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Dosages involving splitting tablets: common but unnecessary?

Christer Berg^{a,b} and Anders Ekedahl^{b,c}

^aNational Corporation of Swedish Pharmacies, Växjö, ^bSchool of Natural Sciences, Linnæus University, Kalmar and ^cR&D Department, National Corporation of Swedish Pharmacies, Malmö, Sweden

Abstract

Objectives Prescribing of treatments with dosages involving split tablets is common. Many patients report they have difficulties in dividing the tablets and in following the prescribed treatment. The objective of this study was to examine to what extent dosages involving split tablets are prescribed in Sweden.

Methods The dosage text strings were analysed on prescriptions dispensed during one month at Swedish pharmacies on all tablet formulations for beta-blockers, calcium blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), lipid-lowering agents, levothyroxine, neuroleptics, anxiolytics, hypnotics/sedatives and selective serotonin reuptake inhibitors (SSRIs). Numbers and percentages of prescriptions with split tablets were compared with all dispensed prescriptions.

Key findings Six hundred thousand prescriptions on tablet formulations for the investigated drugs were dispensed. Ten per cent of the prescriptions had a dosage where tablets have to be split. Hypnotics and SSRIs had the highest proportions, accounting for 22 and 19% of prescriptions involving split tablets. SSRIs constituted 30% of the prescriptions with split tablets. Dosages with split tablets varied with drug across patient age but not across gender. In 45% of the cases with levothyroxine and SSRIs, a tablet strength fitting the prescribed dosage was licensed and available. Furthermore, it would have been possible to avoid splitting tablets by adjusting and combining existing licensed strengths for more than 80% of the prescriptions.

Conclusions Prescribing of dosages involving the splitting of tablets was common and constituted 10% of the prescriptions for tablet formulations. Many prescriptions on dosages with split tablets can be avoided if physicians adjust prescribing to licensed and available strengths fitting the prescribed dosages.

Keywords drug-related problem; pharmacy; prescriptions; split tablets; Sweden

Introduction

Prescribing of dosages involving split tablets is common, and even more so among elderly patients and those with several medications.^[1–4] Difficulties in dividing tablets are also common: one- to two-thirds of patients with prescribed dosages involving split tablets state they have difficulties in dividing the tablets.^[2–9] Elderly patients in particular find it difficult and may fail or be unable to split tablets due to vision problems or motor impairment. Concerns have been raised that tablet splitting may compromise patient safety as well as clinical efficacy.^[10,11] Many tablets are not designed to be split or are difficult to divide, and tablets may break into uneven parts or crumble. The European Pharmacopoeia accepts a dosage accuracy of the individual parts of the tablet within $\pm 15\%$ of the anticipated dose. However, accuracy when splitting tablets is low and the fluctuation in dose may be large.^[12–17] To facilitate splitting of tablets the use of a tablet splitter is recommended, but for a variety of reasons few patients use them.^[2,4] The cost of the tablet splitter may be judged too high, the tablet splitter may be difficult to handle and patients report they have not received any or adequate handling instructions.^[4,6,18] Moreover, the accuracy of tablet splitters in dividing tablets into equal parts often produces halves no better than produced by manual splitting with an unacceptably large deviation from the intended dose.^[12,19]

In many instances when the prescribed dosage involves splitting of tablets, alternatives (other strengths or other administration forms) are available to be prescribed instead.^[4] Dosages with split tablets may be prescribed for a number of reasons, which may vary by

Correspondence: Anders Ekedahl, c/o Apoteket Lejonet, Stortorget 8, SE-211 34 Malmö, Sweden.
E-mail: anders.ekedahl@lnu.se

drug. Due to pharmacokinetic variation among individuals the standardised dose may give rise to a variable response between individual patients; therefore the dose must be individually selected. Children, adolescents and elderly patients often need lower doses. For many brands, few tablet strengths are available and those available may not correspond to the selected dosage. The most common single dose strengths may not be licensed and, furthermore, pharmaceutical companies may be unaware of how their drugs are prescribed. Renewals of prescriptions to patients on chronic medication may be done without adjustment to available strengths. Patients may have trouble swallowing whole tablets. Prescribing of tablets of twice the required strength that are intended to be split may be recommended for cost-containment reasons or even be mandatory for reimbursement, especially for new drugs under patent protection.^[18–26] Patients may also prefer to receive prescriptions for tablets of higher strength and to split tablets in order to decrease their out-of-pocket costs.^[19,27] There may be other reasons as well. For instance, in Sweden, split tablets may not be subject to generic substitution and prescriptions for split tablets of drugs with a cost above the threshold level may be reimbursed. However, the pharmacokinetic profile of the drug may be altered when tablets not intended to be divided are cut in half; the effect may be different from anticipated, which may increase the incidence of adverse drug reactions.

The present study was performed to examine to what extent dosages with split tablets are prescribed in Sweden and if alternative strengths or administration forms are available.

Methods

The setting was Swedish pharmacies. Data on all dispensed prescriptions at Swedish pharmacies, including the dosage text string on the prescription, are stored in the pharmacy transaction database, Apotekets TransaktionsDatabas (ATD).

A cross-sectional study was performed. All prescriptions for tablet formulations dispensed at Swedish pharmacies during one month, October 2004 or October 2005, for selected Anatomical Therapeutic Chemical (ATC) groups, were extracted from ATD. The extracted data included patient

gender and year of birth, dispensed drug (ATC code, name, administration formula, strength, pack size) and the dosage text string.

Inclusion criteria were prescriptions made to humans of the following drugs. In October 2004: ATC groups C07 (beta-blockers), C08 (calcium blockers), N05CD (hypnotics/sedatives) and N06AB (selective serotonin reuptake inhibitors (SSRIs)); in October 2005: ATC groups C09 (angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, ARBs), C10 (lipid-lowering agents), H03 (levothyroxine), N05A (neuroleptics) and N05BD (anxiolytics). Only drugs administered as tablets were included. Prescriptions made to animals were excluded.

The main outcome measures were the numbers and percentages of prescriptions with split tablets compared with all dispensed prescriptions.

The data were placed in a Microsoft Excel spreadsheet for calculations. Twelve undergraduate students were trained and analysed one drug group each using the same method/protocol.

Results

We examined 607 794 prescriptions for 74 different substances in nine ATC groups (see Table 1). Dosages with split tablets were prescribed in 9.7% of all prescriptions for tablet formulas (range 0; 34%). Split tablets were somewhat more prevalent in prescriptions to women than men (12.1 and 10.3%, see Figure 1), and there were differences across age; however, the proportions of prescriptions on split tablets varied with type of drug.

Hypnotics and SSRIs had the highest proportions of prescriptions on dosages where tablets had to be split: 21.9 and 19.2% respectively. Prescriptions for SSRIs and beta-blockers constituted 53% (31 and 22%, respectively) of all prescriptions on dosages with split tablets. Sixteen substances with more than 1000 prescriptions as split tablets ($n = 51\,987$ of 385 513) constituted 64% of the dispensed prescriptions and 88% of the prescriptions with split tablets (see Table 2). For 19 substances, more than 15% of all prescriptions were using split tablets (mean $\pm$ SD, $15.3 \pm 7.1\%$; median, 16.7%) and

Table 1 Proportions of prescriptions with dosages with split tablets in Sweden for 74 studied substances in nine ATC groups of drugs ($n = 607\,794$)

ATC code	Drug group (number of substances)	Dispensed prescriptions <i>n</i>	Prescriptions with split tablets				
			<i>n</i>	%	Mean $\pm$ SD	Median	Range
C07	Beta blockers (10)	148 995	12 798	8.6	10.1 ± 7.1	8.9	0.0–20.4
C08	Calcium blockers (8)	39 858	868	2.2	2.2 ± 2.0	2.0	0.0–5.5
C09	ACE inhibitors (7)/ARBs (5)	84 447	5673	6.7	4.5 ± 2.5	3.8	0.6–8.6
C10	Lipid-lowering agents (10)	115 154	1319	1.1	1.8 ± 3.2	0.7	0.0–10.0
H03	Levothyroxine (1)	44 755	7780	17.4	(17.4)	(17.4)	(17.4)
N05A	Neuroleptics (20)	31 288	2188	7.0	6.6 ± 9.8	2.1	0.0–33.7
N05BA	Anxiolytics (4)	39 942	5935	14.9	12.7 ± 9.5	14.2	0.0–22.2
N05CD	Sedatives/hypnotics (3)	17 573	3995	22.7	22.3 ± 3.2	21.9	19.3–25.7
N06AB	Antidepressants/SSRIs (6)	85 785	18 367	21.4	19.7 ± 5.1	19.2	13.7–27.9
Total	74	607 794	58 924	9.7	11.3 ± 8.0	8.6	1.8–22.3

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATC, Anatomical Therapeutic Chemical classification; SSRI, selective serotonin reuptake inhibitor.

Figure 1 Proportions of prescriptions for split tablets in Sweden with reference to age (left) and gender (right) for levothyroxine (H03, $n = 44\,755$), anxiolytics (N05BA; $n = 39\,942$), sedatives/hypnotics (N05CD; $n = 17\,573$) and selective serotonin reuptake inhibitors (N06AB; $n = 85\,785$).

Table 2 Dispensed prescriptions for 16 drugs with more than 1000 prescriptions with split tablets ($n = 51\,978$), constituting 88.2% of all prescriptions for split tablets and 63.4% (385 513) of all studied prescriptions

ATC code	Drug group	Prescriptions with split tablets	All prescriptions (numbers)	Proportion of prescriptions with split tablets (%)
N06AB05	Paroxetin	2488	8906	27.9
N05CD03	Flunitrazepam	2302	8954	25.7
N06AB04	Citalopram	8440	37 114	22.7
C07AA07	Sotalol	1567	7666	20.4
N06AB06	Sertralin	5374	26 425	20.3
N05CD02	Nitrazepam	1438	7455	19.3
H03AA01	Levothyroxine	7780	44 755	17.4
N05BA01	Diazepam	4175	24 981	16.7
C07AB07	Bisoprolol	1726	10 561	16.3
N06AB10	Escitalopram	1046	7619	13.7
C07AA05	Propranolol	1289	10 193	12.6
N05BA12	Alprazolam	1748	14 904	11.7
C07AB02	Metoprolol	4854	54 263	8.9
C09AA02	Enalapril	3692	48 728	7.6
C09AA05	Ramipril	1268	18 021	7.0
C07AB03	Atenolol	2791	54 968	5.1
Total		51 978	385 513	13.5

constituted 92.8% of all investigated prescriptions with dosages on split tablets. Of prescriptions with split tablets, 41% for cardiovascular drugs were to patients of 70 years or more compared with 21% for SSRIs.

Levothyroxine and SSRIs were studied separately. For 44.7% a tablet strength fitting the prescribed dosage was available. Avoiding use of split tablets would have been possible in more than 80% (95.3 and 81.8%, respectively) of instances had existing licensed tablet strengths been used or combined.

Discussion

Our study shows that prescribing of dosages with split tablets is common in Sweden, especially for psychotropic drugs. If

licensed and available strengths had been prescribed in the first place for levothyroxine and SSRIs, four out of five prescriptions for split tablets could have been avoided.

There are certain limitations to the study. The point of measure is the prescription and the only information on patients is gender and age but there are no individual data, which would have made cross-linking with other databases (outcome data) possible. The prescriptions studied were collected from two different periods and are thus not truly cross-sectional. However, the drugs studied are usually used continuously. Overall results may not be representative for all other drugs, and the two subgroups of drugs we examined to see if there were tablet strengths that fitted the prescribed dosage (levothyroxine and SSRIs) may not have been representative of the other drugs. However, these two subgroups,

with a high prevalence of prescriptions for split tablets, constituted a large part (44%) of all studied prescriptions for dosages involving split tablets.

The prevalence of prescriptions with split tablets was higher in previous studies than in our study, 20 to more than 35%,^[1,2,4,7,28] and the prevalence of elderly patients with at least one prescription requiring tablet splitting varied from 35 to 67%.^[1,3] Rodenhuis *et al.* found that for 46% of the prescriptions with tablet splitting, alternatives (tablets with half or quarter strength, or oral solution) were available,^[7] similar to our findings. However, many of previous studies were small and may not have been representative.

There are conflicting data on the impact of tablet splitting on patient adherence to prescribed therapy: some studies indicate that tablet splitting increases non-adherence^[26,29] as well as medication errors,^[26] and others state no impact on adherence or clinical outcome.^[18,19,27,30,31] Most studies are with selected patient groups and splitting is often accompanied by an economic incentive (the out-of-pocket co-payment for the patient may be decreased substantially). However, as elderly patients use many medications and are frailer and subject to visual and motor impairment, it is reasonable to assume that every addition to regimen complexity will increase the risk for non-adherence and medication errors as well as adverse drug reactions.^[29]

Prescriptions with dosages requiring that tablets be split and patients' difficulty in splitting the tablets are common;^[4–7] so common that this may be overlooked by pharmacists. However, difficulties in splitting tablets are simple to identify and in many instances easy to solve. Pharmacists should be encouraged to ask patients how they manage to adhere to the prescribed treatment. If a patient has difficulty in splitting tablets, there may be a licensed strength or other administration formula to fit the dosage, or it may be possible to adjust the dosing schedule without compromising the efficacy before suggesting that the patient use a tablet splitter, followed by adequate instruction in its use.

Our study constitutes an analysis of more than 600 000 prescriptions for tablet formulations, covering all prescriptions made in Sweden dispensed during one month for the selected drug groups. The Swedish pharmacy benefit scheme (PBS) allows a maximum of 90 days'/3 months' treatment to be dispensed with reimbursement at each fill. Accordingly, patients with continuous medication will have a refill every third month. Our results imply that at least 180 000 prescriptions to more than 125 000 patients on continuous medication in Sweden have a dosage involving split tablets, corresponding to at least 40 000 patients on continuous medication having difficulties in splitting the tablets and adhering to the prescribed treatment.

The results of this study suggest that (a) pharmacists should be permitted to adjust dispensing to a strength that fits with the prescribed dosage level, (b) price policies with flat prices need to be revised to eliminate economic incentives to prescribe dosages with split tablets and (c) physicians, pharmacists and patients should demand that the pharmaceutical companies license tablet strengths that fit the prescribed dosages. A decrease in the use of split tablets would result in both an increased ability for patients to comply with the prescribed therapy and a decrease in changes in clinical effect

and adverse drug reactions due to unpredicted pharmacokinetic differences in the preparations.

In future studies we aim to interview an extended group of patients on how they manage to split tablets and follow the prescribed treatment and to observe what information pharmacists give patients with prescriptions for split tablets.

Conclusions

Prescribing in Sweden of dosages involving split tablets is common and constituted 10% of the prescriptions examined in the present study. Dosages with split tablets can be avoided if physicians adjust prescribing to licensed and available strengths fitting the prescribed dosages.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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