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SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) – STUDY ON UTILIZATION OF INFORMATION PRESENTED IN SMPC BY DIFFERENT GROUPS OF PHYSICIANS

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Abstract: Cross-sectional survey study was done, investigating whether information included in SmPC (changing often due to safety reasons) is actually used, properly used or not used at all by cardiologists, GP's (general practitioners), internists and internal diseases physicians. Conducting readability test of Patient Information Leaflet, required by European Commission improved utilization of medical information included in it by European patients. Since there was no such requirement on Summary of Product Characteristics (SmPC), we examined utilization of information presented in Summary of Product Characteristics by physicians. Investigated were six drugs used in antiplatelet therapies, ATC (Anatomical, Therapeutic Chemical classification system) code B01AC. A random sample of 800 physicians took part in the study. They were physicians (300 cardiologists and 300 GP's) chosen from The Polish Chamber of Physicians and Dentists (PCPD) database interviewed using regular mail and 200 physicians interrogated during the XV International Congress of Polish Cardiac Society.Physicians. They were asked to complete a questionnaire consisting of 20 questions (13 concerning active substances, 6 general questions and one open question "Indicate the best way of receiving safety information"). Questions were constructed on the basis on new safety information included in actualized SmPC after submission of Periodic Safety Update Reports (PSURs) for medicinal products concerned. The overall response rate was 16.5% (132 filled in of 800 questionnaires). Of the respondents there were 65 and 67 from group I (cardiologists) and group II (GP's, internists and internal diseases), respectively. Eligible questionnaires (85) were obtained during the Congress (64.4%). Only 47 were received *via* regular mail (35.6%). Most correct answers were noted for clopidogrel and ASA (acetylsalicylic acid), 72.98% and 72.73%, respectively. The less known substance appeared eptifibatide, only 34.47% of answers were correct. Analyzing both groups (I and II), there were no significant differences regarding percent of correct answers, however, a statistical tendency level has been reached for "drugs for hospital use only" (abciximab, eptifibatide and tirofiban). For the open question, concerning best pipeline for receiving safety information according to respondents, both groups were relatively similar. Most popular were e-mail alerts, web pages/portals and drug compendiums, 44.37 and 24 indications, respectively. Study has limitation of a small sample size. The results are based on small amount of received questionnaires. Due to small sample size, it can be assumed that there are no significant differences between two compared groups (I – cardiologists; II – GP's, internists and internal diseases physicians) with regard to utilization of information from SmPC; however, beside two substances – clopidogrel and ASA, the level of knowledge is below expected. It also should be emphasized that "drugs for hospital use only" pointed out tendency that cardiologists can have better knowledge regarding these substances.

Keywords: SmPC, readability test, antiplatelet drugs, medical information

According to Polish Pharmaceutical Law (1) and European Commission Directive (2) every medicinal product to be marketed in EU should have complete and up to date information before gaining marketing authorization. This includes information for patients (Patient Leaflet) as well as information for healthcare providers (Summary of Product Characteristics – SmPC) and labelling.

Medicinal Products information appropriation Patient Leaflet

A document called "Patients Leaflet" is prepared on the basis of SmPC. First package leaflets were required in US. In 1968 FDA obliged a manufacturer of izoprenaline to include to every single box of drug product warning that there is probability of causing respiratory problems by this product

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(3). Patient leaflet is available in every package of medicinal product as a separate printout authorized during the registration process. Products without package leaflet should have proper information printed on outer package or direct package. Main function of leaflet is to provide patients with information, what can improve recovering process. Studies show that great majority of patients are interested in safety profile and potential adverse events (4). European Commission wanted its citizens to have a wide access to such information, thus, since announcement of EU directive in 1992, concerning package leaflets and labelling (5), leaflets were full of information, but mostly not easy to understand for non-healthcare related patients. On that ground, to help people understand leaflet information, a guideline on readability test of the label and package leaflet has been presented by European Commission in 1998. According to this document, all newly (both novel and generic) medicinal products under registration should be tested against its readability by patients (6).

Summary of Product Characteristics

SmPC is a document prepared on the basis of core information about the product owned by pharmaceutical company, called CCDS (Company Core Data Sheet). It consists of all relevant information collected since the beginning of early phase's trials. It describes clinical and safety profile with professional terminology, thus SmPC, based on it, has similar information. It is the main reason of SmPC to be appropriate for healthcare professionals only.

Neither European Directives, nor Polish Pharmaceutical Law and other regulations oblige marketing authorization holders to test SmPC against its readability and understanding similarly to leaflet testing, before registration. No studies show exact level of utilization of information in SmPC by physicians. A great number of medical errors, an eight causes of deaths in USA, including pharmacotherapy errors can support hypothesis that utilization of this information is not as good as expected (7).

Therefore, survey study was performed to test whether new safety information reaches physicians in a proper time. Whether or not they know all important information regarding adverse events or proper clinical use

The results of analyses were divided into two parts. First, focuses on studied population profile and descriptive statistics for variables analyzed in the study. Second, investigates whether analyzed results differ between groups with concerns to analyzed variables.

METHODS

Study design

Active substances under investigation were six substances used in antiplatelet therapies (we did not use brand names on purpose): abciximab, clopidogrel, eptifibatide, integrilin, ASA and ticlopidine. Decision of choosing such group of drugs was based on size of population treated with those substances for various cardiovascular diseases worldwide. Heart diseases are leading cause of death in the United States (8). It has been estimated that around 17 million people suffering from cardiovascular diseases died in 2008 (9). Similar situation can be observed in UK, where after age of 35, heart diseases are most common cause of death (10). In Poland, in 2001, comparing with other European countries, mortality due to cardiovascular diseases was almost twice higher (11).

As a target two groups were chosen: cardiologists (group I), because it is their scope of specialization, and GP's, internists and internal diseases physicians (gathered in group II), as a comparator, because in majority of cases, it is GP, internist or internal disease physician whom patient meets first.

A survey type study consisted of three steps. First step focuses on gaining information to develop a questionnaire. For every active substance two SmPC's have been chosen (actual for 2005 and 2009 respectively[1]). To find changes, two SmPC for every substance were compared. Information included in PSUR's for each substance were analyzed. Total amount of PSURs for 5 years period was 35. Distribution, due to different PSUR submission calendar, was not regular. Every information from comparison of SmPC's matching to information about planed or done changes (to SmPC) from PSUR, was converted into question and included into questionnaire. Final version of questionnaire consisted of 13 questions for active substances and 6 general questions concerning registration processes, safety concerns etc. Except clopidogrel (which has 3 questions), rest of active substances have two questions.

Second step was distribution of prepared questionnaire by sending them *via* post. Due to Personal

[1] Except ASA and ticlopidine, which both were represented by Patient Leaflet in 2005. There were no SmPC for those substances by that time in Poland.

Data Protection Act, it is impossible to get addresses of physicians, hence authors contacted The Polish Chamber of Physicians and Dentists (PCPD), who has database of all Polish physicians, their addresses, and has the right to use them for correspondence purposes. Six hundred questionnaires along with short description, letter from the President of PCPD and stamped addressed envelope each, were sent with even distribution to 300 cardiologists and 300 GP's in Poland.

Study's third step was visiting XV International Congress of Polish Cardiac Society taking place in Wrocław (06–08 October, 2011). On the first day of the congress participants were given two hundred questionnaires and asked to fill them in during the congress. On the last day of the congress, the filled in questionnaires were collected.

Study population

Physicians enrolled in the study were classified into two groups. The first group consisted of cardiologists only. The second group gathered physicians from one of the following specializations: GP's, internists and internal diseases. This second group was treated as a comparator to cardiologists, because it was believed that cardiologists, as highly specialized physicians, should have better knowledge about procedures, safety and indications of studied drugs. The mentioned groups prescribe studied drugs in daily routine, except "drugs for hospital use only". Second do not use those drugs, but still they can get some information about safety or indications from publications, congresses and medical press.

Statistical analysis

Data analysis was performed using SPSS for Windows. Descriptive statistics were performed for all variables. Kolmogorov-Smirnov test was chosen for testing the distribution. For value of p less than 0.05 distribution was not considered as normal. Due to not normal distribution, comparisons were made using Mann-Whitney *U* test.

RESULTS

Survey response and target groups

The overall response rate for both mail and congress was 16.5 % (132/800 physicians). Forty seven from 600 (47/132; 35.6%) questionnaires were received by mail and 85 from 200 (85/132; 64.4%) were collected during the congress. Six hundred sixty eight responses were not received (85.5%). Table 1 shows distribution of responses.

Clopidogrel and ASA were two with highest rate of correct answers (more than 70%), and the lowest rate was for eptifibatide. Table 2 shows percent of correct answers in sum for all physicians.

Table 1. Distribution of responses.

Specialization	Amount	Percent of received questionnaires	Total percent
Cardiologists	65	49.24	8.125%
GP's, internists, internal diseases	67	50.76	8.375%

Table 2. Percent of correct answers for different questions in sum for all physicians.

Question groups	Correct answers (%)	Standard deviation (%)
Abciximab[1]	50.38%	27.28
Eptifibatide[1]	34.47%	33.35
Clopidogrel	72.98%	22.98
Tirofiban[1]	65.15%	33.23
Ticlopidine	65.15%	35.46
ASA	72.73%	32.32
Active substances in general	61.13%	14.92
General knowledge	69.82%	16.49
[1]Drugs for hospital use only	50.00%	21.50

Table 3. Descriptive statistics for percent of correct answers for different groups of questions with stratification on studied groups.

Group of questions	Studied groups	Correct answers (%)	Standard deviation (%)	Average significance
Abciximab	Group I	53.85	22.20	70.38
	Group II	47.01	31.24	62.74
Eptifibatide	Group I	38.46	36.20	70.03
	Group II	30.60	30.09	63.07
Clopidogrel	Group I	75.38	22.26	70.05
	Group II	70.65	23.59	63.05
Tirofiban	Group I	70.77	29.17	71.72
	Group II	59.70	36.14	61.43
Ticlopidine	Group I	66.15	34.36	67.22
	Group II	64.18	36.73	65.81
ASA	Group I	70.00	31.62	63.01
	Group II	75.37	33.00	69.89
Drugs in general	Group I	63.43	14.52	71.24
	Group II	58.90	15.06	61.90
General questions	Group I	71.28	16.00	69.32
	Group II	68.41	16.95	63.77
Drugs for hospital use only	Group I	54.36	20.04	72.73
	Group II	45.77	22.16	60.46

As per results of Kolmogorov-Smirnov test, distribution was not normal, hence comparison of percent of correct answers in both groups of physicians was made using Mann-Whitney *U* test. Table 3 shows descriptive statistics for the mentioned analyses.

Mann-Whitey *U* test delivered the following results:

- Abciximab: Z = 1.43; p = 0.153
- Eptifibatide: Z = 1.15; p = 0.250
- Clopidogrel: Z = 1.15; p = 0.250
- Tirofiban: Z = 1.70; p = 0.088
- Ticlopidine: Z = 0.23; p = 0.817
- ASA: Z = 1.16; p = 0.245
- Drugs in general: Z = 1.42; p = 0.155
- General questions: Z = 0.88; p = 0.376
- Drug for hospital use: Z = 1.90; p = 0.057

The analyses performed did not show statistically significant changes between two compared groups. It should be stressed that statistical tendency level has been observed for "drugs for hospital use only" (abciximab, eptifibatide and tirofiban) mainly. This can be interpret that there is tendency that cardiologists have better knowledge about this drugs. However, still results are not statistically significant ($p < 0.05$), what can lead to observation that, even though group II (GP's, internists, internal diseases) does not use "drugs for hospital use only" in a daily routine, they have knowledge about indications, procedures and safety of use of those drugs.

Final analysis concerning open question "Indicate the best way of receiving safety information", shows no significance differences in answers for both groups. Most popular were e-mail alerts, alerts *via* regular post and web sites for health providers.

DISCUSSION

In the light of results obtained during the study, there are no significant differences between compared groups of physicians according to utilization of information included in SmPC. Body of evidence shows that even though GP's, internists and internal diseases physicians do not use in a daily manner "drugs for hospital use only", as cardiologists do, they have knowledge about safety profile, indications or procedures accompanying their administration. However, it should be emphasized that except two drugs (clopidogrel and ASA), both studied groups have general knowledge below expected. Study also pointed out that correspondence method for survey does not work properly in Poland because

the amount of questionnaires sent back was very low.

Regular mail was chosen instead of electronic mail, because authors believed that traditional form of correspondence would be preferred. Many sites in Poland still consider "paper" form to be more valuable than electronic. It is changing (Ministry of Health Act concerning medical records to be in paper or electronic has been in force for three years now) but physicians are still more affectionate to conventional paper form. It has its limitations, as shown in the results. Only 8.7% of 600 survey letters was send back. This finding seems very interesting, according to the answers to open question, a great majority of respondents indicated regular mail as a best form of gaining information. On the one hand, letters are desired, and on the other, physicians do not will to send them back.

On the basis of results, knowledge about drugs or general knowledge is below expected. Only clopidogrel and ASA are known quite well. Both drugs are very popular among two studied groups, and are used widely in many cardiovascular afflictions (12–14). As for ASA, group II has higher percent of correct answers than group I. This was considered as the effect of using ASA for much more indications than only for cardiovascular indications. ASA is often used for headaches and migraines (15, 16), reducing fever (17) and many other cases.

Correctness of answers for rest of the drugs and general questions is satisfactory but below expected. As there are no similar studies, authors assume the reasons of such results as not sufficient access to SmPC. Among the ways of gaining SmPC in Poland are: Polish Authority web site, companies' web sites and medical representatives and independent source of medical information (only one in Poland). Excessive duties and lack of time can be a reason for being not familiar with SmPC, as well as all changes in it during medicinal product market life. There is no medical compendium in Poland with printed official SmPC, nor dedicated webpage like in United Kingdom (18).

No significant differences between correct answers in both groups mean that physicians have some basic knowledge about most of drugs even not related to the specialization. This can be a result of teaching methods in medical schools.

CONCLUSION

The presented study has an important limitation. Even though we chose population of 800 physicians, the final enrolment was only 132 respondents. The subject needs further exploration, especially due to a fact that document SmPC, which supposed to be one of healthcare professional's instruments, actually is not. The importance of this issue has been noticed by European Commission, who prepared Directive 2010/84/EU (15/12/2010) and on that basis a special web site dedicated to SmPC will be prepared by EMA. Moreover, some products will be authorized to additional monitoring and such information will be inscribed into its SmPC. "The Commission should (...) present to the European Parliament and the Council an assessment report regarding the readability of the summaries of product characteristics and the package leaflets and their value to the healthcare professionals and the general public" (19), but till now without further details.

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REFERENCES

1. Polish Pharmaceutical Law Act, 6th of September 2001, Journal of Laws of the Republic of Poland no. 45, 2008 year; article 271.
2. European Commission Directive 2001/83/EC, 6th November 2001.
3. „Labeling Requirements for Prescription Drugs and/or Insulin". Code of Federal Regulations Title 21, 201.57. United States Food and Drug Administration. 2010-04-01. Retrieved 2011-04-01.
4. Carrigan N., Raynor D.K., Knapp P.: Drug Saf. 31, 305 (2008).
5. European Commission. EEC Directive 92/27/EEC on labelling of medicinal products for human use and on package leaflets (OJ No. L113 of 30 April, 1992).
6. European Commission Guideline on the readability of the label and package leaflets of medicinal products for human use. version 29, (1998).
7. Michaels A.D., Ohman M., Alexander K.P. et al.: Circulation 121, 1664 (2010).
8. Miniño A.M., Heron M.P., Murphy S.L., Kochanek K.D.: Deaths: Final data for 2004. National Vital Statistics Reports (United States), 55 (2007).

9. Mendis, S., Puska, P., Norrving, B. Eds.: Global Atlas on Cardiovascular Disease Prevention and Control. World Health Organization, Geneva 2011.
10. Turner R.W.D.: Postgrad. Med. J. 56, 538 (1980).
11. Broda G.: Medical Handbook (Polish). 2004 available at: http://www.poradnikmedyczny.pl/mod/archiwum/4779_choroby_uk%C5%82adu_kr%C4%85%C5%BCenia.html
12. Porosińska A., Pierzchała K.: Neurol. Neurochir. Pol. 40, 313 (2006).
13. Musiał J., Szczeklik A.: Kardiol. Pol. 65, 1 (2007).
14. Hodor J.: Puls of Medicine (Polish) 127, (2006).
15. Farinelli I., Marteletti P.: J. Headache Pain 8, 49 (2007).
16. Kirthi V., Derry S., Moore R.A., McQuay H.J.: Cochrane Database Syst. Rev. 4, (2010).
17. Lans A., McCarthy D., Voelker M., Brueckner A., Senn S., Baron J.A.: Drugs R. D. 11, 277 (2011).
18. http://medicines.org.uk.
19. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010, amending as regards pharmacovigilance, Directive 2001/83/EU on the Community code relating to medicinal products for human use.

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