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RESEARCH ARTICLE

Tablet splitting of narrow therapeutic index drugs: a nationwide survey in Taiwan

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Abstract *Background* Tablet splitting or pill splitting frequently occurs in daily medical practice. For drugs with special pharmacokinetic characters, such as drugs with narrow therapeutic index (NTI), unequal split tablets might lead to erroneous dose titration and it even cause toxicity. *Objective* The aim of this study was to investigate the frequency of prescribing split NTI drugs at ambulatory setting in Taiwan. *Setting* A population-based retrospective study was conducted using the National Health Insurance Research Database in Taiwan. All ambulatory visits were analyzed from the longitudinal cohort datasets of the National Health Insurance Research Database. *Methods* The details of ambulatory prescriptions containing NTI drugs were extracted by using the claims datasets of one million beneficiaries from National Healthcare Insurance Research Database in 2010 in Taiwan. The analyses were stratified by dosage form, patient age and the number of prescribed tablets in a single dose for each NTI drugs. Main outcome measures Number and distinct dosage forms of available NTI drug items in Taiwan, number of prescriptions involved split NTI drugs, and number of patients received split NTI drugs. *Results* A total of 148,548 patients had received 512,398 prescriptions of NTI drugs and 41.8 % (n = 62,121) of patients had received 36.3 % (n = 185,936) of NTI drug prescriptions in form of split tablets. The percentage of splitting was highest in digoxin prescriptions (81.0 %), followed by warfarin (72.0 %). In the elderly patients, split tablets were very prevalent with digoxin (82.4 %) and warfarin (84.5 %). *Conclusion* NTI drugs were frequently prescribed to be taken in split forms in Taiwan. Interventions may be needed to provide effective and convenient NTI drug use. Further studies are needed to evaluate the clinical outcome of inappropriate split NTI drugs.

Keywords Narrow therapeutic index drugs · Prescribing patterns · Splitting frequency · Tablet splitting · Taiwan

Impacts on practice

- Physicians should be more aware of the impact of unequal splitting when prescribing a tablet to be split, especially for a drug with a small gap between a therapeutic dose and a toxic dose.
- The high prevalence of NTI drugs to be split may reveal a lack of broad dosage selections among NTI drugs in clinical practice.

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Introduction

The practice of prescribing a drug that has to be split for use (also known as tablet splitting or pill splitting) is prevalent worldwide [1–3]. The underlying reasons include the lack of drugs of specifically required strengths being on the market [4, 5], the restriction of health insurance reimbursement for cost saving [6, 7], and the pill size adjustment to facilitate swallowing [5]. However, the accuracy of splitting, either by hand or with a cutter, usually gives cause for concern [8, 9]. A grave situation might arise in the case of use of drugs with special pharmaceutical characters, for example, narrow therapeutic index (NTI) drugs.

Drugs with a narrow therapeutic index usually have the following characteristics: (1) a small concentration gap between the therapeutic concentrations and toxic concentrations in the blood; (2) out-of-range concentration that may result in serious treatment failure that is life-threatening or leads to significant disability; (3) necessary therapeutic monitoring of these NTI drugs; (4) a very small adjustable dose range [10]. Warfarin, used for prevention of thromboembolic events, is a typical NTI drug [11]. During warfarin treatment, patients should monitor their international normalized ratio (INR) level response to warfarin. The usual therapeutic range of the INR level is between 2 and 3 [11]. If the INR level is under the therapeutic range, treatment failure may occur, leading to acute thromboembolic episodes. On the other hand, warfarin overdose may result in serious or fatal bleeding [12]. While most studies dealing with NTI drugs paid attention to therapeutic concentration monitoring as no suitable biomarkers exists [13–15], and some studies addressed the importance of not applying tablet splitting to NTI drugs [16, 17], no study has been devoted to the prescription pattern of NTI drugs with tablet splitting in real daily practice.

Aim of the study

The purpose of this study was to measure the frequency of tablet splitting in prescribing NTI drugs in the ambulatory setting in Taiwan by use of a nationwide claims database. Moreover, the analyses would be stratified by dosage form and patient age for each NTI drug.

Ethical approval

This study had been approved by the institutional review board of Taipei Veterans General Hospital, Taipei, Taiwan (2013-01-005E).

Methods

Data source

The National Health Insurance (NHI) program was launched in Taiwan since 1995. At the end of 2010, a total of 23,074,487 beneficiaries were enrolled in the NHI program, equaling 99.6 % of all population [18]. From 1999, the Bureau of NHI started to release the National Health Insurance Research Database (NHIRD) for the research purpose [19]. The NHIRD encrypted all identifiable information for each applicant for privacy protection. In the current study, the data were obtained from the longitudinal cohort datasets of 1,000,000 beneficiaries (LHID2010) of the NHIRD in Taiwan. These one million persons (4.3 %) were randomly sampled from 23,074,487 persons insured under the National Health Insurance program in 2010 (http://nhird.nhri.org.tw/en/index.html). The claims belonging to the cohort were extracted from the whole database to form a specific group of datasets for research use.

Subjects

In the current study, only the datasets of ambulatory visits in 2010 were used; 15,431,528 visit records were cross-linked with 89,492,613 prescription records. The records of visits to hospital emergency departments were also included. While one visit record contained one patient's data, one prescription record represented one prescribed drug item. The master file of drugs was downloaded from the website of the National Health Insurance Administration of the Ministry of Health and Welfare (http://www.nhi.gov.tw/) to identify each drug's active ingredient(s).

From the cohort datasets in 2010, the details of prescriptions containing NTI drugs were extracted, such as patient age, drug name and number of tablets in a single dose. This study adopted the definition of NTI drugs by the North Carolina Board of Pharmacy in 2013 [20]. Eleven kinds of drugs were included: carbamazepine, cyclosporine, digoxin, ethosuximide, levothyroxine, lithium (all salts), phenytoin (all salts), procainamide, theophylline (all salts), warfarin and tacrolimus. Drugs with different brand names, different doses, and different dosage forms were considered as different drug items. For a prescribed NTI drug item of solid forms for oral use, splitting was deemed to have occurred when the number of tablets in a single dose was not an integer. For each kind of NTI drug, we additionally calculated the drug risk ratio [13] as the proportion of prescribed split drug items to all prescribed items of solid forms for oral use.

Table 1 The prescribed drug items with a narrow therapeutic index for oral use in the study cohort

Drug name	Number of distinct items	Number of distinct strengths	Number of items as solution	Available strengths in mg or mg/ml[a]
Carbamazepine	10	4	0	S: 100, 200, 300, 400
Cyclosporine	5	3	1	S: 25, 100 L: 100
Digoxin	7	3	1	S: 0.1, 0.25 L: 0.05
Levothyroxine	10	2	0	S: 0.1, 64
Lithium	4	2	0	S: 300, 400
Phenytoin	12	2	0	S: 50, 100
Tacrolimus	6	3	0	S: 0.5, 1, 5
Theophylline	69	14	8	S: 50[b], 75, 100[b], 125, 130, 150, 200[b], 225, 250, 300, 400 L: 5.34, 8, 25
Warfarin	10	4	0	S: 1, 2.5, 3, 5

[a] *S* solid form, *L* liquid form

[b] Same strengths in different salts

Statistical analysis

Data extraction and computation were performed with the Perl programming language, version 5.18.1 (http://www.perl.org/). The analyses were stratified by the kind of NTI drugs, dosage form and patient age. Only descriptive statistics were displayed.

Results

In total, 133 NTI drug items had been prescribed for oral use in the cohort datasets in 2010. More than half (51.9 %, n = 69) of NTI drug items contained theophylline. Ethosuximide and procainamide were not present. Among all kinds of NTI drugs, liquid forms were available only for cyclosporine, digoxin, and theophylline (Table 1). Of one million beneficiaries, 148,548 patients had received 512,398 prescriptions of NTI drugs. The majority (90.4 %, n = 134,273) of patients were prescribed theophylline, followed by levothyroxine (3.9 %, n = 5823) and digoxin (2.8 %, n = 4086) (Table 2).

In total, 36.3 % (n = 185,936) of the NTI drug prescriptions requiring split tablets were made out to 41.8 % (n = 62,121) of patients from 53,400 patients requiring theophylline to 2 requiring cyclosporine (Table 2). Of 27,266 digoxin prescriptions, 22,018 required split tablets with a drug risk ratio of 0.81. The second-highest ratio was 0.72 for warfarin. The ratio was negligible for cyclosporine and tacrolimus.

While theophylline was widely used in children under 18 years, digoxin and warfarin were mainly prescribed to the elderly age 65 years and over (Table 3). Among children treated with theophylline, 59.7 % (22597/37861) of them had received prescriptions involving split tablets. Split tablets were more prevalent among elderly patients requiring warfarin (84.5 %) or digoxin (82.4 %). Liquid-form NTI drugs were infrequently prescribed except in the case of theophylline for children.

Discussion

In the current study, we found that tablet splitting of NTI drugs occurred frequently in medical practice in Taiwan, with a drug risk ratio of 0.36. Our analysis also showed that this potentially inappropriate prescribing of medications was frequently seen in digoxin and warfarin prescriptions for the elderly.

In the literature, the prevalence of prescriptions with split tablets has been reported to be around 10–35 % [2, 3, 21]. Even when the alternatives, e.g. oral solutions or lower-strength pills, were available, and tablet splitting was therefore unnecessary, a considerable number of drugs were nonetheless prescribed to be taken in split form [2, 22]. This finding also existed in the current study, which, to our knowledge, is the first study using a nationwide claims database to investigate the frequency of NTI drug prescriptions involving split tablets. Over one-third of prescriptions of NTI drugs involved split NTI drugs, with a drug risk ratio of 0.36. The high percentages of split tablets in our study highlighted the magnitude of potential drug-related problems in clinical practice, especially in the case of digoxin and warfarin, with a drug risk ratio of 0.81 and 0.72, respectively.

Table 2 The frequency of splitting among drugs with a narrow therapeutic index for oral use in Taiwan, 2010

Drug name	No. of patients	No. of patients receiving prescriptions involving splitting	No. of prescriptions	No. of prescriptions involving splitting	Drug risk ratio[a]
Carbamazepine	3296	1560	16,582	4978	0.30
Cyclosporine	369	2	3036	2	0.00
Digoxin	4086	3305	27,266	22,018	0.81
Levothyroxine	5823	2617	35,615	13,464	0.38
Lithium	721	47	6051	272	0.04
Phenytoin	2262	137	15,295	791	0.05
Tacrolimus	213	3	2563	9	0.00
Theophylline	134,273	53,400	384,549	128,850	0.36
Warfarin	2874	2337	21,441	15,552	0.72
Total	148,548[b]	62,121[b]	512,398	185,936	0.36

[a] Number of prescriptions with pill splitting divided by the number of total drug prescriptions

[b] Some patients might take two or more kinds of drugs with a narrow therapeutic index

Table 3 Distribution of patients receiving drugs with a narrow therapeutic index in 2010, stratified by patient age and drug form

	Carbamazepine N = 3296	Cyclosporine N = 369	Digoxin N = 4086	Levothyroxine N = 5823	Lithium N = 721	Phenytoin N = 2262	Tacrolimus N = 213	Theophylline N = 134,273	Warfarin N = 2874
<18 y/o	107	28	74	147	16	38	5	37,861	14
Liquid-form	0	7	46	0	0	0	0	9329	0
Whole-pill	65	21	1	72	15	24	5	11,226	7
Split-pill	62	0	29	105	2	18	0	22,597	10
18–64 y/o	2177	301	1111	4318	651	1398	187	74,127	1097
Liquid-form	0	1	4	0	0	0	0	137	0
Whole-pill	1376	300	367	3169	633	1353	186	55,361	584
Split-pill	969	2	833	1850	40	84	2	25,018	838
≥65 y/o	1012	40	2901	1358	54	826	21	22,285	1763
Liquid-form	0	0	0	0	0	0	0	35	0
Whole-pill	589	40	653	886	51	807	21	18,803	645
Split-pill	529	0	2443	662	5	35	1	5785	1489

Frequent dose titrations are often required in prescribing NTI drugs. This may explain the high frequency of tablet splitting in our study. The high splitting rates of digoxin and warfarin were observed in the elderly. Digoxin is used for the management of heart failure and atrial fibrillation. The usual doses are between 0.125 and 0.25 mg daily, and the serum concentration level should be maintained between 0.8 and 2 ng/mL. For patients with renal dysfunction, a lower dose of 0.0625 mg may be used [23, 24]. Some patients may experience digoxin toxicity even if the concentration level is within the range [25]. Therefore, close monitoring of the digoxin concentration level and careful adjustment of the dose are very important. In Taiwan, 0.0625 and 0.125 mg digoxin tablets are not available, so splitting is still common. In Taiwan, patients usually did hand splitting by themselves. Although pill splitting devices are available in community pharmacies, such devices are not reimbursed by the Taiwan NHI program. Thus, splitting-related overdosing may be prone to cause toxicity, such as nausea and vomiting, visual disturbances, arrhythmias, ventricular fibrillation and even cardiac arrest [24]. Similar difficulties occurred among patients receiving warfarin treatment. Although 4 strengths of warfarin tablets were available in 2010, it was unlikely all 4 strengths of tablets available in each hospital. Consequently, splitting tablets was common among patients receiving warfarin treatment. Because aging alters the pharmacokinetics, the possibility of adverse effects due to dose fluctuation is usually higher in the elderly [26, 27]. Sometimes, the consequent increase in health-care costs

was more considerable than the amount of cost-saving from tablet splitting [28, 29].

Theophylline is the widely used medication in the management of asthma, neonatal apnoea and chronic obstructive pulmonary disorder. It often causes acute, acute-on-chronic and chronic toxic symptoms due to its narrow therapeutic index [30, 31]. Theophylline intoxication might occur in both adults and children due to its different indication. The age distribution of patients with theophylline intoxication was reported between 3 months and 98 years [32]. Some patients are asymptomatic; on the other hand, some patients suffer from adverse effects even in the therapeutic range of theophylline concentration. Hocaoğlu et al. [31] have reported that 38.4 % of theophyliine exposure cases were symptomatic and 95 % of these symptomatic patients presented with acute toxicity. The common clinical symptoms of theophylline intoxication are nausea, vomiting, tachycardia, hypokalemia, and tremor. In this study, theophylline was prescribed as split tablets for children, adults and the elderly. A close monitoring of adverse effects and serum concentration are required to ensure patient safety.

Although there were some alternatives with different dose strengths available, physicians were still used to splitting tablets. The reason for this may be that the drugs with suitable formulations were not promoted for use by patients needing lower doses. Although the Taiwan National Health Insurance Administration does not prohibit the use of liquid formulation for adults, physicians are still used to prescribing tablets to adult patients. This prescribing habit could be changed through a clinical decision-making system integrated into the physician order-entry system to provide information about alternative medications and suitable formulations for NTI drugs when physicians prescribe an NTI drug to be split. Previous studies have reported the effectiveness of a clinical decision-making system on the prevention of prescriptions for inappropriate splitting [3, 33]. However, if no alternatives to smaller doses were available, splitting NTI drugs would be unavoidable. In this study, some NTI drugs with high percentages of splitting lacked a wide spectrum of alternatives. For example, the most frequently prescribed tablet of digoxin 0.25 mg had only one alternative oral solution for dose switching. The price for digoxin was only 2 New Taiwan dollars (around 0.07 US dollars) for a 0.25 mg tablet (http://www.nhi.gov.tw/), so some economic incentives would be required to produce and sell more tablets than the liquid formulations. This phenomenon exists in the Taiwan National Health Insurance Program [34]. Other incentives from the authority are needed to increase the number of drug products available with different dose strengths.

Elliott et al. [35] have reported the accuracy of tablet splitting by comparing the deviation in the theoretical expected weight of half tablets and weight loss. The results showed that both scored and unscored tablets were divided inaccurately. In the Elliott et al. study, the greater deviation between expected weight and weight loss was shown in unscored tablets. However, a significant inaccurate split was also seen for digoxin despite a score line on the digoxin tablets. The reason for this might be that digoxin tablets were small, crumbly and difficult to divide equally. In addition, the greatest difference between the expected weight and weight loss observed in the tablets' half portion was shown by dividing the powder content of the capsules [35]. These results showed an inaccurate split in scored and unscored tablets and also in capsules. Therefore, in this study, the solid forms of NTI drugs, including tablets and capsules, were analyzed.

It may be common for physicians to prescribe alternate-day dosing for some NTI drugs. For example, patients may be instructed to take one 5 mg tablet of warfarin on 1 day and to skip the dose the next day. The total number of warfarin tablets to be taken within 30 days is 15 tablets, and the calculated single dose is not an integer. However, in this study, tablets were considered as split when the number of tablets in a single dose was not an integer. From the NHIRD, the single dose could be extracted. Thus, for NTI drugs, each single dose was checked rather than the total doses for a period. Based on this, a physician prescribing a single dose which was not an integer tablet is meant to split the tablet. The alternate-day dosing was therefore not included in the scope of this study.

There are some limitations in our current study. We did not explore the prescribing habit of each physician, especially with respect to specialty. Furthermore, although we have listed different strengths and forms of NTI drugs nationwide, the formulary in each clinic and pharmacy was not analyzed. Perhaps the prescribing of split NTI drugs was conditioned by the inventory. Full information pertaining to a tablet with or without a score line and the recommendation regarding tablet splitting were lacking in the NHIRD database and the master file of drugs. In addition, the total number of NTI drugs might be underestimated from this sampled cohort. Finally, although ethosuximide and procainamide were listed in the North Carolina Board of Pharmacy in 2013 as NTI drugs, these two drugs did not exist in the Taiwanese market in 2010. Therefore, we could not know the situation with respect to tablet splitting of these two drugs.

Conclusion

NTI drugs were frequently prescribed to be taken in split forms in Taiwan. Incentives from the authority are needed to increase the number of available drug products with

different dose strengths and forms. Interventions may be needed to provide effective and convenient NTI drug use. Further studies are needed to evaluate the clinical outcome of inappropriately split NTI drugs.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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