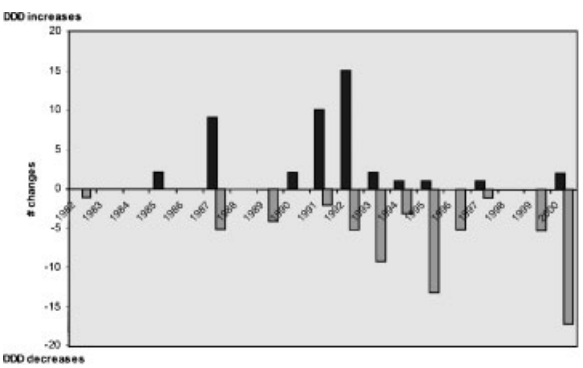

Figure 1. DDD increases and decreases 1982–2000

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Table 1. Characteristics of 115 DDD changes in 1982–2000

	N	DDD increases *n* (%)	DDD decreases *n* (%)
Registration year			
Pre-1980	47	25 (53.2)	22 (46.8)
1980–1989	41	14 (34.1)	27 (65.9)
1990–1999	15	1 (6.7)	14 (93.3)
Unknown/not marketed	12	5 (41.7)	7 (58.3)
Administration			
Parenteral only	46	21 (45.7)	25 (54.3)
Oral and other	69	24 (34.8)	45 (65.2)
Antibiotics	39	20 (51.3)	19 (48.7)
Antibacterials for systemic use	33	19 (57.6)	14 (42.4)
Antivirals for systemic use	4	1 (25.0)	3 (75.0)
Antimycotics for systemic use	1	0 (0.0)	1 (100.0)
Antimycobacterials	1	0 (0.0)	1 (100.0)
Cardiovascular	27	7 (25.9)	20 (74.1)
ACE inhibitors	7	0 (0.0)	7 (100.0)
Cardiac therapy	5	5 (100.0)	0 (0.0)
Beta blocking agents	5	0 (0.0)	5 (100.0)
Serum lipid reducing agents	3	1 (33.3)	2 (66.7)
Antihypertensives	2	0 (0.0)	2 (100.0)
Diuretics	2	0 (0.0)	2 (100.0)
Calcium channel blockers	2	0 (0.0)	2 (100.0)
Peripheral vasodilators	1	1 (100.0)	0 (0.0)
Antithrombotic agents	17	4 (23.5)	13 (76.5)
Respiratory	12	8 (66.7)	4 (33.3)
Anti-asthmatics	6	5 (83.3)	1 (16.7)
Cough and cold preparations	3	1 (33.3)	2 (66.7)
Nasal preparations	2	1 (50.0)	1 (50.0)
Antihistamines for systemic use	1	1 (100.0)	0 (0.0)
Neurological	8	2 (25.0)	6 (75.0)
Psycholeptics	4	1 (25.0)	3 (75.0)
Psychoanaleptics	2	0 (0.0)	2 (100.0)
Analgesics	1	1 (100.0)	0 (0.0)
Antiepileptics	1	0 (0.0)	1 (100.0)
Urogenital and sex hormones	4	0 (0.0)	4 (100.0)
Muscular	4	2 (50.0)	2 (50.0)
Gastrointestinal	3	1 (33.3)	2 (66.7)
Anthelmintics	1	1 (100.0)	0 (0.0)

had a decrease in DDD. Oral, nasal and inhalation preparations more often showed a decrease in DDD, compared to drugs administered parenterally.

Antibiotics were by far the class of drugs with most changes in DDD, which were mostly increases, especially in the 1980s. Cardiovascular drugs on the other hand more often underwent decreases in DDD. All changes in DDDs of ACE inhibitors were decreases. Antithrombotic agents are also among the drug classes with the most DDD changes, with decreases in the majority.

Of the 115 DDD changes, we excluded 12 that occurred with drugs that were either not marketed or for which date of registration was unavailable. Furthermore, we included only the first change in DDD, leaving a total of 86 drugs (cases). We randomly selected 190 controls with no DDD change to which the same inclusion/exclusion criteria were applied. The results of the case–control analysis are presented in Table 2. Drugs approved for marketing in the period 1980–1989 show the peak of DDD changes. Moreover, there is a trend among recently introduced drugs toward earlier occurring changes in DDD, i.e. in the first 4 years after marketing. No difference in DDD changes between US and non-US company-originated drugs was seen. Antibiotics, ACE inhibitors, and antithrombotics were the three drug classes predominately linked with DDD changes.

DISCUSSION

We found noteworthy patterns of DDD changes in the period 1982–2000. Two 'waves' of DDD changes in time can be distinguished: one with frequent DDD increases in the early 1990s, and one with predominately DDD decreases in the mid- and late 1990s. Two drug classes appear to predominate in the overall picture: antibiotics with equal numbers of decreases and increases, scattered over the whole period of the study, and cardiovascular drugs with high frequencies of DDD decreases, predominantly in the mid- and late 1990s.

In the case of antibiotics, the DDD changes probably reflect the dynamics of prescribing antibiotics in the context of changes of bacterial sensitivity to the various antibiotics in use, reflected in changes in required minimum inhibitory concentrations (MIC) and area under the inhibitory concentration curve (AUIC) values.[16] There is also the additional factor of large variability between countries and clinical settings in antibiotic prescribing. A recent study by Cars *et al.* revealed that prescribing of antibiotics as measured in DDDs/1000 persons/day varies more than fourfold in Europe: France (36.5), Spain (32.4), Portugal (28.8), and Belgium (26.7) have the highest utilization, whereas the Netherlands (8.9), Denmark (11.3), Sweden (13.5), and Germany (13.6), the lowest.[17] They also found extreme variation in use of different classes of antibiotics. These differences reflect not only national differences with respect to concepts of which clinical conditions to treat or not treat with antibiotics, but also different ideas about both dose and duration of treatment when the decision is taken to treat. As in other areas, the aggregate parameter, DDD, could probably usefully be broken into its component parts, to avoid the averaging of qualitatively different sets of data from high- and low-use countries.

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Table 2. Drugs with a first DDD change (cases, $n = 86$) compared to a random sample of drugs with no changes (controls, $n = 190$)

	Cases ($n = 86$)	Controls ($n = 190$)	Odds ratio (95% CI)
Registration year			
Before 1980	42 (48.8)	132 (69.5)	(reference)
1980–1989	31 (36.0)	27 (14.2)	3.6 (1.9–6.7)
1990–1999	13 (15.1)	31 (16.3)	1.3 (0.6–2.7)
Time since registration			
>10 years	52 (60.5)	162 (85.3)	(reference)
5–10 years	22 (25.6)	19 (10.0)	3.6 (1.8–7.2)
0–4 years	12 (14.0)	9 (4.7)	4.2 (1.7–10.4)
Manufacturer			
Non US-based	54 (62.8)	91 (47.9)	(reference)
US-based	19 (22.1)	28 (14.7)	1.1 (0.6–2.2)
Drug class			
Antibiotics	22 (25.6)	11 (5.8)	5.6 (2.6–12.2)
ACE inhibitors	7 (8.1)	3 (1.6)	5.5 (1.4–21.9)
Cardiac therapy	5 (5.8)	8 (4.2)	1.4 (0.4–4.4)
Beta blocking agents	5 (5.8)	4 (2.1)	2.9 (0.8–11.0)
Antithrombotic agents	7 (8.1)	4 (2.1)	4.1 (1.2–14.5)
Anti-asthmatics	1 (1.2)	10 (5.3)	0.2 (0.0–1.7)
Cough and cold preparations	5 (5.8)	4 (2.1)	2.9 (0.8–11.0)
Psycholeptics	4 (4.7)	12 (6.3)	0.7 (0.2–2.3)
Psychoanaleptics	2 (2.3)	7 (3.7)	0.6 (0.1–3.1)
Urogenital and sex hormones	2 (2.3)	6 (3.2)	0.7 (0.1–3.7)

The pressure of 'less is best' has led to dose-duration changes with unwanted effects. Historical examples of reduced drug exposure from decreased doses (i.e. cefaclor, clarithromycin, or ciprofloxacin), directly correlate with drug resistance.[16] In addition, new antibiotic agents have been developed with long half-lives, allowing for reduced impact of common errors in patient compliance with the prescribed dosing regimens, but with fewer possibilities for time–dose titration to cater for individual needs.

Cardiovascular drug therapy has its well-known antecedents of agents entering the market with exceedingly high doses. Some of the more striking earlier examples of postmarketing reductions in dose are provided by Temple, with hydrochlorothiazide and captopril in hypertension being the most dramatic,[1] both falling by 6–8-fold. The late Gilbert MacMahon, author of a widely-used textbook on hypertension, remarked that 'the currently optimal dose of hydrochlorothiazide in hypertension is 100 mg/day divided by the edition number of the latest edition of my book', which metaphorically epitomizes the series of changes that have brought clinical practice from 100 mg to the currently recommended dose to 12.5 mg/day.[18]

Our findings concur, in general, with those reported by Cross *et al.*, which were based on the historical record of FDA-authorized changes in the label-recommended doses of drugs registered in the US during the past several decades.[19] This correspondence provides an important ratification of the basic findings, for the FDA-mandated changes reflect a regulatory response to data of various origins, while the WHO–DDD data reflect drug utilization and market research data, not necessarily preceded by, or even reflected in, regulatory actions. Naturally, both FDA-authorized labelling changes and DDD revisions are subject to bureaucratic delays between the time that evidence is first adduced and when official changes are published, though the dynamics of the two may differ.

Economic factors

Changes in recommended or generally-used dosing regimens usually have important economic consequences, as many pharmaceutical products are priced on a weight basis,[20] in which case halving the initially recommended dose will result, as a first approximation, in a halving of revenues from the product.[21] Exceptions can and do occur, when products are priced in a dose-independent manner, e.g. as some delivery system products have been priced, with multiple products providing different rates of drug release, all carrying the same price. If it is possible to cut a dosage form in halves or quarters without altering its characteristics of drug release and absorption, then purchasers have the option to purchase

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the highest-dose product and create from it multiple smaller-dose entities. The impact of such practice on the seller's revenues from the product line thus depends upon several factors, including the pricing of different strength forms of the product.

As pharmaceutical prices have steadily risen, these considerations have gained in economic importance, creating unprecedented motivation to seek clinical evidence that can justify reductions in initially recommended doses, as a cost-containment manoeuvre. Naturally, this approach is reinforced by the principle that 'less is best', provided that therapeutic effectiveness is maintained.

Reimbursement considerations

A number of governments have adopted policies that use the ATC/DDD system as a basis for reimbursement.[20] Under those policies, changes in the official ATC and/or DDD may influence the level of reimbursement for the drug. These policies can have, therefore, potentially substantial economic consequences for the research-based pharmaceutical industry, governments, and patients. These economic uses of the ATC/DDD system make it vulnerable to non-scientific bias. An illustrative case was the debate on the DDD decrease of some of the statins, leading to a decision by the Dutch reimbursement authority to peg reimbursement to the downwardly revised DDD.[2,21] Here is another instance in which it is necessary to understand the market dynamics that led to the reduction in official DDD. Computerized dispensing data for the HMG-CoA reductase inhibitors in the PHARMO network of community pharmacies (300 000 people) in The Netherlands showed that when treatment was begun with simvastatin, more than three out of four patients received 0.67 DDD, and most of the remainder received 1.33 DDD.[2] This distribution represented a shift, as prescriptions were refilled, from initial prescriptions at the label-recommended dose, towards two in three simvastatin recipients being prescribed 0.67 DDD and most of the remainder being prescribed 1.33 DDD. Scarcely anyone was prescribed 1.00 DDD equivalent. The reimbursement policy was such that recipients of the lower dose were reimbursed at 0.67 of the DDD-based rate, and recipients of the higher dose had themselves to pay the extra one-third. As a result, both manufacturers and patients objected to the policy. The DDD, as computed and published, does not distinguish between unimodal and multimodal frequency distributions, so that its (mis)use in setting reimbursement levels discourages individualization of prescribing.

Institutional changes

In an earlier era, individual prescribers were the chief decision-makers regarding all aspects of the use of prescribed drugs. There was little regard for costs, and, in the absence of overtly dose-dependent toxicity, only the non-specific motivation of minimizing drug exposure challenged recommended doses. As medicine has grown in complexity, with general increases in costs of all aspects of health care and, in particular, steeply increased drug costs, formulary controls and practice guidelines have become pervasive. In this new environment, questions of dose optimization have gained in importance, especially where they hold out the promise of reducing drug costs by challenging manufacturer-recommended dosing regimens. In certain settings, e.g. American managed care organizations, drug formulary committees have both the economic incentive and the potential power over prescribing, through the setting and enforcement of practice guidelines, to change as well as to enforce dosing recommendations among prescribers working within the managed care organization. These administrative changes have accelerated and strengthened attacks on initially recommended dosing regimens. Once such changes become known, their propagation from one care system to another is accelerated by the prospect of dose-dependent cost-reduction. An illustrative case is that of the antifungal agent, itraconazole, whose initially recommended regimen of daily dosing for 3 months, for nail-bed infections, was successfully challenged and revised downward to daily dosing over 1 week per month during 3 months, thus quartering the drug cost.[22]

Origins of overestimated dosing requirements

Why have both we and Cross *et al.* found clear evidence of an acceleration in the rate of products undergoing postmarketing reduction in recommended or prevailing dose?[19] As with any other epidemiological change, the main factor may be either, or both, higher incidence of the phenomenon in question or more efficient identification against a background of unchanged incidence. Possibilities are: (a) misjudgement of the drug's dose–response characteristics during premarket development, (b) changes in prevailing severity of disease(s) treated by the drug in question, (c) more efficient postmarketing processes for identifying and changing suboptimal doses in the postmarketing environment.

We would offer the hypothesis that one contributor to this trend, besides the facilitated discovery mechanisms already described, has been the rapid growth in

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pharmacokinetic concepts and practice during drug development, which may have induced a certain exaggeration of the importance of maintaining drug concentrations above certain presumed minima, thought to be needed for sustained drug action. Many drugs have pharmacodynamic characteristics such that their actions persist at therapeutically effective levels for substantially longer than they persist at measurable concentrations in plasma. In that case, the idea of dosing to maintain a minimum, non-zero trough concentration will result in an overestimated dosage requirement. This idea is undoubtedly distasteful to those who struggled to bring pharmacokinetic principles into drug development, but not atypical of overshooting pendulum swings in clinical concepts. Its validity could be assessed in a meta-analysis of PK-PD attributes of products that have undergone substantial dose reductions to see if certain concentration–effect relations prevail more commonly among dose-reduced than among non-dose-reduced products. This matter is beyond the scope of this paper, but a worthy topic for investigation.

CONCLUSION

Changes in drug doses after market introduction, as measured by DDD changes over time, offer a powerful tool in what Sheiner has called the 'learning cycle of drug development'.[23] The changes reflect the dynamics of current knowledge of appropriate pharmacotherapy, advances in clinical pharmacology, and changing practices in drug development, but also the erratic nature of the economics of the pharmaceutical market-place. There is a need for more research on drug dosing, and how we can minimize the gap between pre-marketing studies and clinical practice, thereby improving patient outcomes.[24] Hopes are high that pharmacogenetics may also contribute to a better understanding of dosing dynamics, as genetically-determined between-patient variability in response to different doses is understood and systematically measured.[5] The concept of 'tailor-made' medicine on the basis of the gene map is on the horizon of pharmacotherapy, and will, if its promises are realized, force changes in drug utilization research that will give us a multimodal distribution of usage data, instead of the simple averages of today.

KEY POINTS

- A substantial minority of marketed prescription drugs undergo substantial changes in prescribed dosage, relative to initially recommended dosages. These changes are reflected by the changes in DDDs as compiled by the WHO
- Most frequently changed dosages are those of antibiotics (mainly increases) and cardiovascular drugs (mainly decreases)
- These changes reflect gaps between pre-market studies and subsequent clinical practice, sometimes resulting in substantive consequences for clinical outcomes, for revenues to the manufacturer, and for levels of reimbursement

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